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ORIGINAL RESEARCH

Aberrant Expression of miR-592 Is Associated with Prognosis and Progression of Renal Cell Carcinoma

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Xianbao Lv[1,*]
Jingang Shen[1,*]
Zhen Guo[2,*]
Lingwei Kong[1]
Guangchun Zhou[1]
Hao Ning[3]

[1]Department of Urology, Chengwu People's Hospital, Heze, Shandong, 274200, People's Republic of China; [2]Department of Urology, Central Hospital Affiliated Shandong First Medical University, Jinan, Shandong, 250033, People's Republic of China; [3]Department of Urology, Shandong Provincial Hospital, Jinan, Shandong, 250021, People's Republic of China

*These authors contributed equally to this work

Purpose: MicroRNAs have recently reported playing a vital role in the development of cancers. However, the role of miR-592 in renal cell carcinoma (RCC) has not been explored. In this study, the potential role of miR-592 was investigated in RCC.

Patients and methods: The expression of miR-592 was evaluated in RCC tissues and cell lines using qRT-PCR assays. The Kaplan-Meier analysis and Cox proportional hazards model analysis was used to analyze the prognostic value of miR-592 in RCC. The effects of miR-592 on cell proliferation, migration, and invasion were determined by cell counting kit-8 (CCK-8) and Transwell assays in vitro.

Results: The results showed that miR-592 was significantly increased both in RCC tissues and cell lines. Overexpression of miR-592 was significantly associated with lymph node metastasis, TNM stage, and poor overall survival. And functional studies in two RCC cell lines (786-O and Caki-1) have shown that overexpression of miR-592 promoted cell proliferation, migration, and invasion, while silence of miR-592 inhibited cell proliferation, migration, and invasion. SPRY2 was a direct target of miR-592.

Conclusion: Overall, overexpression of miR-592 may be a prognostic biomarker and therapeutic strategy for patients with RCC, which is correlated with the progression of RCC.

Keywords: miR-592, renal cell carcinoma, prognosis, proliferation, migration, invasion

Introduction

Renal cell carcinoma (RCC), a common human kidney cancer, represents approximately 3% of all adult malignancies, which is the third leading cause of death in urological cancers.[1,2] There are five histological types of RCC, mainly include clear cell RCC and papillary RCC.[3] At present, surgery remains the mainstay of treatment for located RCC.[4] However, approximately one-third of RCC patients have had metastasis at initial diagnosis and were resistant to chemotherapy and radiotherapy.[5,6] Although considerable advances have been made in the therapeutic strategies, these patients at advanced stages usually have an extremely poor prognosis with a median survival of approximately 13 months.[7] Therefore, it is urgently to identify novel therapeutic targets and accurate prognostic biomarkers to improve treatment and prognosis for RCC patients.

MicroRNAs (miRNAs) are a group of small noncoding RNA molecules (approximately 19–22 nucleotides in length), known to negatively regulate their target genes at the post-transcriptional level by binding to the 3′-UTR of target mRNAs.[8] Increasing evidence has been identified miRNAs involved in diverse cellular processes, such as

Correspondence: Hao Ning
Department of Urology Surgery, Shandong Provincial Hospital, No. 324, Jingwu Road, Jinan, Shandong 250021, People's Republic of China
Tel +86 531 68776310
Email haotiecg4792@163.com

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cell proliferation, differentiation, invasion, and apoptosis.[9–11] Recently, numerous studies demonstrated that aberrant miRNAs expression was closely related to the development and progression of cancers and functioned as promising therapeutic targets or biomarkers for cancers.[12–14] miR-592 has been reported aberrantly expressed in a variety of cancers, such as glioma,[15] hepatocellular carcinomas,[16] and colorectal cancer.[17] Although a previous literature search study showed that miR-592 was upregulated in RCC,[18] its role and clinical significance have not yet been clarified in RCC.

In the present study, we explored the expression levels of miR-592 in RCC tissues and cells. The relationship between the expression of miR-592 and clinicopathological characteristics of RCC patients was also investigated. What's more, we explored the clinical significance of miR-592 and its role in RCC and implored it is as a promising biomarker and therapeutic target for RCC.

Materials and Methods

Patients and Tissue Specimens

Ethical approval for this study was obtained from the Research Ethics Committee of Chengwu People's Hospital. All patients signed written informed consent prior to sampling. The paired RCC tissue specimens and adjacent normal tissue specimens were obtained from 114 RCC patients who underwent surgical resection at Chengwu People's Hospital between February 2011 and December 2013. Tissues were immediately snap-frozen in liquid nitrogen until RNA extraction. No patients received preoperative chemotherapy or radiotherapy prior to surgical resection. The corresponding clinical characteristics of RCC patients (shown in Table 1) and 5-year follow-up information were collected and recorded.

