

Downregulation of lncRNA SDPR-AS is associated with poor prognosis in renal cell carcinoma

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Abstract: Renal cell carcinoma (RCC) is a common type of kidney cancer. Normally, surgical treatment can prolong life, but only for patients with early stage tumors. However, it is difficult for early detection strategies to distinguish between benign and malignant kidney tumors. Therefore, potential biomarkers for early diagnosis and prognosis of RCC are needed. Intriguingly, mounting evidence has demonstrated that many long noncoding RNAs (lncRNAs) are strongly linked to cancers. Indeed, promising RCC-associated lncRNA biomarkers have also been identified. However, the functional and prognostic roles of the antisense (AS) serum deprivation response (*SDPR*) lncRNA (SDPR-AS) in RCC remain largely unknown. The aims of this study were to investigate the expression and prognostic relevance of SDPR-AS in RCC. We uncovered the downregulated expressions of both lncRNA SDPR-AS and its protein-coding gene, *SDPR*, in RCC tissues compared to the matched normal tissues. Furthermore, SDPR-AS and *SDPR* expressions were positively correlated. Overexpression and knockdown experiments suggested that SDPR-AS and *SDPR* were coregulated in RCC cell lines. In addition, overexpression of SDPR-AS suppressed cell migration and invasion, but not cell growth. Furthermore, expression of SDPR-AS was associated with tumor differentiation and lymphatic metastasis. Kaplan–Meier survival and log-rank tests demonstrated the association of elevated expression of SDPR-AS with increased overall survival. In conclusion, our results suggest that the SDPR-AS may serve as a prognostic biomarker and therapeutic target of RCC.

Keywords: long noncoding RNAs, metastasis, prognosis, renal cell carcinoma, suppressor

Introduction

Renal cell carcinoma (RCC) accounts for approximately 2%–4% of all human malignancies and is one of the most common cancers in urology.^{1,2} Because kidney diseases are mostly asymptomatic during the early stages, many RCC patients are diagnosed with advanced stage metastatic diseases that are often resistant to chemotherapy, and therefore this is associated with high mortality.³ Despite the great advances made in the diagnosis and treatment of RCC, therapeutic options are limited and prognosis remains unfavorable.⁴ Therefore, there is a need to identify effective biomarkers for predicting the progression and prognosis of RCC and to advance the development of new targeted therapies.

During the past decades, numerous studies have revealed that a large portion of the human genome is universally transcribed into noncoding RNAs (ncRNAs).⁵ Long ncRNAs (lncRNAs) are RNA molecules that are larger than 200 nucleotides in length and with no protein coding capabilities.^{6,7} Recently, many studies have shown that lncRNAs are involved in carcinogenesis, including invasion and metastasis of kidney,

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breast, and colorectal cancers.^{8–10} Particularly in RCC, it has been reported that high expression of lncRNA ATB promotes cell migration and invasion, and correlates with metastases,¹¹ while low expression of lncRNA NBAT-1 increases cell proliferation, migration, and invasion, and is also associated with poor prognosis.¹² In addition, many other lncRNAs, including TUG1,¹³ BX357664,¹⁴ and MEG3,¹⁵ have been demonstrated to participate in the development and progression of RCC. Despite the identification of numerous lncRNAs in RCC, the majority remain unexplored, and this is therefore the reason for conducting this study.

Through in vitro experiments, Burgener et al¹⁶ in 1990 discovered serum deprivation response (*SDPR*), also named cavin-2, located on chromosome 2q32-q33 as a substrate for protein kinase C isoforms. *SDPR* has been confirmed to be involved in inducing membrane curvature and caveolae formation, and it is strongly linked to gut electrophysiological pacing functions, cell proliferation, and migration.^{17–19} Importantly, previous studies have indicated that *SDPR* is down-regulated in kidney, prostate, and breast cancers.^{20,21} *SDPR* has also been reported to be a possible biomarker for early detection and discrimination of malignant kidney tumors.²² Through bioinformatic analysis, we uncovered an lncRNA, termed AC098617.1, which is located at chromosome 2q32.3, ranging from 192,711,265 to 192,901,485, with the full length up to about 190,221 bp (data from UCSC website). AC098617.1 (Ensembl Gene ID: ENSG00000233766) with 13 transcripts is also known as LOC105373813 Gene or Uncharacterized LOC105373813. Of particular note is that the lncRNA is the antisense (AS) transcript of *SDPR* (*SDPR-AS*) and is located on the upstream of the gene. The expression and functions of lncRNAs are often associated with their adjacent protein coding genes.²³ It is therefore tempting to speculate that the expression and functions of *SDPR-AS* may also be associated with the progression and prognosis of RCC. In this study, we first investigated the expression profiles of *SDPR-AS* and *SDPR* in RCC. Subsequently, the functional roles of *SDPR-AS* in RCC cells were evaluated. Additionally, the correlations between *SDPR-AS* expression and clinical variables, as well as prognosis, were examined.

