

# The Long Non-Coding RNA *IDH1-AS1* Promotes Prostate Cancer Progression by Enhancing IDH1 Enzyme Activity

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**Purpose:** Long non-coding RNAs (lncRNAs) are involved in the development of various tumors including prostate cancer. The purpose of this study was to explore the function of a natural antisense RNA, *IDH1-AS1*, exerting potential carcinogenic effects in prostate cancer through a novel molecular mechanism.

**Materials and Methods:** GEPIA and CCLE databases were searched to identify alterations in the expression of *IDH1-AS1*, which were then verified by RT-qPCR in 20 pairs of matched tumor and normal tissue samples. Subsequently, CCK-8, EdU, and transwell assays were conducted to investigate the carcinogenic effect of *IDH1-AS1*. RT-qPCR, Western blot, and isocitrate dehydrogenase 1 (IDH1) enzyme activity assays were used to explore the functional relationship between *IDH1-AS1* and its sense gene IDH1.

**Results:** IDH1-AS1 expression was found to be significantly increased in prostate cancer tissues and cell lines. *IDH1-AS1* knockdown significantly inhibited the proliferation and migration of prostate cancer cells. Interestingly, RT-qPCR and Western blot analyses revealed that *IDH1-AS1* did not significantly affect the expression of IDH1 mRNA or protein but was involved in the regulation of IDH1 enzyme activity in prostate cancer cells.

**Conclusion:** Our experiments revealed that the carcinogenic effects of *IDH1-AS1* in prostate cancer may depend on a new molecular mechanism, which directly alters IDH1 enzyme activity. Our findings indicate that *IDH1-AS1* is a novel candidate target for prostate cancer treatment.

**Keywords:** antisense RNA, divergent transcription, bioinformatics analysis, enzyme activity

## Introduction

Worldwide, prostate cancer (PCa) is the most diagnosed malignant tumor in men and the leading cause of mortality among tumors of the urinary tract.<sup>1</sup> In the past decade, PCa exhibited the highest incidence rate in China, causing an increase in overall tumor-related mortality, and gradually becoming a serious social problem.<sup>2</sup> The main therapeutic strategies for PCa at initial diagnosis include radical surgery and radiotherapy, but high incidence of metastasis and recurrence are still major clinical issues. Moreover, PCa patients undergoing conservative androgen deprivation therapy (ADT) eventually progress to castration-resistant prostate cancer (CRPC).<sup>3</sup> PCa progression to end-stage CRPC greatly increases the risk of invasion and metastasis, and contributes to poor patient survival.<sup>4</sup> Currently, prostate-specific antigen (PSA, also known as KLK4) is widely used for clinical screening. However, its low specificity may result in overdiagnosis and overtreatment.<sup>5</sup> In-depth

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understanding of PCa pathogenesis may help predict PCa and develop more effective treatment strategies.

Long non-coding RNAs (lncRNAs), longer than 200 bp, have been recently discovered owing to the advancements in sequencing technologies.<sup>6,7</sup> lncRNAs have vital biological functions, as they participate in the regulation of diverse biological processes.<sup>8</sup> Emerging evidence shows that lncRNAs are involved in tumorigenesis and cancer progression by regulating the proliferation, metastasis, and invasion of cancer cells.<sup>9</sup> For example, in glioma, the lncRNA, *MALAT1*, serves as a competing endogenous RNA of zinc fingers and homeoboxes 1 (*ZHX1*), and *MALAT1* knockdown attenuates the viability of glioblastoma cells.<sup>10</sup> Furthermore, *DLGPI-AS1* is significantly upregulated in hepatocellular carcinoma and promotes tumor progression by regulating the *miR-486-5p*/H3F3B axis.<sup>11</sup> Natural antisense RNAs, a type of lncRNAs, are characterized by a complementary or overlapping position with its homologous RNA in gene location.<sup>12</sup> Natural antisense RNAs are classified as trans-natural and cis-natural depending on their location with respect to their sense RNAs.<sup>12</sup> Natural antisense RNAs control their sense RNAs by a specialized divergent transcription, which is recently attracting increasing attention.<sup>13</sup> In particular, *FGFR3-AS1* upregulates the transcription of its sense gene, *FGFR3*, thus maintaining gene stability in osteosarcoma.<sup>14</sup> Previous studies have reported that *IDHI-AS1* is aberrantly upregulated in prostate cancer and is considered as an oncogene.<sup>15</sup> The gene for isocitrate dehydrogenase-1 (*IDHI*) is located on the sense strand with respect to *IDHI-AS1*. However, the interaction between *IDHI-AS1* and *IDHI* and its role in PCa remains unclear. We hypothesized that *IDHI-AS1* could induce PCa progression by regulating its sense gene.