Table 1 Clinicopathological Characteristics of RCC Patients and Their Association with miR-592 Expression

Characteristics	Cases n = 114	miR-592 Expression		*P* values
		Low (n = 54)	High (n = 60)	
Gender				0.920
Male	67	32	35	
Female	47	22	25	
Age				0.708
≤ 60	57	28	29	
> 60	57	26	31	
Tumor size (cm)				0.662
≤ 7	63	31	32	
> 7	51	23	28	
Fuhrman grade				0.333
I–II	60	31	29	
III–IV	54	23	31	
Histological type				
Clear cell	93	45	48	0.647
Papillary	21	9	12	
Lymph node metastasis				0.029
Negative	66	37	29	
Positive	48	17	31	
TNM stage				0.020
I–II	63	36	27	
III–IV	51	18	33	

Note: Differences were analyzed using Pearson's chi-square test.

Cell Culture and Transient Transfection

Human renal carcinoma cell lines 786-O, ACHN, Caki-1, 769-P and normal renal epithelial cells (HK-2) were all purchased from the Institute of Cell Research, Chinese Academy of Sciences (Shanghai, China). 786-O, ACHN, Caki-1, and 769-P cells were cultured in RPMI-1640 (HyClone, Logan, UT, USA) supplemented with 10% FBS (HyClone). HK-2 cells were cultured in keratinocyte serum-free medium (K-SFM; Invitrogen, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% FBS (HyClone). All cells were cultured in a humidified incubator with 5% CO_2 at 37°C.

For overexpression and downregulation of miR-592, the miR-592 mimic, mimic negative control (mimic NC), miR-592 inhibitor, and inhibitor NC used in this study were chemically synthesized by Shanghai GenePharma Co., Ltd. (Shanghai, China) and transfected into cells using Lipofectamine 3000 (Thermo Fisher Scientific, Waltham, MA, USA).

RNA Extraction and Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

Total RNA was extracted from RCC tissues and cells using TRIzol reagent (Thermo Fisher Scientific, Waltham, MA, USA) following the manufacturer's protocol. The RNA quality and quantity were verified with a NanoDrop 1000 (Thermo Fisher Scientific). Then, the TaqMan MicroRNA Reverse Transcription Kit (Thermo Fisher Scientific) was used to synthesize cDNA from total RNA following the manufacturer's instructions. Subsequently, qRT-PCR was

performed to measure miR-592 expression using a TaqMan MicroRNA Assay kit (Thermo Fisher Scientific) on an ABI 7500 PCR System. The relative expression levels of miR-592 were calculated using $2^{-\Delta\Delta Ct}$ methods and normalized to those of U6.

Cell Proliferation Assay

The proliferative abilities of RCC cells were measured using a Cell Counting Kit-8 (CCK-8; Beyotime, Shanghai, China). In brief, approximately 3×10^3 transfected cells in culture medium were plated onto 96-well plates and incubated at 37° C with 5% CO_2. At 0, 24, 48, 72 h, 10 μL CCK-8 reagent was added into each well and the absorbance values were read at 450 nm with a microplate reader.

Cell Migration and Invasion Assays

The migration and invasion abilities of RCC cells were measured using a 24-well Transwell plate (8 μm; BD Biosciences, San Jose, CA). Chambers without or with Matrigel (BD Biosciences, San Jose, CA, USA) were used to determine the migration ability and invasion ability of RCC cells, respectively. Serum-free culture medium containing 2×10^4 transfected cells was added into the upper chamber and culture medium supplemented with 10% FBS was added to the lower chamber as a chemoattractant. Following culturing at 37°C for 24 h, cells that migrated to or invaded the bottom chambers were fixed, stained, and counted in five random fields under a microscope.

Bioinformatics Analysis

Bioinformatics prediction was used to analyze the putative targets of miR-592 using publicly available algorithms, the TargetScan (http://www.targetscan.org/).

Luciferase Reporter Assay

For dual reporter luciferase assay, the SPRY2 3′-UTR oligonucleotides containing the wild type (Wt) or mutant (Mut) miR-592 binding sites were constructed by GenePharma Co., Ltd (Shanghai, China). The SPRY2 Wt or Mut 3′-UTR was cloned into the pGL3 luciferase reporter vector (Promega, Madison, WI, USA). Caki-1 cells were seeded in 24-well plates and co-transfected with Wt-SPRY2-3′-UTR or Mut-SPRY2 and miR-592 mimic, mimic NC, miR-592 inhibitor, or inhibitor NC using Lipofectamine 3000 (Thermo Fisher Scientific, Waltham, MA, USA) according to manufacturer's instructions. After transfection for 24 h, transfected cells were collected and luciferase activity was measured using a dual reporter assay system (Promega, Madison, WI, USA) that was normalized to *Renilla* luciferase activity.