Materials and methods

Statement of ethics

The tissue specimens and clinical materials used in this study were collected after each participant gave written informed consent, which was in accordance with our institutional ethical guidelines. The ethical committee of the Chinese

People's Liberation Army (PLA) General Hospital approved the utilization of tumor tissues for this study.

Patients and samples

In total, 56 RCC patients who underwent initial surgery at the Chinese PLA General Hospital between 2005 and 2007 were enrolled into this research. Tumor and adjacent normal tissues were immediately snap-frozen in liquid nitrogen after resection, then maintained at -80°C until use.

Cell culture

The human RCC cell lines, OS-RC-2, 786-O, 769-P, Caki-1, Caki-2, and ACHN, as well as normal renal cell line HKC were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). All cells were cultured in Dulbecco's Modified Eagle's Medium (Hyclone, UT, USA), containing 10% heat-inactivated fetal bovine serum, penicillin (100 U/mL), and streptomycin (100 $\mu\text{g}/\text{mL}$) in a 5% CO_2 and humidified atmosphere at 37°C .

SDPR-AS overexpression experiments

The universally available pcDNA3.1 vector was used for cDNA-*SDPR-AS* plasmid construction. Following the manufacturer's instructions, the *SDPR-AS* low-expressing OS-RC-2 cells were transfected with pcDNA-*SDPR-AS* using Lipofectamine 2000 (Invitrogen). The transfected cells were harvested for RNA isolation and functional assays.

SDPR-AS knockdown experiments

Small interfering RNAs (siRNAs) for the target *SDPR-AS* (*SDPR-AS-si*) and negative-control siRNAs (NC-si) were obtained from GenePharma (Shanghai, People's Republic of China), and the sequences are listed in Table 1. The *SDPR-AS* high-expressing 769-P cell line was selected for transfection with *SDPR-AS-si*. Prior to transfection, 12-well plates were seeded with approximately 50% of the cells and cultured for 24 h. Then, siRNA transfections were carried out with X-treme GENE transfection reagents (Roche) according to the manufacturer's instructions. RNA was isolated after 48 h of transfection and used to perform functional assays.

RNA isolation and reverse transcription

Total RNA was isolated from cells and tissues using Trizol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. NanoDrop ND2000 (Thermo Scientific Inc., Santa Clara, CA, USA) was used to determine the purity and quantify the concentration of RNA.

Table 1 List of primers and their sequences used in this study

Gene	Sequence (5'-3')
Primers for GAPDH	
GAPDH	
Forward	AATGGACAACCTGGTCGTGGAC
Reverse	CCCTCCAGGGGATCTGTTTG
Primers for SDPR	
SDPR	
Forward	CTCCGGGTGGGTTTTTACGAC
Reverse	CTGCGTTTTGGTGACTIONGATG
Primers for SDPR-AS	
SDPR-AS	
Forward	GTTGCCCTATCCTGCTTTTAC
Reverse	AGACTGGGGATTAGCCTGGTGT
SDPR-AS-si1	
SDPR-AS-si1	
Forward	CACAUCAACCGUCAUACUAGUUGT
Reverse	ACAACUAGUAUGACAGGUUGAUGUGGC
SDPR-AS-si2	
SDPR-AS-si2	
Forward	GAGCUUGGUGAGGUCAUUCUGGATG
Reverse	CAUCCAGAAUGACCUCACCAAGCUCUC

Abbreviations: GAPDH, glyceraldehyde-3-phosphate dehydrogenase; SDPR, serum deprivation response; SDPR-AS, antisense (AS) transcript of SDPR; SDPR-AS-si, small interfering RNA (siRNA) for target SDPR-AS.

A First Strand cDNA Synthesis Kit (TakaRa, Dalian, People's Republic of China) was used to perform reverse transcription.

