Original Article

SMARCC1 expression is positively correlated with pathological grade and good prognosis in renal cell carcinoma

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Background: Renal cell carcinoma (RCC), which is derived from the renal tubular epithelium, is now the most common urological cancer. Of the four RCC subtypes, clear cell RCC (ccRCC) is the most common subtype and accounts for 75–80% of all RCC cases. SMARCC1, also known as BAF155, together with SMARCA4, SMARCA2, and SMARCB1, comprises the SWI/SNF protein family. It has been reported that the expression of SMARCC1 was correlated with some human cancers including prostate cancer, colon cancer, and pancreatic cancer. However, the mechanisms and regulatory roles of SMARCC1 in ccRCC are not well defined.

Methods: Our current study primarily investigated the expression of SMARCC1 and its clinical importance in two common histological types of ccRCC using microarrays (HKidE180Su02, MecDNA-HKidE030CS01).

Results: The results showed that the expression of SMARCC1 in ccRCC tissues was significantly decreased compared with that in corresponding para-tumor tissue (4.370±2.036 *vs.* 6.167±1.162, P=0.001). SMARCC1 expression was positively correlated with pathological grade (r=0.224, P=0.011). Moreover, ccRCC patients with high SMARCC1 expression had a better prognosis than those with low SMARCC1 expression (40.0% *vs.* 95.2%, P=0.000) in the following sub-groups: pathological grade (III and IV), male sex (73.5% *vs.* 95.3%, P=0.004), and tumor size >5 cm (62.5% *vs.* 89.5%, P=0.044).

Conclusions: A further study is necessary to explain the mechanism of the occurrence and progression of ccRCC.

Keywords: SMARCC1; prognosis; renal cell carcinoma (RCC)

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Introduction

Chromatin remodeling is an important aspect of epigenetics, as it regulates DNA replication, repair, and recombination through dynamic structural changes in chromatin. SMARCC1, also known as BAF155, together with SMARCA4, SMARCA2, and SMARCB1, comprises the SWI/SNF protein family (1). SMARCC1 functions as a helicase and ATPase that can regulate the transcription of certain genes by changing the chromatin structure around these genes. SMARCC1 is part of the ATP-dependent SWI/

SNF chromatin remodeling complex and contains a leucine zipper motif that binds to many typical transcription factors. It has been reported that the expression of SMARCC1 is correlated with some human cancers including prostate cancer, colon cancer, and pancreatic cancer (2,3). For example, the expression of SMARCC1 was shown to be upregulated and positively correlated with tumor recurrence and dedifferentiation in prostate cancer (3,4). MicroRNA-202-5p targets SMARCC1 and acts as a tumor suppressor in colorectal carcinoma (5). In addition, SMARCC1 expression mediates drug resistance in pancreatic cancer cells and is regulated by miR-320c (6). We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/tau-20-935).

Renal cell carcinoma (RCC), which is derived from the renal tubular epithelium, is the most common urological cancer (7). The four common subtypes of RCC are as follows: clear cell RCC (ccRCC), papillary RCC (PRCC), chromophobe RCC (ChRCC), and collecting duct carcinoma. ccRCC accounts for as many as 75–80% of all RCC cases, whereas the other three subtypes of PRCC, ChRCC, and collecting duct carcinoma account for the other 20–25% of RCC cases (8-11). In 2018, it was reported that mutations in or loss of SMARCC1 are associated with the dedifferentiation subsets of RCC (9). However, the mechanisms and regulatory roles of SMARCC1 in ccRCC require further research.

The aim of our study was to explore the expression of SMARCC1 in ccRCC as well as the correlation between SMARCC1 expression and the clinical parameters and overall survival of patients with ccRCC.