Statistical Analyses

All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) or GraphPad 5.0 (GraphPad Software, Inc., La Jolla, CA, USA). Each experiment was performed at least three times. Data were presented as the mean ± SD. Kruskal–Wallis test was used to confirm whether the data are parametric. The statistical differences between two groups were analyzed using a 2-tailed Student's t-test. A one-way ANOVA followed by Tukey's post-hoc test was used for multiple groups comparison. The association between miR-592 expression and clinical characteristics of patients was analyzed using Pearson's chi-square test. The Kaplan-Meier analysis was used to estimate the overall survival of patients with different miR-592 expression. Multivariate Cox regression analysis was adopted to analyze prognostic factors. Differences with $P < 0.05$ were considered to be statistically significant.

Results

Expression of miR-592 in RCC Tissues and Cell Lines

To clarify whether the miR-592 expression is associated with RCC progression, RCC tissues and adjacent normal tissues, as well as RCC cells were analyzed using qRT-PCR. Firstly, miR-592 expression was detected by qRT-PCR in 114 paired fresh tumor tissues and adjacent normal tissues. Compared with adjacent normal tissues, miR-592 expression was significantly higher in tumor tissues ($P < 0.001$, Figure 1A). Then we examined the miR-592 expression in RCC cells. As shown in Figure 1B, miR-592 expression was upregulated in RCC cells compared with that in normal renal epithelial HK-2 cells ($P < 0.001$).

Relationship Between Clinicopathological Characteristics and miR-592 Expression in RCC Patients

We classified the patients into a low miR-592 expression group and a high miR-592 expression group according to the relative mean expression level of miR-592 in RCC tissues. Next, the patients' clinicopathological characteristics of RCC patients were analyzed using the chi-square test (Table 1). The analysis results showed that miR-592 expression was significantly associated with lymph node metastasis ($P = 0.029$) and TNM stage ($P = 0.020$).

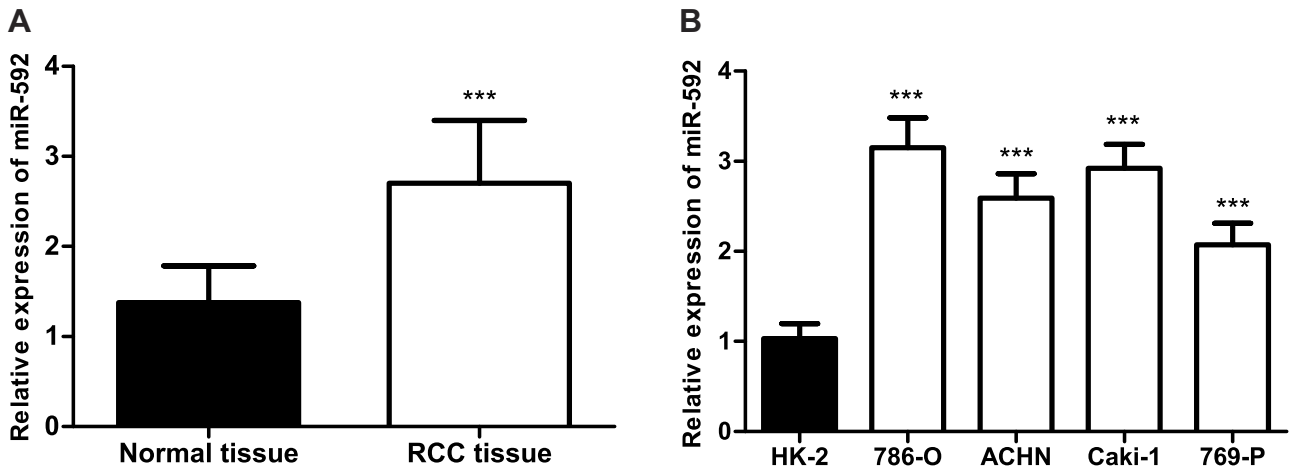

Figure 1 Relative miR-592 expression in RCC tissues and cell lines. (**A**). The qRT-PCR analysis showed the expression of miR-592 in the RCC tissues and the adjacent normal tissues. Differences were analyzed using 2-tailed Student's t-test. (**B**). qRT-PCR analysis of miR-592 in RCC cancer cell lines and normal renal epithelial HK-2 cells. Differences were analyzed using one-way ANOVA followed by Tukey's post-hoc test. ***$P < 0.001$.