Real-time quantitative polymerase chain reaction

Primers used for real-time quantitative polymerase chain reaction (RT-qPCR) were obtained from GenePharma (Shanghai, People's Republic of China), and the sequences are listed in Table 1. According to the manufacturer's instructions, RT-qPCR was performed using the SYBR Prime-Script RT-PCR kit (Takara) in an Applied Biosystems 7500 fluorescent quantitative PCR system (Applied Biosystems, Foster City, CA, USA). The reaction started at 95°C for 5 min, followed by 40 cycles of 95°C for 30 s, 59°C for 30 s, and 72°C for 30 s. GAPDH was used as the internal reference to normalize qPCR results. Relative gene expression levels were measured using cycle threshold (CT) in the $\Delta\Delta$ CT calculation.

Cell proliferation assay

The CCK8 assay was used to examine the proliferation of RCC cells. After 48 h of transfection, cells were seeded into 96-well plates together with the CCK8 reagent and incubated for 1 h at 37°C. The Tecan infinite M200 multimode microplate reader (Tecan, Mechelen, Belgium) was then used

to detect cell density at 450 nm absorption wavelength. All experiments were performed in triplicate.

Scratch wound-healing assay

The scratch wound-healing assay was used to evaluate the migratory properties of RCC cells. Cells were seeded into 12-well plates to achieve a confluent monolayer after 48 h of transfection. Then, uniform wounds were scraped with sterile 200 μ L pipette tips. To remove floating cells, each well was washed thrice with PBS. The initial distance (0 h) and the distances traveled by cells after 24, 48, and 72 h of scratching were detected microscopically.

Cell invasion assay

Transwell assays were conducted with 8 mm pore size Matrigel Invasion Chambers (Millipore Corporation, Billerica, MA, USA) to evaluate the invasive properties of RCC cells. After 48 h of transfection, single-cell suspensions were seeded into the upper chamber, with the lower chamber filled with 600 μ L Dulbecco's Modified Eagle's Medium containing 10% fetal bovine serum. After 24–48 h of incubation, the noninvading cells were wiped off from the upper surface of the membranes, whereas cells that had invaded were stained with 0.5% crystal violet solution after cell fixation in 95% methyl alcohol. The images of migrated cells per well were captured and counted in random fields using a microscope. Each experiment was conducted in triplicate.

Statistical analyses

Statistical analyses were performed with SPSS version 18.0 (SPSS, Chicago, IL, USA). All experiments mentioned above were repeated three times, and data were presented as mean \pm standard deviation. Two-tailed *t*-test and χ^2 test were used for comparisons between different groups. Kaplan–Meier estimator was used to perform survival analysis. $P < 0.05$ was considered statistically significant.

Results

Downregulation of both SDPR-AS and SDPR expression in RCC tissue samples

The expression levels of SDPR-AS and its protein coding gene *SDPR* were examined by RT-qPCR in panel-paired specimens obtained from the 56 patients with RCC. Compared to the matched normal tissues, the expression levels of SDPR-AS (Figure 1A, *** $P < 0.001$) and *SDPR* (Figure 1B, *** $P < 0.001$) in tumor tissues were significantly downregulated.

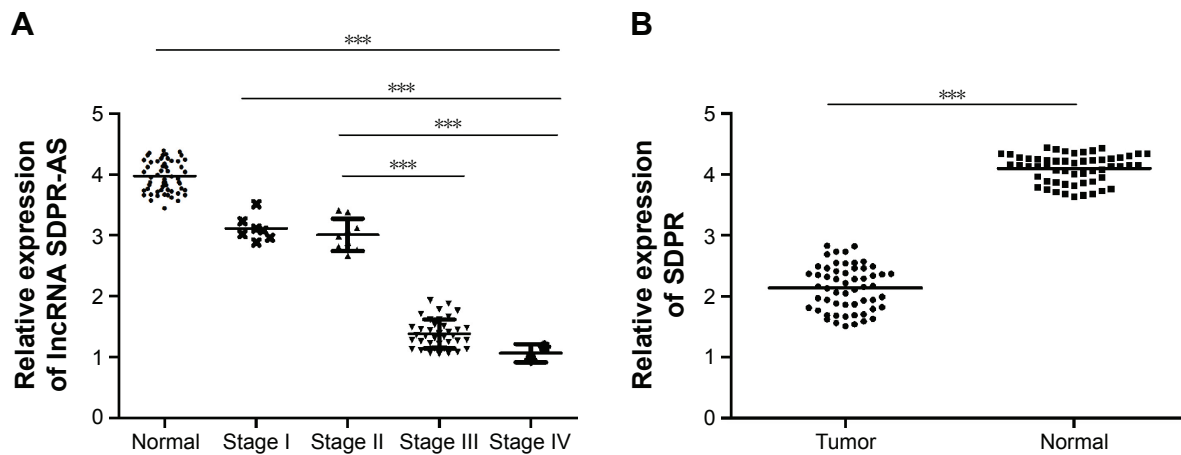


Figure 1 Downregulation of both SDPR-AS and SDPR expression in RCC tissue samples.