The purpose of this study was to characterize the *IDHI-AS1*/*IDHI* interaction and elucidate its role in PCa. First, we employed bioinformatics tools and RT-qPCR to explore *IDHI-AS1* expression in PCa. Subsequently, the impact of *IDHI-AS1* on the proliferation and migration of PCa cell lines was addressed. Finally, *IDHI-AS1*-induced regulation of *IDHI* expression and activity was examined by RT-qPCR, Western blot, and enzyme activity assays. Our study provides new insights into the function of *IDHI-AS1* and identifies this molecule as a promising therapeutic target in PCa.

## Materials and Methods

### GEPIA and CCLE Databases

Gene Expression Profiling Interactive Analysis (GEPIA, <http://gepia.cancer-pku.cn>)<sup>16</sup> is a public database containing information on 9736 tumor samples and 857 normal tissue samples, and is normally used to identify genes with differential expression in human tumors. The Cancer Cell Line Encyclopedia (CCLE, <https://portals.broadinstitute.org/ccle>)<sup>17</sup> is an ongoing project allowing for free integrated computational analyses on human tumors, and provides detailed molecular information on more than 1100 cell lines.

### Tissue Collection

Our twenty pairs of tumor tissues and adjacent normal prostate epithelial tissues were obtained from PCa patients of the Second Affiliated Hospital of Nanjing Medical University who underwent radical resection without neoadjuvant chemotherapy or endocrine therapy prior to surgery. All samples were collected within 30 min after isolation, and stored in the refrigerator at  $-80^{\circ}\text{C}$ . Liquid nitrogen was used to transport samples to the laboratory for subsequent experiments. All samples were confirmed to be tumor or normal tissue samples by two independent pathologists. Patients were informed about their participation in the controlled clinical trial, and signed an informed consent document before the trial. This study was approved by Ethics Committee of the Second Affiliated Hospital of Nanjing Medical University.

### Cell Culture and Transfection

PCa (PC3, DU145, LNCaP, 22RV1) and normal control cells (WPMY-1) were purchased from Zhong Qiao Xin Zhou Biotechnology (Shanghai, China). PC3 and DU145 cells were cultured in F-12K medium, LNCaP and 22RV1 cells in 1640 medium, and WPMY1 cells in DMEM medium. Complete medium was obtained by adding 10% fetal bovine serum (FBS, ScienCell, USA) and 1% penicillin and streptomycin. The cell incubator was set at  $37^{\circ}\text{C}$  and 5%  $\text{CO}_2$ . The small interfering RNAs (si-RNAs) for cell transfection and the transfection kit were purchased from RiboBio company (Guangzhou, China). The transfection procedure was conducted according to the manufacturer's instructions.

### RT-qPCR

For RT-qPCR, total RNA was isolated from cells or tissues using TRIzol Reagent (TaKaRa, Dalian, China).

A PrimerScript RT-PCR kit (TaKaRa, Dalian, China) was used for reverse transcribe 1  $\mu\text{g}$  of total RNA into cDNA according to the manufacturer's protocol. Then, cDNA, gene-specific primers, and SYBR Green PCR kit (TaKaRa, Dalian, China) reagents were mixed. Real-time PCR was performed by using a Roche LightCycler 480II machine (Roche, Switzerland), and the procedure was performed according to the product instructions. The relative expression of RNAs was calculated by the  $2^{-\Delta\Delta\text{Ct}}$  method, with *GAPDH* as an internal control. The primers were as follows: IDH1-AS1-forward: GTCATGGAGGTGTCTGTGTTAG.

IDH1-AS1-reverse: GTCACTCTGCGGATGTTTCT; IDH1-forward: GGCTGAAGAAGCAGAGGATAG, IDH1-reverse: TTCACCACTCTGTCGGTTTAG; U6-forward: CTCGCTTCGGCAGCACA, U6-reverse: AACGCTTCACGAATTTGCGT; GAPDH-forward: GGTGTGAACCATGAGAAGTATGA, GAPDH-reverse: GAGTCCTTCCACGATACCAAAG.