However, no significant association was found between miR-592 expression and other characteristics, such as gender, age, tumor size, and differentiation ($P > 0.05$).

Upregulation of miR-592 Is Associated with Poor Prognosis in RCC Patients

In order to assess the prognostic value of miR-592, Kaplan-Meier survival curves and log rank tests were performed. The results showed that the overall survival of patients with high miR-592 expression was significantly worse than those with low miR-592 expression ($P = 0.009$, Figure 2). Further multivariate Cox regression analyses showed that miR-592 expression (HR = 2.265, 95% CI: 1.048–4.899, $P = 0.038$) and TNM stage (HR = 2.134, 95% CI: 1.006–4.527, $P = 0.048$) were associated with overall survival and independent prognostic factors for RCC (Table 2).

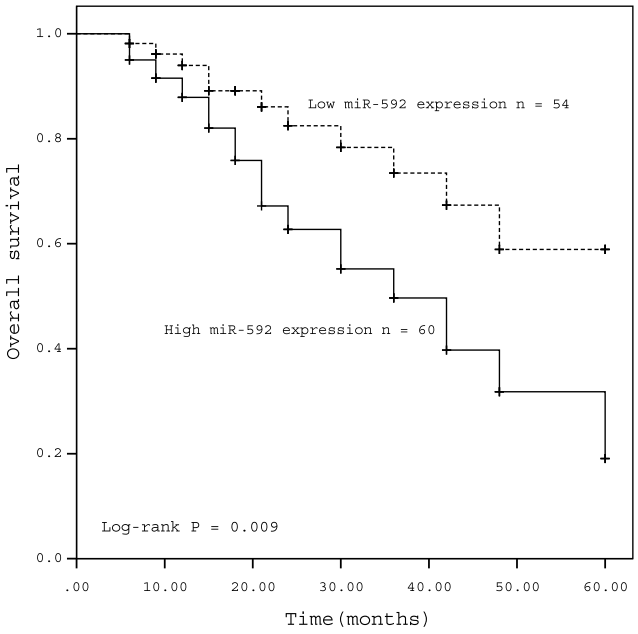

Figure 2 Kaplan-Meier curves for patients with RCC expressing high and low levels of miR-592 (log rank test: $P = 0.009$).

Upregulation of miR-592 Promotes Proliferation, Migration, and Invasion of RCC Cells in vitro

To further evaluate the functional role of miR-592 in RCC, the impact of its overexpression or downregulation on the proliferation, migration, and invasion of RCC cells was investigated. 786-O and Caki-1 cells were selected for functional experiments because of their higher expression levels of miR-592, which were transfected with miR-592 mimics or miR-592 inhibitors. The overexpression or downregulation of miR-592 was confirmed by qRT-PCR

Table 2 Multivariate Cox Analyses of Overall Survival of RCC Patients

Characteristics	Multivariate Cox Analysis		
	HR	95% CI	*P* value
miR-592	2.265	1.048–4.899	0.038
Gender	1.657	0.805–3.412	0.170
Age	0.777	0.411–1.472	0.439
Tumor size	0.666	0.335–1.322	0.245
Fuhrman grade	1.847	0.893–3.820	0.098
Histological type	0.578	0.288–1.160	0.123
Lymph node metastasis	1.764	0.891–3.492	0.103
TNM stage	2.134	1.006–4.527	0.048

Note: Data are analyzed using multivariate Cox regression analysis.

in 786-O and Caki-1 cells following transfection with miR-592 mimics or inhibitors ($P < 0.001$, Figure 3A). A CCK-8 assay was used to investigate the proliferative ability of RCC cells. As shown in Figure 3B, the proliferative abilities of 786-O and Caki-1 were significantly promoted by miR-592 overexpression, while the proliferative abilities were markedly inhibited by the knockdown of miR-592, compared with that in untreated cells ($P < 0.05$). The Transwell assays were performed to determine the effect of miR-592 on cell migration and invasion. The results revealed that upregulation of miR-592 accelerated the migration and invasive capabilities of 786-O and Caki-1 cells, while downregulation of miR-592 resulted in attenuation of migration and invasive capabilities, compared with that of untreated cells ($P < 0.01$, Figure 4).