Methods

Clinical materials

All 150 patients were diagnosed with ccRCC based on the World Health Organization/International Society of Urological Pathology (WHO/ISUP) classification system of renal cell tumors. All included patients in this study received no extra therapy from February 2008 to September 2010 before surgery, and were followed up after surgery until August 2015. All the patients with ccRCC were graded using the WHO/ISUP grading system and divided into two groups by tumor pathology: the clear cell renal carcinoma group and the clear cell renal carcinoma group with other pathological types (clear cell carcinoma with sarcomatoid degeneration, clear cell carcinoma with PRCC, and clear cell carcinoma with ChRCC). In addition, all the patients were divided into several sub-groups by gender (male or female), pathological grade (low pathological grade: grades I and II, high pathological grade: grades III and IV), and tumor size (≤5 or >5 cm). The American Joint Committee on Cancer (AJCC) 7th Edition Cancer Staging System was used for all included cases in this study. The clinical characteristics of patients were described in detail in *Table 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained, and the study was approved by The Ethics Boards of Huashan Hospital (No. 2020-529). All experiments were carried out in accordance with institutional guidelines. Written informed consent was obtained from the patients undergoing surgery.

Tissue microarray

A kidney cancer tissue microarray (HKidE180Su02, Shanghai Outdo Biotech Co., Ltd.), was used to explore the expression of SMARCC1 in ccRCC patients and its impact on survival of ccRCC patients. The tissue microarray included 150 cancer tissues and 30 adjacent tissues (1.5 cm away from the carcinoma) from ccRCC patients. The tissue microarray was made by using a core needle to punch a core column from the wax block with a fixed diameter of 1.5 mm. The tissue cores were selected from most high-grade areas of tumor, and 128 cores were taken from tumor and normal renal parenchyma. After the array block was completed, 4 μm slices were cut out.

Immunohistochemistry

The tissue sections were subjected to antigen retrieval using EDTA buffer at high temperature and high pressure. Then, the sections were incubated with a primary rabbit polyclonal antibody against SMARCC1 (1:10,000, Abcam, AB22355) at 4 ℃ overnight. The sections were then incubated with an HRP-labeled anti-mouse secondary antibody (DAKO). After washes in PBS and visualization with diaminobenzidine and hematoxylin counterstain, the sections were observed and analyzed under a microscope.

Each section was scored and grouped according to positive staining intensity and percentage of cells stained. According to the proportion of positively stained cancer cells, the percentage of positively stained cells by IHC was defined as follows: “Negative” received a score of 0, “0–1%” indicated a score of 1, “21–40%” a score of 2, “41–60%” a

Table 1 Detailed clinical information of the clear cell renal cell carcinoma (ccRCC) patients

Clinical index	N	Lost	Total N
Gender		0	150
Male	107		
Female	43		
Age		0	150
≤60 years	95		
>60 years	55		
Tumor size		0	150
≤5 cm	94		
>5 cm	56		
T stage		0	150
T1	122		
T2–T3	28		
N stage		0	150
N0	147		
N1	3		
M stage		0	150
M0			
M1	2		
Clinical stage		0	150
Stage I	122		
Stage II	16		
Stage III	11		
Stage IV	1		
Pathological grade		0	150
I–II	103		
III	47		
Groups		0	150
Clear cell renal cell carcinomas	136		
Clear cell renal carcinoma group with other pathological types	14		

score of 3, "61–80%" a score of 4, and "81–100%" a score of 5. The scores for staining intensity were as follows: "Negative" received a score of 0, "1+" indicated a score of 1, "2+" a score of 2, and "3+" a score of 3. Patients were divided into two groups according to the total score, which was obtained by multiplying the "positive staining rate score" and the "staining intensity score". Samples with scores ≤2.5 were considered the low expression group, whereas samples with scores >2.5 were considered the high expression group. The negative control was included by adding PBS instead of the primary antibody.