## CCK-8 Assay

PCa cell proliferation capacity was measured using a CCK-8 kit (Beyotime, Shanghai, China) according to the manufacturer's instruction. After cell counting, 100  $\mu\text{L}$  of cell suspension containing  $4 \times 10^3$  cells was added to each well of a 96-well plate. Ten microliters of CCK-8 reagent were added at each time point. At 2 h after the addition of CCK-8 reagent, a Microplate Reader (Thermo, USA) was used to measure the absorbance at 450 nm, reflecting the rate of cell proliferation.

## EdU Assay

The EdU assay was conducted to determine the proliferative activity of PCa cells. According to the protocol of the Cell-light™ EdU Kit (Ribobio, China), PC3 and LNCaP cells were harvested and seeded into 96-well plates ( $1 \times 10^5$  cells/well). After labeling with EdU reagent (50  $\mu\text{M}$ ) for 2 h and fixation with glycine and 4% paraformaldehyde for 30 min, the cells were stained with DAPI solution for 30 min. EdU-positive cells were observed and counted by using a fluorescence microscope (Olympus, Japan).

## Transwell Assay

A transwell assay was used to determine the migration ability of PCa cells. After cell counting, about  $1.5 \times 10^4$  cells per well were seeded into the upper chamber of the transwell compartment with 100  $\mu\text{L}$  of serum-free medium, and 600  $\mu\text{L}$  of 20% FBS-containing medium was

added to the lower chamber. The cells were cultured under standard conditions for 24 h, and the cells that had migrated to the lower chamber were collected, fixed with 4% formaldehyde, and stained with 0.5% crystal violet dye for 10 min. Finally, the migrated cells were washed with PBS and placed under a microscope for observation and counting.

## Subcellular Fractionation

To separate nuclear and cytosolic fractions of PCa cells, subcellular fractionation was conducted by using a PARIS Kit (Life Technologies, USA) according to the manufacturer's instructions. Specifically, the Cell Disruption Buffer was used to cells lysis on ice for 5mins. The Cell Fractionation Buffer was added into the obtained cell lysate, then nuclear and cytoplasmic fractions were separated by centrifugation at 4°C. The subsequent experiments including RNA isolation and protein analysis were then performed.

## Western Blot

PCa cell proteins were extracted with RIPA buffer (Beyotime, Shanghai, China) and boiled for denaturation. Subsequently, the protein samples were separated by 10% SDS-PAGE and transferred to PVDF membranes (Millipore Corporation). The membranes were blocked with non-fat milk and incubated overnight at 4°C with primary antibodies against IDH1 or GAPDH. Finally, the membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies (Abcam, UK), and protein bands visualized by enhanced chemiluminescence.

## IDH1 Enzyme Activity Assay

As already mentioned, the IDH1 enzyme mainly functions in the cytoplasm.<sup>18</sup> After protein extraction, IDH1 was purified by affinity chromatography. Enzyme activity was measured according to the instructions of the IDH Activity Assay Kit (Sigma, Shanghai, China). In brief, 38  $\mu\text{L}$  of IDH assay buffer, 8  $\mu\text{L}$  of developer, 2  $\mu\text{L}$  of IDH substrate, 2  $\mu\text{L}$  of NADP<sup>+</sup>, and 2  $\mu\text{L}$  of NAD<sup>+</sup> were mixed at 37°C. Then, IDH1 enzyme activity was calculated by measuring the OD 450 nm. The mean values of triplicate experiments were reported.

## Statistical Analyses

All data were obtained from three independent experiments. The mean  $\pm$  standard deviation was used for statistical analysis. Unpaired sample *t*-test was applied for

two-group comparisons, while Pearson correlation analysis was used for the correlation of gene expression values. The threshold of statistical significance was set at  $P < 0.05$ . The data were analyzed by using GraphPad7.0 software.