SPRY2 Is a Direct Target of miR-592 in RCC Cells

TargetScan was used to predict the potential targets of miR-592. The results showed that SPRY2 was a predicted target of miR-592 and there was a binding site of miR-592 in the 3′-UTR of SPRY2 (Figure 5A). Then, the luciferase reporter assay was performed with RCC Caki-1cells, which were transfected with luciferase constructs containing Wt-3′-UTR and Mut-3′-UTR of SPRY2. Overexpression of miR-592 reduced the expression of SPRY2, while the miR-592 inhibitor increased the SPRY2 expression ($P < 0.05$, Figure 5B). Furthermore, dual-luciferase assays showed that the relative luciferase activity was significantly decreased in Caki-1 cells cotransfected with miR-592 mimic and Wt SPRY2 vector,

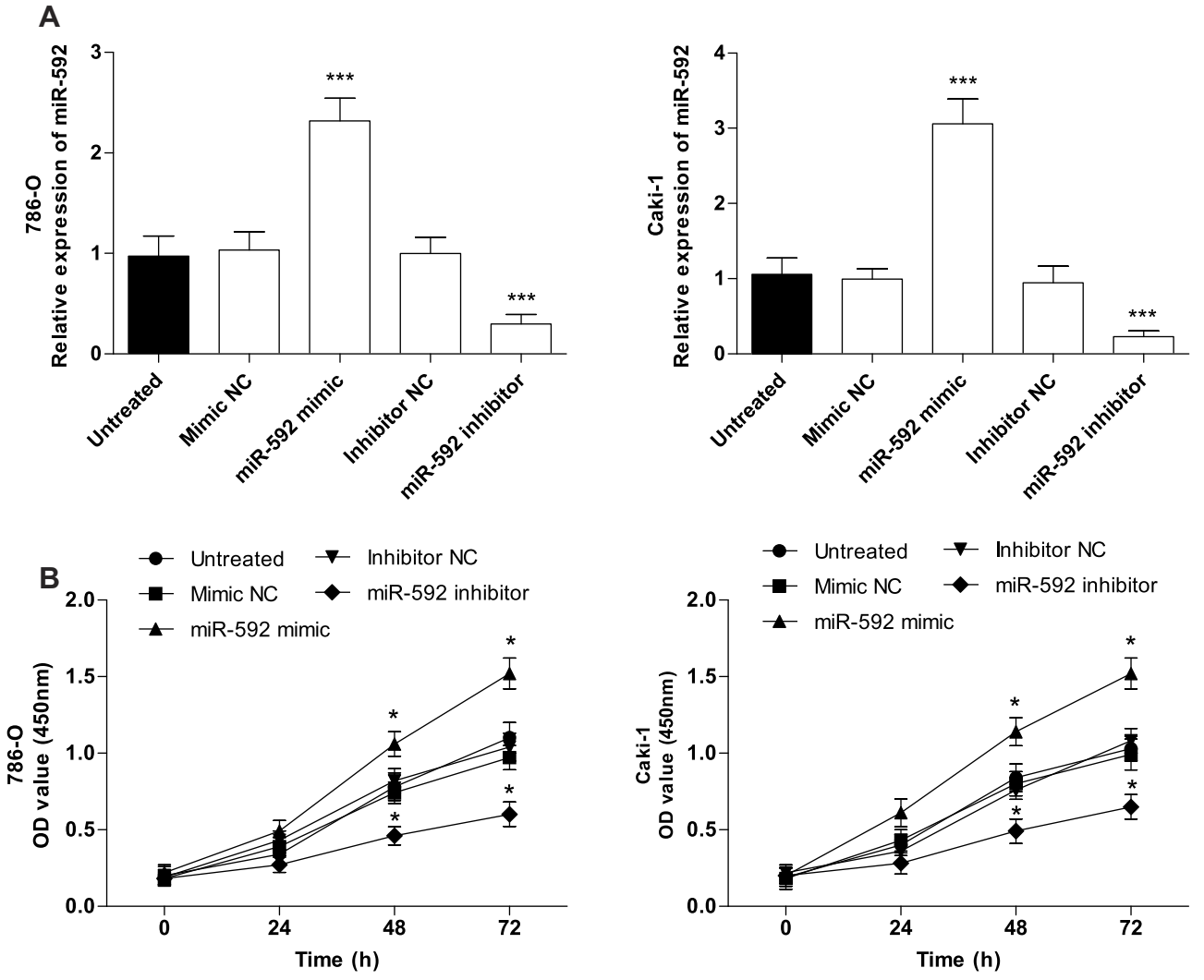

Figure 3 Effects of miR-592 on the proliferation of 786-O and Caki-1 cells. Differences were analyzed using one-way ANOVA followed by Tukey's post-hoc test. (**A**). miR-592 mimics, miR-592 inhibitors or NCs were transfected into 786-O and Caki-1 cells, and transfection efficiency was measured using qRT-PCR. (**B**). Cell proliferation was measured by CCK-8 assays. *$P < 0.05$, ***$P < 0.001$.