Notes: (A) The expression level of SDPR-AS was significantly reduced in tumor tissues, especially in TNM stage III and stage IV ($***P<0.001$). (B) The expression level of SDPR-AS was significantly downregulated in tumor tissues ($***P<0.001$).

Abbreviations: SDPR, serum deprivation response; SDPR-AS, antisense (AS) transcript of SDPR; RCC, renal cell carcinoma; TNM, tumor node metastasis.

Expressions of SDPR-AS and SDPR are positively correlated

To investigate the relationship between SDPR-AS and SDPR, we assessed the correlation of their expression levels by RT-qPCR. The result showed a positive correlation in the levels of their expression (Figure 2, $N=56$, $R=0.66$, $P<0.01$).

SDPR expression was coregulated with SDPR-AS overexpression or knockdown in RCC cell lines

RT-qPCR was performed to determine the expression levels of SDPR-AS and SDPR in six RCC cell lines (OS-RC-2, 786-O, 769-P, Caki-1, Caki-2, and ACHN) and the normal cell line (HKC). The results indicated that the expression levels of SDPR-AS and SDPR were significantly lower in the six RCC cell lines compared to the normal HKC cell line (Figure 3A and B, $*P<0.05$). In addition, as shown in Figure 3A and B, among the six RCC cell lines, the expression

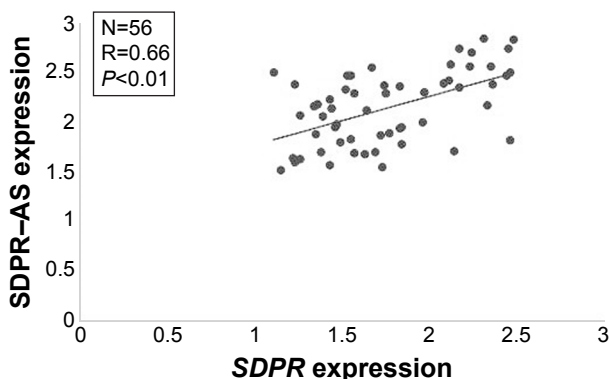


Figure 2 Expressions of SDPR-AS and SDPR are positively correlated.

Abbreviations: SDPR, serum deprivation response; SDPR-AS, antisense (AS) transcript of SDPR.

levels of SDPR-AS and SDPR were highest in the 769-P and lowest in the OS-RC-2 cell lines. After being transfected with pcDNA-SDPR-AS plasmid, SDPR-AS was overexpressed in the OS-RC-2 cell line, while the expression level of SDPR was apparently upregulated (Figure 3C, $*P<0.05$). On the contrary, SDPR and SDPR-AS expressions were significantly decreased in the 769-P cell line transfected with SDPR-AS-si (Figure 3D, $*P<0.05$). The data indicated that SDPR and SDPR-AS were coregulated in the RCC cell lines.

Overexpression of SDPR-AS suppressed the migration and invasion of OS-RC-2 cell line but had no evident association with proliferation

To further investigate the functional role of SDPR-AS, we examined its effects on OS-RC-2 cells transfected with pcDNA-SDPR-AS or the pcDNA control. There was no significant difference in the growth of OS-RC-2 cells transfected with either pcDNA-SDPR-AS or pcDNA control (Figure 4A). However, the wound healing assay showed significant inhibition of cell migration by pcDNA-SDPR-AS compared to pcDNA control (Figure 4B, $*P<0.05$). The matrigel invasion assay also revealed remarkable suppression of cell invasion by pcDNA-SDPR-AS compared to pcDNA control (Figure 4C, $*P<0.05$).