## Results

### Bioinformatics Analysis Revealed Aberrant Expression of *IDH1-AS1* and *IDH1* in PCa Tissues and Cells

GEPIA and CCLE databases were employed to investigate the mRNA levels of *IDH1-AS1* and *IDH1* in PCa tissues and cells. A total of 492 tumor cases and 152 normal controls were examined. We found that the expression of both *IDH1-AS1* and *IDH1* was markedly upregulated in PCa tissues compared to normal tissues (Figure 1A and B). Then, a correlation analysis was performed by using the GEPIA plug-in, which showed the absence of correlation between *IDH1-AS1* and *IDH1* expression (Figure 1C). However, data visualization from GEPIA database showed that *IDH1-AS1* expression in prostate cancer was outstanding among various cancers (Figure 1D). To confirm the aberrant expression of *IDH1-AS1* in cancer cells, we used the CCLE database to analyze the level of *IDH1* in multiple tumor cell lines. Human prostate cancer cell lines exhibited the highest level of *IDH1-AS1* expression (Figure 1E). The expression of *IDH1-AS1* was consistently high in different PCa cell lines (Figure 1F). In conclusion, the combined analysis of GEPIA and CCLE databases revealed that *IDH1-AS1* was highly expressed in PCa.

### *IDH1-AS1* and *IDH1* are Complementary Strand Genes Highly Expressed in Clinical PCa Samples

According to the University of California, Santa Cruz (UCSC, <http://genome.ucsc.edu>) website, *IDH1-AS1* and its sense mRNA, *IDH1*, were located head-to-head with a short gap on chromosome 2 (Figure 2A). PCa samples and cells were analyzed by RT-qPCR. *IDH1-AS1* was expressed at a significantly higher level in PCa tissues compared to adjacent normal prostate epithelial tissues (Figure 2B). Consistently, higher levels of *IDH1-AS1* were detected in PCa cells than in normal prostatic epithelial cells (Figure 2C). We further examined *IDH1* mRNA level in clinical samples, and found it upregulated in tumors compared to normal tissues (Figure 2D). Next, we performed a correlation analysis in PCa samples,

which clearly showed the absence of unequivocal correlation between *IDH1-AS1* and *IDH1* expression (Pearson's correlation, Figure 2E). On the other hand, previous studies suggested that both *IDH1-AS1* and *IDH1* play pivotal roles in tumorigenesis.<sup>18</sup> Therefore, the functional relationship between *IDH1-AS1* and *IDH1* in PCa might not be based on a mechanism distinct from *AS1-IDH1*-mediated regulation of *IDH1* transcription.