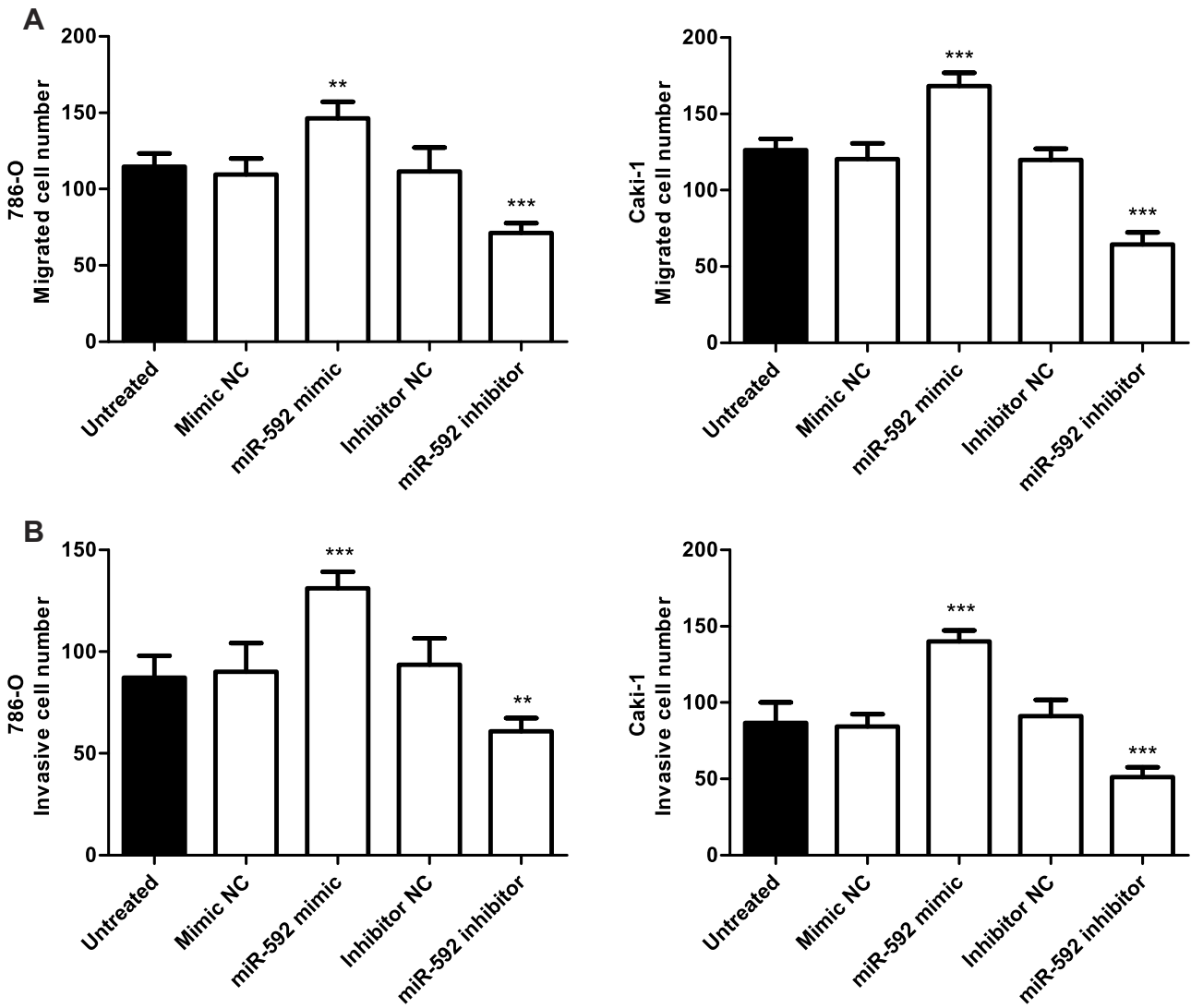

Figure 4 Effects of miR-592 on migration and invasion of 786-O and Caki-1 cells. Differences were analyzed using one-way ANOVA followed by Tukey's post-hoc test. (**A**). Transwell migration assays were used to determine the migration abilities of 786-O and Caki-1 cells following transfection of miR-592 mimics or miR-592 inhibitors. (**B**). Transwell invasion assays were used to measure the invasive abilities of 786-O and Caki-1 cells. $^{**}P < 0.01$, $^{***}P < 0.001$.

while no significant change in luciferase activity was observed in the Mut SPRY2 group ($P < 0.05$, Figure 5C).