Knockdown of SDPR-AS promoted the migration and invasion of 769-P cell line but showed no evident association with proliferation

To further validate the functional role of SDPR-AS in RCC cells, we performed knockdown experiments by transfecting

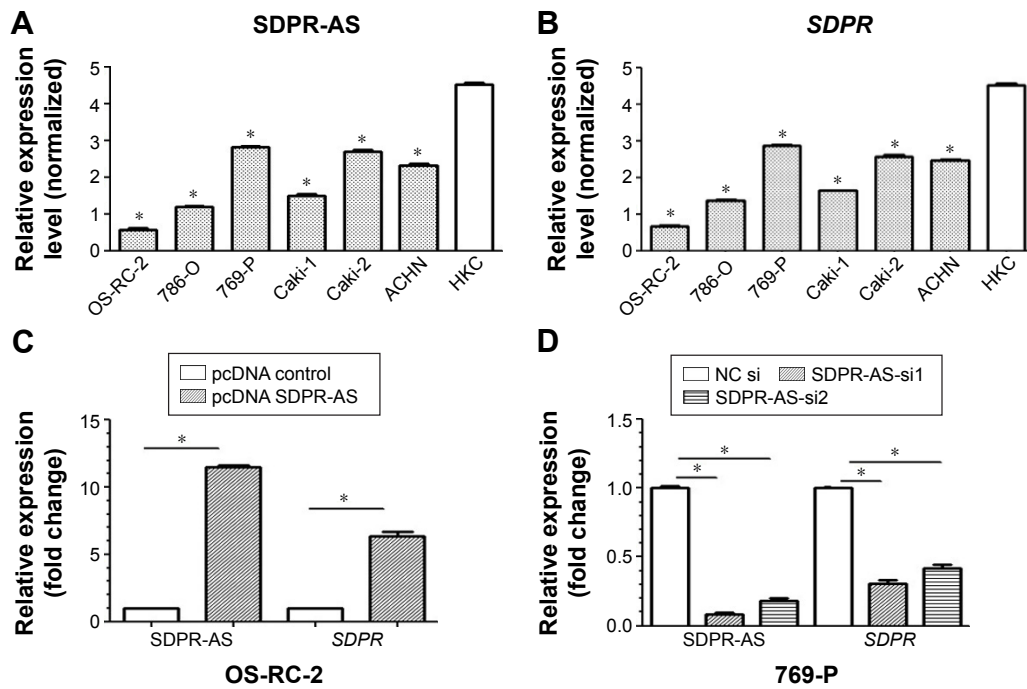


Figure 3 SDPR expression was co-regulated with SDPR-AS overexpression or knockdown in RCC cell lines. **Notes:** (A, B) The expression levels of SDPR-AS and SDPR were highest in the 769-P and lowest in the OS-RC-2 cell lines among the six RCC cell lines (* $P < 0.05$). (C) After being transfected with pcDNA-SDPR-AS plasmid, SDPR-AS was overexpressed in the OS-RC-2 cell line, while the expression level of SDPR was apparently up-regulated (* $P < 0.05$). (D) SDPR-AS expression was significantly decreased in the 769-P cell line transfected with SDPR-AS-si (* $P < 0.05$). **Abbreviations:** SDPR, serum deprivation response; SDPR-AS, antisense (AS) transcript of SDPR; NC, negative control; pc, plasmid complementary; HKC, renal tubular cell.