### *IDH1-AS1* Promotes the Proliferation and Migration of PCa Cells

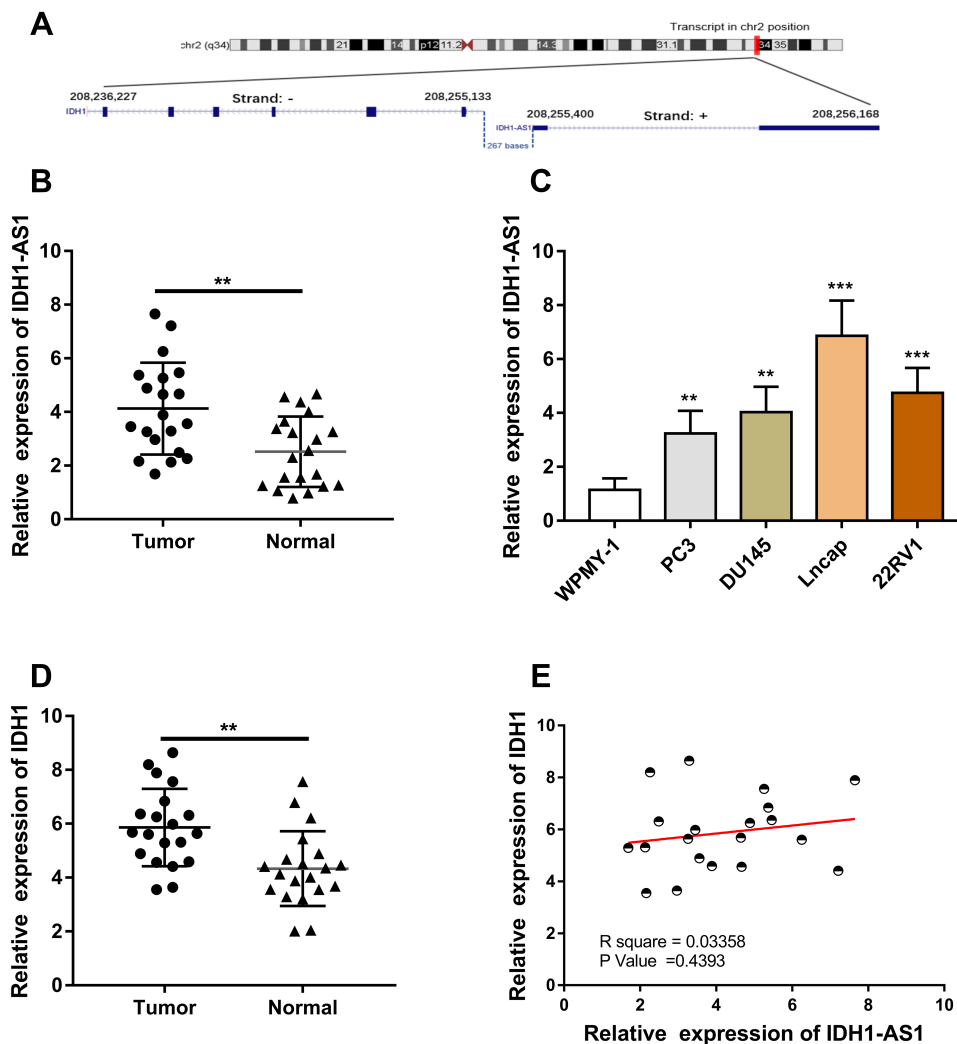
In order to clarify the exact role of *IDH1-AS1* in PCa progression, we designed loss-of-function experiments, based on the use of a specific small interfering RNA (siRNA) in two selected prostate cancer cell lines, PC3 and LNCaP. RT-qPCR was used to verify the efficiency of *IDH1-AS1* silencing (Figure 3A and B). *IDH1-AS1* knockdown inhibited the proliferation of PCa cells, as determined by CCK-8 assays (Figure 3C and D). Consistently, EdU assays showed a decline in the proliferation of both PC3 and LNCaP cells under the same conditions (Figure 3E). Finally, transwell experiments revealed that *IDH1-AS1* knockdown reduced the migration ability of PCa cells (Figure 3F). Collectively, these data indicated that *IDH1-AS1* played an important role in PCa progression and tumor cell migration.

### *IDH1-AS1* is Involved in the Regulation of *IDH1* Enzyme Activity in PCa Cells

To further explore the involvement of *IDH1-AS1* in transcriptional or post-transcriptional *IDH1* regulation, RT-qPCR, Western blot, and *IDH1* enzyme activity assays were performed in PC3 and LNCaP cells knocked down for *IDH1-AS1*. *IDH1-AS1* knockdown did not affect the level of *IDH1* mRNA (Figure 4A and B) or *IDH1* protein (Figure 4C), as determined by RT-qPCR and Western blot, respectively. Then, the intracellular distribution of *IDH1* was examined after subcellular fractionation. Both *IDH1* (Figure 4D) and *IDH1-AS1* (Figure 4E) were predominantly localized in the cytoplasm. So that we can purify *IDH1* enzyme from its abundant family enzyme proteins. *IDH1* is known to play a key role in tumor progression, by controlling the oxidative decarboxylation of isocitrate to 2-oxopentanoic acid and participating in important aspects of mitochondrial metabolism.<sup>20</sup> The impact of *IDH1-AS1* knockdown on the activity of cytoplasmic *IDH1* was determined. *IDH1* activity was reduced in both PC3 and