Discussion

Increasing evidence has demonstrated that miRNAs are frequently aberrantly expressed in various cancers and are associated with tumor progression and survival of various cancers.[19–21] For instance, the miR-629-3p expression is upregulated in human lung adenocarcinoma tissues and cell lines, and it promotes cell proliferation and predicts poor survival in lung adenocarcinoma.[22] In RCC, a number of miRNAs have identified associated with the prognosis of patients and functioned as prognostic biomarkers,[23] such as miR-30a[24] and miR-660-5p.[25] A recent study demonstrated that the upregulation of miR-142-3p is correlated with poor prognosis of RCC patients and may be a prognostic biomarker.[26] Therefore, investigation of cancer-associated miRNAs that are crucial for the progression of RCC may provide more therapeutic targets and prognosis improvement for RCC patients.

In the present study, miR-592 may exhibit tumor oncogene action in RCC. The key findings of the present study were as follows. The miR-592 expression was significantly upregulated in RCC tissues and cell lines. High miR-592 expression was markedly associated with lymph node metastasis and TNM stages. In addition, increased miR-592 expression was associated with the poor prognosis of RCC patients. Moreover, overexpression of miR-592

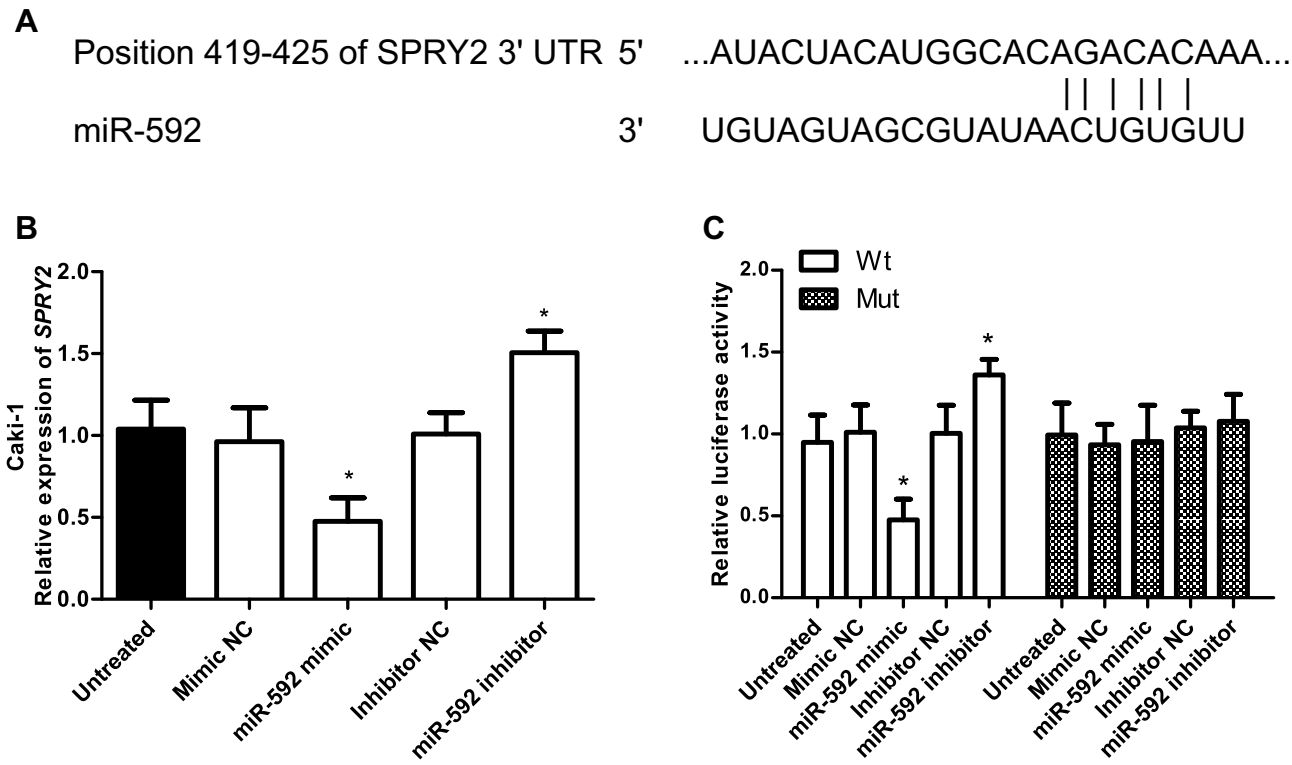

Figure 5 Identification of SPRY2 as a direct target of miR-592 in RCC cells. (**A**) Sequence alignment of miR-592 and the 3′-UTR of SPRY2. (**B**) The qRT-PCR analysis was conducted to detect the SPRY2 mRNA in Caki-1 cells transfected with miR-592 mimic, mimic NC, miR-592 inhibitor, or inhibitor NC. Differences were analyzed using one-way ANOVA followed by Tukey's post-hoc test. (**C**) Luciferase reporter assay in Caki-1 cells that were co-transfected with miR-592 mimics, mimic NC, miR-592 inhibitor, or inhibitor NC and Wt-type SPRY2 3′-UTR vector of Mut-type vector. Differences were analyzed using one-way ANOVA followed by Tukey's post-hoc test. *$P < 0.05$.