qRT-PCR

A total of 30 tissue samples (15 cancer tissues and 15 adjacent tissues) were prepared for the cDNA microarray (MecDNA-HKidE030CS01, Shanghai Outdo Biotech Co., Ltd.) according to the manufacturer's instructions. Real-time PCR was performed using a SYBR® Premix Ex Taq™ II (Tli RNaseH Plus, RR820Q) in 96-well reaction plates according to the manufacturer's instructions. The forward primer sequence was SMARCC1-F: 5'-TGAGGAGGATTATGAGGTGG-3', and the reverse primer sequence was SMARCC1-R: 5'-CGTGATTCTGTTGGTGTCG-3'. The PCR product length was 177 bp. β-Actin served as a reference gene, and the primers used were as follows: Human β-actin-F1: 5'-GAAGAGCTACGAGCTGCCTGA-3' Human β-actin 5'-CAGACAGCACTGTGTTGGCG-3'. The β-actin PCR product length was 191 bp.

Each sample was prepared in a total volume of 50 μL containing 2 μL of 0.4 μmol/L primer mix, 25 μL SYBR Green master mix, 4 μL DNA template, and 16 μL RNase/DNase-free sterile water. The initial denaturation was performed at 95 ℃ for 30 s, followed by 40 cycles at 95 ℃ for 5 s, and 60 ℃ for 30 s. The fluorescence data were collected in the 60 ℃ extension phase.

Statistical analysis

The data of SMARCC1 expression in ccRCC tissues was analyzed by Npar Tests. The relationship between SMARCC1 expression and clinical factors was calculated using the Spearman rank correlation coefficient. The correlation between SMARCC1 expression and clinical data as well as the overall survival time was evaluated using the Kaplan-Meier method and the log-rank test. Finally, variables that were statistically significant in the univariate analysis were included in a Cox multivariate regression survival analysis. $P<0.05$ was considered statistically significant.

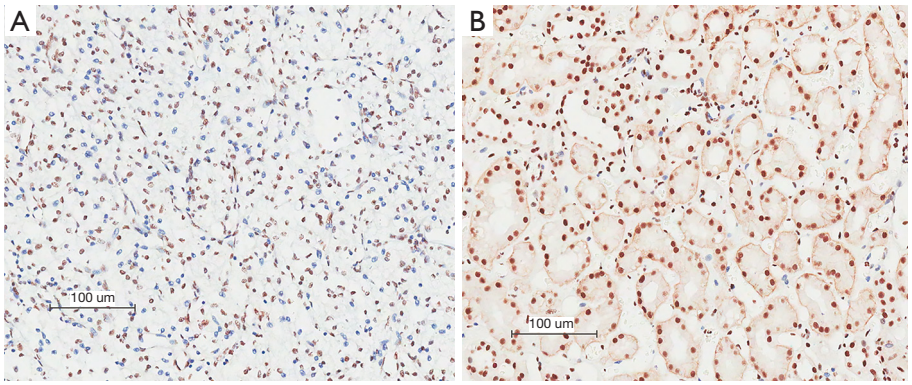

Figure 1 Representative immunohistochemistry images of SMARCC1 expression in clear cell renal cell carcinoma (ccRCC) (A) and paired para-tumor tissue samples (B).

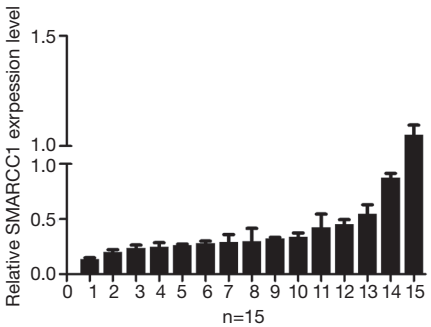

Figure 2 $2^{-\Delta\Delta Ct}$ represents the multiple differences in gene expression in cancer and adjacent normal tissues: SMARCC1 was over-expressed in clear cell renal cell carcinoma (ccRCC) tissues if $2^{-\Delta\Delta Ct}$ >1, whereas SMARCC1 was under-expressed when $2^{-\Delta\Delta Ct}$ <1.