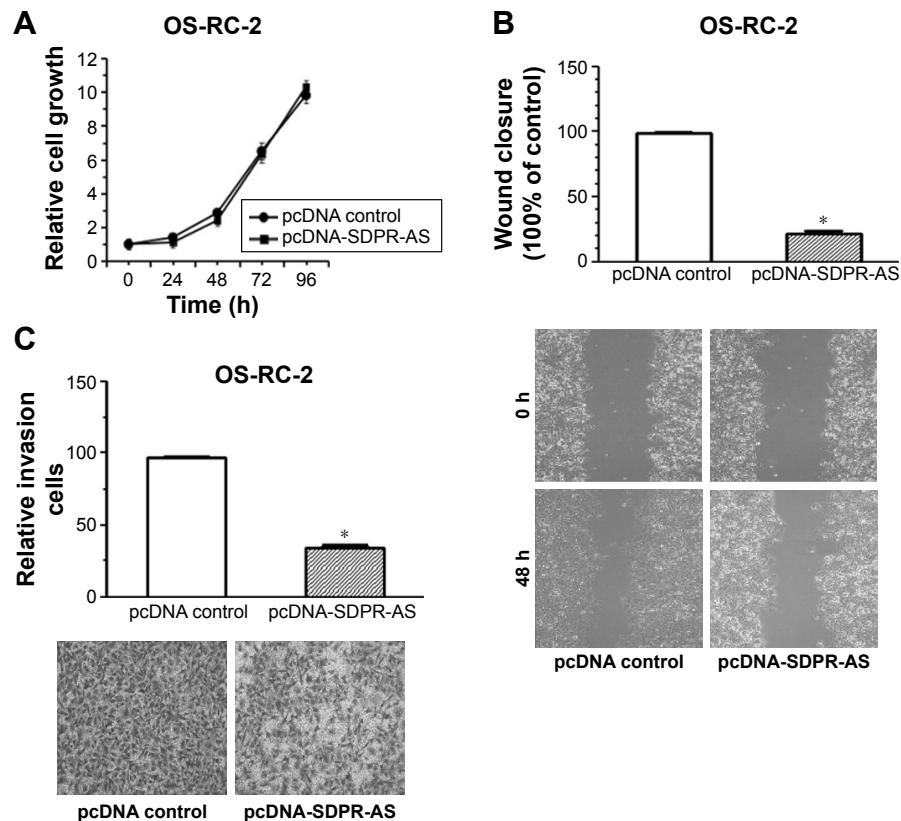


Figure 4 Overexpression of SDPR-AS suppressed the migration and invasion of OS-RC-2 cell line but had no evident association with proliferation. **Notes:** (A) There was no significant difference in the growth of OS-RC-2 cells transfected with either pcDNA-SDPR-AS or pcDNA control. (B) The wound healing assay showed significant inhibition of cell migration by pcDNA-SDPR-AS compared to the pcDNA control (* $P < 0.05$). (C) The matrigel invasion assay also revealed remarkable suppression of cell invasion by pcDNA-SDPR-AS compared to the pcDNA control (* $P < 0.05$). 40 \times magnification. **Abbreviations:** pc, plasmid complementary; SDPR, serum deprivation response; SDPR-AS, antisense (AS) transcript of SDPR.

the 769-P cell line with SDPR-AS-si or NC si and examined their effects on cellular activity. There was no evident difference in proliferation of 769-P cells transfected with either SDPR-AS-si or NC si (Figure 5A). The wound healing and matrigel invasion assays, however, revealed significantly enhanced migration and invasion abilities of 769-P cells treated with SDPR-AS-si compared with those treated with NC si (Figure 5B and C, $*P < 0.05$).

Correlation analyses of SDPR-AS expression and clinical variables of RCC patients

Studies were carried out to assess the correlation between SDPR-AS and clinical characteristics of RCC patients.

The statistical analysis revealed an evident association of SDPR-AS expression levels with differentiation grade, tumor node metastasis (TNM) stage, and lymph node metastasis (Table 2). However, no statistically significant associations were found in other clinicopathological features, including age, tumor size, and tumor location.

The association between SDPR-AS expression and prognosis of RCC patients

Kaplan–Meier survival and log-rank tests were performed to determine the association between SDPR-AS expression and prognosis. The overall expression levels of SDPR-AS were classified based on the mean relative expression ratio