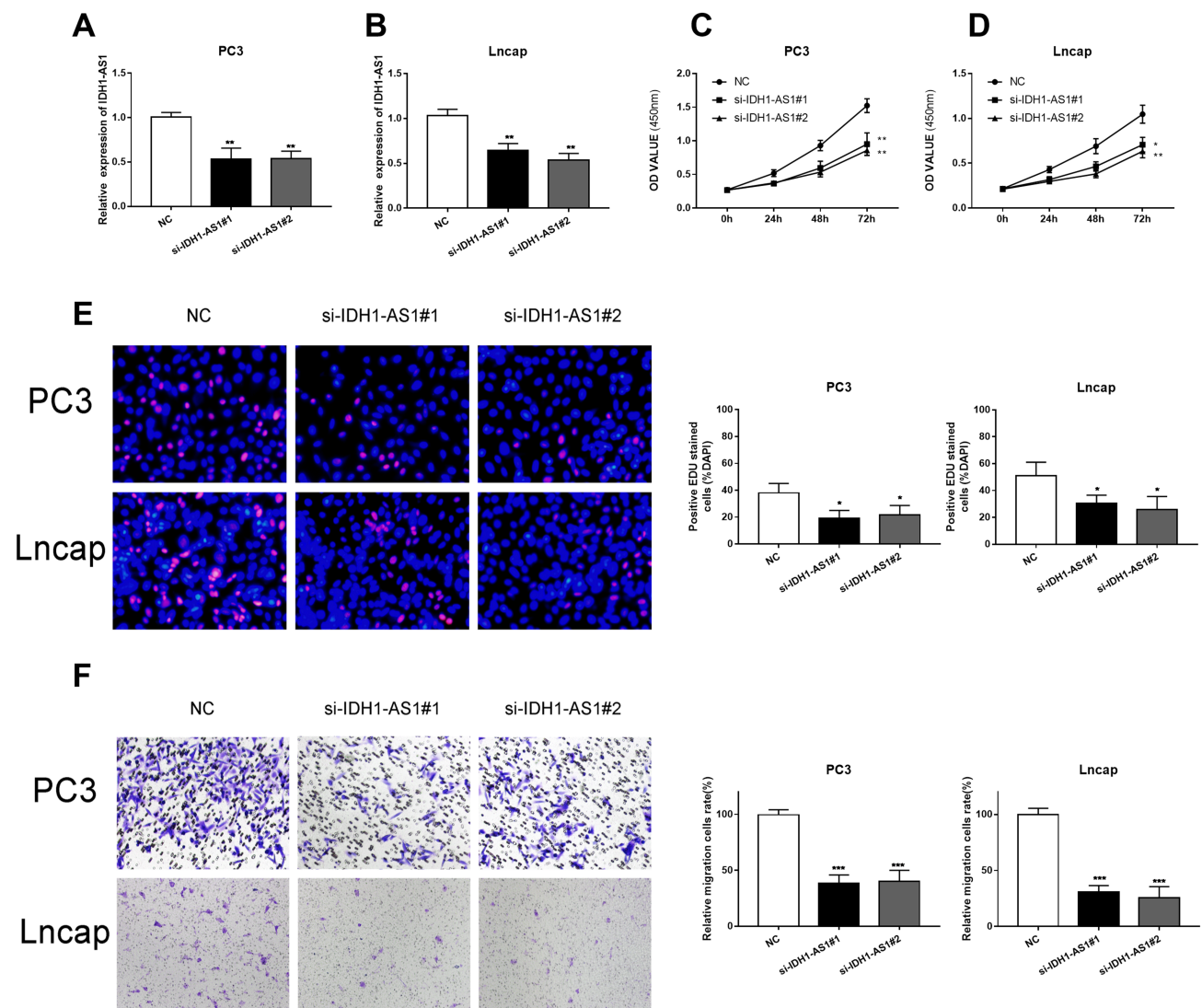


**Figure 2** Chromosomal location and expression characteristics of *IDHI-ASI* and *IDHI* genes in PCa samples. **(A)** *IDHI-ASI* and *IDHI* are located head-to-head on complementary strands in the chr2(q34) region. **(B, C)** qRT-PCR analysis revealed that *IDHI-ASI* was upregulated in PCa tissues and cell lines compared to normal tissues and non-tumor cell lines. **(D)** qRT-PCR analysis revealed that *IDHI* was upregulated in PCa tissues compared to adjacent normal tissues. **(E)** Pearson analysis showed no significant correlation between *IDHI-ASI* and *IDHI* expression in PCa samples. \*\*p<0.01, \*\*\*p<0.001.

## Discussion

Prostate cancer is a common urologic tumor, but the mechanism of tumorigenesis is still unclear.<sup>19</sup> A high proportion of patients with prostate cancer suffer from metastasis and tumor recurrence due to ineffective treatment strategies.<sup>20</sup> Therefore, improved diagnosis and treatment of PCa are urgently needed to control this growing clinical and social issue. A large number of lncRNAs have been found dysregulated in tumors, and these changes are correlated with tumorigenesis and tumor progression.<sup>21,22</sup> Recent studies revealed that the level of prostate cancer-associated lncRNAs reflects the stage of tumor development. These lncRNAs appear to have crucial functions in various signaling pathways,