Results

SMARCC1 expression in ccRCC tissues was significantly lower than that in paired para-tumor tissues

The expression of SMARCC1 in ccRCC tissues was significantly lower compared with their corresponding paired para-tumor tissues (4.370±2.036 *vs.* 6.167±1.162, P=0.001), especially in the cortex (*Figure 1*). Consistently, the result obtained from the ccRCC cDNA tissue microarray also showed that SMARCC1 mRNA expression in ccRCC tissues was significantly lower than that in para-tumor tissues. The results were shown in detail in *Figure 2*.

The expression of SMARCC1 was significantly correlated with high pathological grade

The relationship between SMARCC1 expression and the clinical characteristics of the ccRCC patients, including gender, age, tumor size, pathological grade, TNM stage, and clinical stage, was analyzed. The results revealed a significant positive correlation between SMARCC1 expression and high pathological grade (r=0.224, P=0.011). No significant link was found between SMARCC1 and age, gender, tumor size, T stage, N stage, or clinical stage. The results were shown in detail in *Table 2*.

High SMARCC1 expression was correlated with a good prognosis in ccRCC

The relationship between SMARCC1 expression and the overall survival of patients with ccRCC was analyzed. The results showed that patients with high SMARCC1 expression had a better prognosis than those with low SMARCC1 expression (80.6% *vs.* 93.4%, P=0.028). The results also showed that high SMARCC1 expression was correlated with a better prognosis compared with low SMARCC1 expression (40.0% *vs.* 95.2%, P=0.000) in the high pathological grade (grades III and IV), male (73.5% *vs.* 95.3%, P=0.004), and tumor size >5 cm (62.5% *vs.* 89.5%, P=0.044) sub-groups. The results were shown in detail in *Figure 3*.

Subsequently, the multi-factor survival analysis showed that SMARCC1 expression could serve as an independent predictive factor for ccRCC (P=0.008). The results of the analysis were shown in detail in *Table 3*.

Discussion

It has been reported that SMARCC1 plays a dual

Table 2 The expression of SMARCC1 is significantly correlated with pathological grade

Variable	Gender	Age	Pathological grade	Tumor size	T	N	Clinical stage
Correlation coefficient	–0.025	0.128	0.224*	–0.082	–0.021	–0.018	–0.021
Sig. (2-tailed)	0.782	0.151	0.011	0.358	0.816	0.838	0.816
N	128	128	128	128	128	128	128

*, P<0.05.