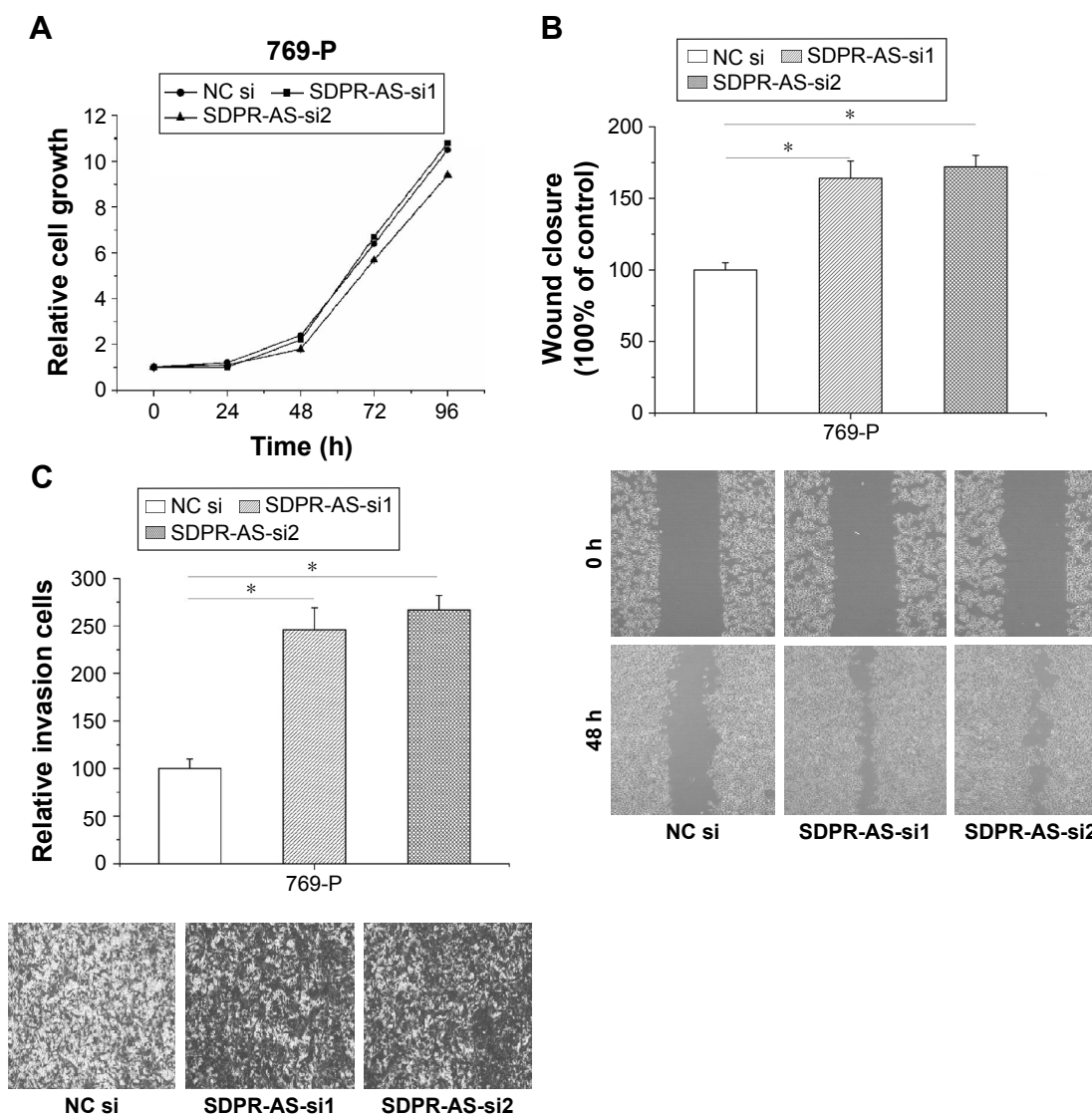


Figure 5 Knockdown of SDPR-AS promoted the migration and invasion of 769-P cell line but showed no evident association with proliferation.

Notes: (A) There was no evident difference in proliferation of 769-P cell line transfected with either SDPR-AS-si or NC si. (B, C) The wound healing and matrigel invasion assays revealed a significantly enhanced migration and invasion abilities of 769-P cells treated with SDPR-AS-si compared with those treated with NC si ($*P < 0.05$). 40 \times magnification.

Abbreviations: NC, negative control; SDPR, serum deprivation response; SDPR-AS, antisense (AS) transcript of SDPR.

Table 2 Correlation between SDPR-AS expression and clinicopathologic features of RCC patients

Clinicopathologic features	Number of cases	SDPR-AS expression		χ^2	P-value
		Low ^a	High ^a		
Total	56	35	21		
Age (years)				0.005	0.945
<50	27	17	10		
≥50	29	18	11		
Tumor size (cm)				2.124	0.145
≤4.0	25	13	12		
>4.0	31	22	9		
Tumor location				2.221	0.329
Upper pole	17	10	7		
Middle	20	15	5		
Lower pole	19	10	9		
Differentiation grade				4.065	0.044
Low	20	9	11		
High	36	26	10		
TNM stage				5.973	0.015
Stage I-II	16	6	10		
Stage III-IV	40	29	11		
Lymph node metastasis				6.310	0.012
Positive	38	28	10		
Negative	18	7	11		