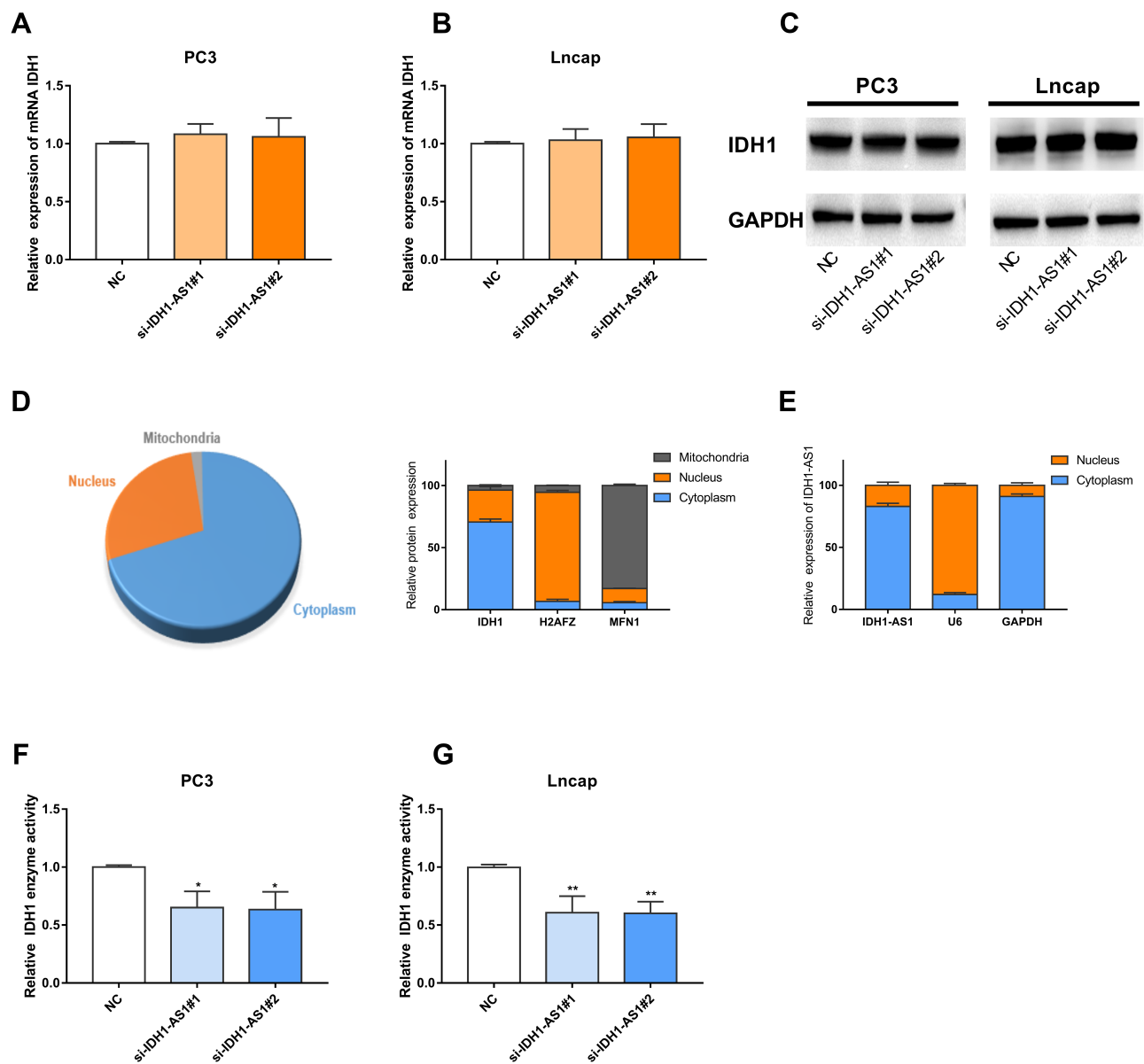
functioning as transcriptional or post-transcriptional regulators, and acting as oncogenes or tumor suppressors.<sup>23</sup> In previous studies, it was found that the lncRNA, *IDHI-ASI*, is an oncogene involved in PCa.<sup>15</sup> A critical finding of the latter study was that *IDHI-ASI* is involved in autophagy. In particular, *IDHI-ASI* participates in a novel molecular pathway, acting as a competing endogenous RNA (ceRNA) that regulates *ATG5* mRNA in PCa.<sup>15</sup> Nevertheless, to date, the possible role of *IDHI-ASI* as a natural antisense RNA and its functional relationship with the corresponding sense RNA has been largely neglected. On the other hand, evidence for a role of the *IDHI-ASI-IDHI* axis in PCa growth was previously reported.<sup>24</sup>