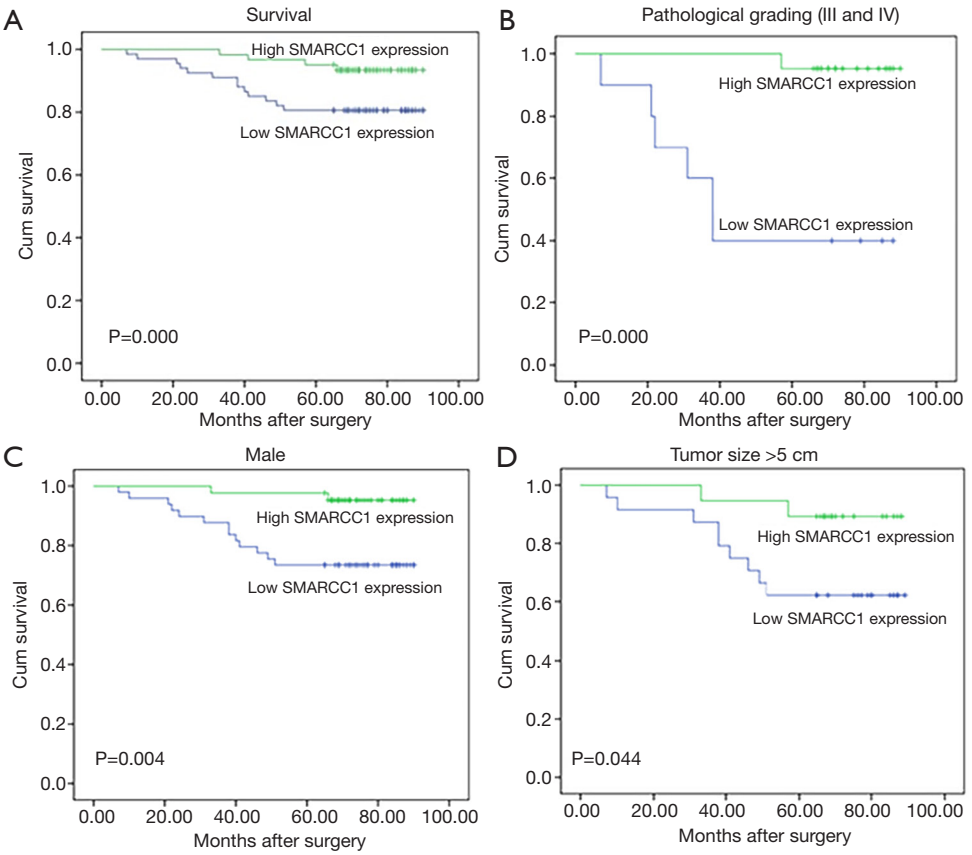

Figure 3 Overall survival analysis according to different SMARCC1 expression levels: (A) all the patients; (B) the sub-group of high pathological grade (III and IV); (C) male sub-group; (D) the sub-group of tumor size >5 cm.

regulatory role of oncogene and tumor suppressor in cancer (12,13). SMARCC1 expression is up-regulated in prostate cancer and is positively correlated with tumor recurrence and differentiation (14). Moreover, the arginine methyltransferase CARM1 targets SMARCC1 to promote tumor progression and metastasis. However, higher SMARCC1 expression was found to be significantly correlated with a better overall survival in both colorectal cancer and prostate cancer (4,15).

Our study primarily investigated the expression of SMARCC1 and its clinical importance using microarrays of two common histological types of ccRCC (HKidE180Su02 and MecDNA-HKidE030CS01). The results showed that the expression of SMARCC1 was significantly decreased in ccRCC tissues and that SMARCC1 expression was significantly correlated with high pathological grade (r=0.224, P=0.011). High SMARCC1 expression was correlated with a better prognosis compared with lower SMARCC1 expression (40.0% *vs.* 95.2%, P=0.000) in the high pathological grade (grades III and IV), male (73.5%

Table 3 SMARCC1 expression serves as an independent predictive factor for clear cell renal cell carcinoma (ccRCC)

Variable	B	SE	Wald	Df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Age	10.055	0.522	40.088	1	0.043	20.871	10.033	70.979
Pathological grade	0.871	0.420	40.299	1	0.038	20.389	10.049	50.442
Tumor size	10.081	0.583	30.439	1	0.064	20.948	0.940	90.242
T	0.467	0.424	10.214	1	0.271	10.595	0.695	30.662
N	1.924	10.474	10.704	1	0.192	60.851	0.381	123.161
Clinical stage			0	0[†]	0			
SMARCC1 expression	–1.701	0.646	60.929	1	0.008	0.183	0.051	0.648

[†], degree of freedom reduced because of constant or linearly dependent covariates.

vs. 95.3%, P=0.004), and tumor size >5 cm (62.5% *vs.* 89.5%, P=0.044) sub-groups, which is consistent with the database (https://www.proteinatlas.org) that shows that renal cancer patients with high SMARCC1 expression have a significantly better 5-year prognosis.

In conclusion, our study revealed that SMARCC1 expression was significantly decreased in ccRCC tissues, and that SMARCC1 expression was significantly correlated with pathological grade. Compared with lower SMARCC1 expression, high SMARCC1 expression was correlated with a better prognosis. Future studies are needed to explain the mechanism of the occurrence and progression of ccRCC.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-20-935). QD serves as an unpaid editorial board member of *Translational Andrology and Urology* from Mar 2012 to Feb 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained, and the study was approved by The Ethics Boards of Huashan Hospital (No.2020-529). All experiments were carried out in accordance with institutional guidelines. Written informed consent was obtained from the patients undergoing surgery.

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