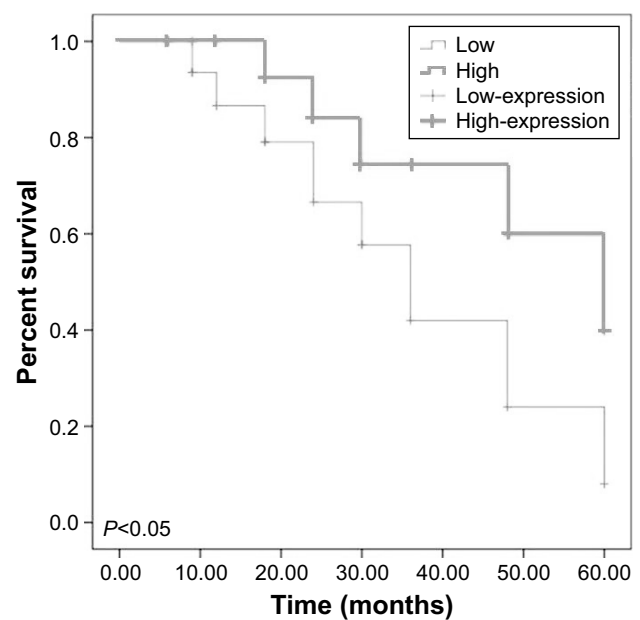
Notes: ^aLow, SDPR-AS expression ratio \leq median ratio, n=56; High, SDPR-AS expression ratio \geq median ratio, n=21.

Abbreviations: RCC, renal cell carcinoma; SDPR, serum deprivation response; SDPR-AS, antisense (AS) transcript of SDPR; TNM, tumor node metastasis.

in RCC tissue specimens as high (SDPR-AS expression ratio \geq median ratio, n=21) and low (SDPR-AS expression ratio \leq median ratio, n=35). The data suggested that high expression of SDPR-AS was significantly associated with increased overall survival, whereas low expression indicated poor overall survival outcomes. Thus, SDPR-AS expression may be associated with prognosis of RCC patients (Figure 6, * $P < 0.05$).

Discussion

Dozens of lncRNAs have recently been discovered through RNA sequencing and are annotated by the GENCODE project.²⁴ Interest has been generated as a result of the fact that numerous lncRNAs are strongly linked with various cancers. For example, Chen et al⁹ reported that long intergenic non-coding RNA ROR (lincRNA-ROR) was involved in breast cancer invasion through participating in the epithelial-mesenchymal transition process. Huang et al²⁵ demonstrated that low expression of DGCR5 was an important negative prognostic factor for hepatocellular carcinoma. In RCC, a number of lncRNAs, including CRNDE,²⁶ TCL6,²⁷ and MALAT-1²⁸ have been reported to be aberrantly expressed. Although alterations of lncRNAs in RCC have already been recognized, the functional roles of many remain to be

**Figure 6** The association between SDPR-AS expression and prognosis of RCC patients.

Abbreviations: RCC, renal cell carcinoma; SDPR, serum deprivation response; SDPR-AS, antisense (AS) transcript of SDPR.

understood. In the present study, we analyzed the functional roles of the lncRNA SDPR-AS and its prognostic relevance in RCC.

Recently, a number of studies have demonstrated that AS lncRNAs can regulate their sense mRNA partners in a discordant or concordant fashion.^{29,30} Numerous AS lncRNAs have been identified to be associated with a variety of malignant tumors.^{31,32} Generally, they modulate their sense partners by epigenetic regulation at the promoter regions or through other mechanisms.^{33,34} lncRNA SDPR-AS is the AS partner of the mRNA of SDPR. It has also been demonstrated that SDPR is an important tumor suppressor in certain cancers, including prostate cancer,^{20,35} breast cancer,^{21,36} and hepatocellular carcinoma.³⁷ In particular, a previous study reported that SDPR was remarkably downregulated in RCC cells,²² which sparked our interest in conducting this study to investigate the functional and prognostic roles of its AS lncRNA in RCC.

In the present study, we first demonstrated the significant downregulation of SDPR-AS in RCC tissues in comparison to their matched nontumorous tissues. By loss-of-function and gain-of-function approaches, we confirmed that SDPR-AS played a critical role in cell migration and invasion, but had no evident effect on cell proliferation. In addition, the results also demonstrated a positive correlation between SDPR and SDPR-AS expression. Based on clinical data analysis, we determined that low expression of SDPR-AS was associated with tumor differentiation grade, TNM stage and

lymph node metastasis. However, no statistically significant associations were found in other clinicopathological features, including age, tumor size, and tumor location. Furthermore, a multivariate analysis suggested that SDPR-AS expression level could serve as an independent prognostic predictor for RCC. Taken together, these results revealed a key role of SDPR-AS in RCC metastasis, possibly through modulation of the levels and functions of its sense partner. To our knowledge, our data may provide the first evidence for clarifying the functional and prognostic roles of SDPR-AS in RCC.

Conclusion

This study revealed the molecular mechanistic insights of SDPR-AS in RCC. In addition, this study provides some evidence that SDPR-AS may act as an independent prognostic predictor of RCC patients.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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