promoted cell proliferation, migration, and invasion of RCC cells. Overall, these results suggested that miR-592 may be a potential prognostic biomarker or therapeutic target for patients with RCC.

Previous studies have reported that miR-592 was aberrantly expressed and associated with the progression of several cancer types.[15–17] For instance, miR-592 functions as a suppressive role in breast cancer and inhibits cell proliferation, clone formation, migration, and invasion in breast cancer.[27] The miR-592 expression is downregulated in non-small cell lung cancer (NSCLC) and plays tumor suppressor functions on NSCLC proliferation, colony formation, migration, and invasion by targeting SOX9.[28] On the contrary, in some other studies, miR-592 plays an oncogenic role in tumorigenesis of several cancers, such as gastric cancer,[29] colorectal cancer,[30] and prostate cancer.[31] Considering the expression pattern of miR-592 in different cancers, we deemed that miR-592 may act as either an oncogene or a tumor suppressor gene depending on cancer type. In the present study, miR-592 was significantly upregulated in RCC tissues and cell lines, compared with that in adjacent normal tissues and normal HK-2 cells, respectively. Our findings are similar to previous studies in which miR-592 contributed to the oncogenesis of gastric cancer, colorectal cancer, and prostate cancer.[29–31] Moreover, high expression of miR-592 was found significantly associated with lymph node metastasis and TNM stages. These results suggested miR-592 may be associated with the development of RCC. Kaplan-Meier curve analysis and multivariate Cox analysis results showed miR-592 expression was a prognostic factor for overall survival of RCC patients. The above outcomes suggested that miR-592 may serve as a potential independent prognostic marker for RCC, which functioned similarly to several miRNAs in RCC, such as miR-154-5p,[32] miR-23a-3p,[33] and miR-663a.[34]

Next, we investigated the role of miR-592 on cell proliferation, migration, and invasion using 786-O and Caki-1 cells. The results showed that overexpression of miR-592 promotes the proliferation, migration, and invasion of RCC cell lines, while inhibition of miR-592 suppresses these cellular behaviors, compared with untreated cells. Thus, we speculate that miR-592 may serve as an oncogene in RCC. In colorectal cancer, miR-592 also plays an oncogenic role in tumorigenesis by targeting Forkhead Box O3A (FoxO3A).[30] In gastric cancer, the ectopic expression of miR-592 promoted gastric cancer

proliferation, migration, and invasion and facilitated tumorigenesis through the PI3K/AKT and MAPK/EPK signaling pathways by targeting Spry2.[29] SPRY2 is a member of the signaling pathway-specific inhibition protein sprouty family, which has significant biological effects.[35–37] For instance, downregulation of SPRY2 gene expression mediated by miR-21 promotes the proliferation and invasion of multiple myeloma cells.[38] A previous study by Li et al have demonstrated SPRY2 was downregulated in RCC tissues and was associated with prognosis and inhibited cell proliferation and invasion in RCC cell lines.[39] In our investigation, Targetscan predicted that SPRY2 was the direct target of miR-592 and luciferase reporter assays showed that SPRY2 3′-UTR was the direct target of miR-592. According to previous study by Li et al[39] and our present results, we speculate that miR-592 may promote tumor cell proliferation, migration, and invasion by targeting SPRY2. In the present study, these findings suggested that miR-592 may function as an oncogene and a potential prognostic biomarker in RCC. To date, we investigated the clinical significance of miR-592 and its potential cellular function in vitro, and it would be interesting to further investigate the detailed molecular mechanism of miR-592 in RCC.

Conclusion

Taken together, this study showed that miR-592 expression was upregulated in human RCC tissues and cell lines, and miR-592 directly targeted the expression of SPRY2 in RCC cells. Overexpression of miR-592 may promote proliferation, migration, and invasion of RCC cells by targeting SPRY2. Therefore, these data suggested that miR-592 may function as a novel oncogene that regulates RCC progression, which may provide valuable evidence for miR-592 as a prognostic biomarker and therapeutic target for RCC.

Disclosure

The authors report no conflicts of interest in this work.

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