**Figure 3** *IDHI-AS1* silencing suppressed PCa cells proliferation and migration. (**A, B**) Relative expression of *IDHI-AS1* in PC3 and LNCaP cells transfected with si-NC and si-*IDHI-AS1*, as determined by qRT-PCR. (**C–E**) *IDHI-AS1* knockdown inhibited cell proliferation, as determined by both CCK-8 (**C, D**) and EdU assays (**E**). (**F**) *IDHI-AS1* knockdown inhibited cell migration, as determined by transwell assay. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

It is well known that, in addition to regulating the stability of specific genes,<sup>25, 26</sup> similarly to most other lncRNAs, natural antisense RNAs regulate the transcription and function of their sense genes involved in tumor progression.<sup>27–29</sup> *IDHI-AS1* is located on chromosome 2, almost head-to-head, with a short gap, against the *IDHI* gene, which encodes an enzyme catalyzing the oxidative decarboxylation of isocitric acid, resulting in the production of alpha-ketoglutarate.<sup>30</sup> *IDHI* proteins are key enzymes regulating citric acid metabolism, and their expression and activity are closely related to PCa progression.<sup>31</sup> In PCa, reduced *IDHI* activity leads to abnormal isocitrate oxidation and production of oxalosuccinic acid, which induces a series of epigenetic changes.<sup>32</sup>

These reports indicate that *IDHI* plays an important role in the development of PCa. According to some studies, *IDHI* is a potential target of therapies aimed at interfering with energy metabolism in cancer.<sup>33</sup> Notably, a new way of *IDHI-AS1*-mediated regulation of *IDHI* enzyme activity, independent of *IDHI* transcription, has been previously demonstrated in HeLa and HCT116 cells.<sup>25</sup> However, to date, no evidence for this mechanism has been reported in PCa. We hypothesized that the *IDHI-AS1* gene could regulate the expression or activity of the enzyme encoded by its sense gene, *IDHI*, thus contributing to continuous prostate tumor progression. To verify this hypothesis, the effect of *IDHI-AS1* knockdown on *IDHI* gene transcription, protein translation, and *IDHI* enzyme activity was



**Figure 4** *IDH1-AS1* altered IDH1 enzyme activity without affecting IDH1 mRNA or protein level. (A–C) IDH1 mRNA and protein levels were comparable in PC3 and LNCaP cells transfected with si-NC and si-IDH1-AS1. (D) IDH1 protein was detected predominantly in the cytoplasm. (E) *IDH1-AS1* was also mainly detected in the cytoplasm, where it exerted post-translational regulation. (F, G) *IDH1-AS1* knockdown inhibited IDH1 enzyme activity in PC3 and LNCaP cells. \* $p < 0.05$ , \*\* $p < 0.01$ .

investigated. Small fluctuations in IDH1 enzyme activity were observed within 1–2 days of transfection. In line with a previous study, our results suggested that *IDH1-AS1* altered IDH1 enzyme activity without affecting IDH1 mRNA or protein level. However, the details of this regulatory mechanism are still unknown. Notably, IDH1 functions as a homodimer.<sup>34</sup> Therefore, it is reasonable to hypothesize that *IDH1-AS1* may alter the stability of IDH1 heterodimers. This hypothesis needs to be verified by further experiments.

## Conclusions

The present study confirmed that *IDH1-AS1* was upregulated in PCa and functioned as an oncogene. In addition, we demonstrated a novel *IDH1-AS1*-mediated regulatory mechanism involved in PCa progression, based on post-translational regulation. We found that both *IDH1-AS1* and *IDH1* were highly expressed in prostate cancer tissues, and implicated in the proliferation and invasion of PCa cells. Our experiments discovered a new underlying mechanism of IDH1-AS1, and it may become a new target for prostate cancer therapy.



## Ethical Approval

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanjing Medical University.

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## Disclosure

The authors report no conflicts of interest in this work.

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