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A-kinase interacting protein 1 high expression correlates with advanced tumor stage and poor overall survival in surgical patients with clear cell renal cell carcinoma

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Abstract

The present study aimed to detect the A-kinase interacting protein 1 (AKIP1) expression in clear cell renal cell carcinoma (ccRCC) tumor tissues and adjacent tissues, and further investigate the correlation of tumor AKIP1 expression with clinicopathological features and survival profile in ccRCC patients.

Totally 210 ccRCC patients who underwent resection were retrospectively reviewed, and their tumor and adjacent tissue specimens were acquired for immunohistochemical detection of AKIP1 expression. The survival data of patients were collected for overall survival (OS) assessment.

AKIP1 was upregulated in ccRCC tumor tissues compared with adjacent tissues ($P < .001$). Tumor AKIP1 expression was positively associated with T stage ($P = .019$), N stage ($P = .032$), and TNM stage ($P = .005$) in ccRCC patients. According to AKIP1 expression in tumor tissues, all patients were grouped as AKIP1 low and high expression (AKIP1 high expression were further divided into AKIP1 high+, high++, and high+++ expression). OS was the lowest in the patients with AKIP1 high+++ expression, followed by those with AKIP1 high++ expression and AKIP1 high+ expression, and then patients with AKIP1 low expression ($P < .001$). Furthermore, multivariate Cox regression exhibited tumor AKIP1 high expression ($P = .017$), age (>60 years) ($P = .030$), pathological grade (G2/G3 vs G1) ($P = .037$), and TNM stage (II/III vs I) ($P < .001$) were independent predictive factors for decreased OS in ccRCC patients.

AKIP1 presents potency to be a novel biomarker for tumor progression and prognosis surveillance in ccRCC.

Abbreviations: AKIP1 = A-kinase interacting protein 1, ccRCC = clear cell renal cell carcinoma, EMT = epithelial-mesenchymal transition, NF-Kb = NF-kappaB, NSCLC = non-small-cell lung cancer, OS = overall survival, RCC = renal cell carcinoma.

Keywords: A-kinase interacting protein 1, clear cell renal cell carcinoma, clinicopathological features, immunohistochemical detection, overall survival

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Clear cell renal cell carcinoma (ccRCC), as the most common renal cell carcinoma (RCC), accounts for 70% to 80% of RCC cases, which presents the highest mortality rate in urogenital cancers.[1,2] Common therapeutic treatments against ccRCC include nephrectomy, systematic adrenalectomy, immunotherapy, targeted treatment, conventional radiotherapy, and so on, while clinical outcomes of most ccRCC patients remain unsatisfaction due to the risk of complications as well as adverse events.[3–5] In addition, considering the increased possibility of recurrence and metastasis, emerging experts suggest the necessity of routinely follow-up survivorship.[6] Hence, novel biomarkers, which can be accepted for prognosis surveillance in clinical use, are required for ccRCC patients.

A-kinase interacting protein 1 (AKIP1) is reported to interact with protein kinase A catalytic subunit, and regulate the action of cAMP-dependent protein kinase (PKA) signaling pathway on the NF-kappaB (NF-κB) activity.[7] Existing evidence indicates that AKIP1 promotes the angiogenesis, metastasis, progression of several tumors through activating NF-κB activity and epithelial-mesenchymal transition (EMT) program.[8–13] One functional experiment in non-small-cell lung cancer (NSCLC) demonstrates that AKIP1 overexpression promotes cell migration, invasion, and EMT, with the upregulation of mesenchymal markers and downregulation of epithelial marker.[8] Clinically, AKIP1 is

observed to be elevated in colorectal cancer compared with noncancerous colorectal mucosa, and its overexpression is correlated with increased tumor diameter, advanced TNM stage, lymph node metastasis, undesirable prognosis in colorectal cancer patients.[10] However, the clinical significance of AKIP1 in the field of ccRCC has not been studied. Therefore, we performed the present study to detect AKIP1 expression in ccRCC tumor tissues and adjacent tissues, and further investigate the association of tumor AKIP1 expression with clinicopathological features and prognosis in ccRCC patients.

2. Methods

2.1. Patients

This study retrospectively reviewed 210 ccRCC patients who underwent resection in The Hospital of Bayannaoer, Inner Mongolia Autonomous Rogion between January 2009 and December 2013. The patients' data were extracted from the database of our hospital, and the screening criteria were:

(1) diagnosed as primary RCC;
(2) histologically confirmed as ccRCC;
(3) age between 18 and 80 years old;
(4) underwent partial or radical nephrectomy;
(5) tumor and adjacent tissues were well preserved and eligible for immunohistochemical (IHC) detection;
(6) had complete clinical data before resection;
(7) had complete follow-up data that could be used to calculate overall survival (OS);
(8) without distant metastases or other malignancies;
(9) no neoadjuvant therapy.

The Ethics Committee of The Hospital of Bayannaoer, Inner Mongolia Autonomous Rogion approved this study, and all patients or their guardians provided the written informed consents.

2.2. Clinical feature and sample collection

Demographic characteristics and tumor features were collected from database of The Hospital of Bayannaoer, Inner Mongolia Autonomous Rogion. Tumor and adjacent tissue specimens were acquired from the Pathology Department of The Hospital of Bayannaoer, Inner Mongolia Autonomous Rogion, and all tissue specimens were formalin-fixed and paraffin-embedded.

2.3. IHC

The tissue specimens were deparaffinized and rehydrated after cutting into 4 μm sections, and antigen was retrieved using microwave heating. Subsequently, 0.3% H_2O_2 was used to block peroxidase activity, and 10% normal goat serum (Sigma-Aldrich, Burlington, MA) was used to prevent nonspecific binding. Then the sections were incubated with rabbit anti-AKIP1 antibody (1:100, Abcam, Cambridge, MA) at 4°C overnight. Next day, the sections were incubated with horseradish peroxidase-conjugated goat-anti-rabbit immunoglobulin G antibody (1:1000, Abcam) at 37°C for 60 minutes. Finally, the staining and counterstaining of the sections were performed with diaminobenzidine (Dako, Santa Clara, CA) and hematoxylin (Sigma-Aldrich) respectively. After the sections were sealed with neutral resin (Sango Biotech, Shanghai, China), the immunostaining results were observed on Nikon ECLIPSE E200 microscope (Nikon Instruments, Melville, NY) and assessed by a semi-quantitative scoring method as previously described.[14] The total IHC score was ranging from 0 to 12, and all tissues were classified as AKIP1 high expression (total IHC score >3) and AKIP1 low expression (total IHC score ≤3). Moreover, AKIP1 high expression tissues were further divided into tissues with AKIP1 high+ expression (total IHC score ranging from 4 to 6), tissues with AKIP1 high++ expression (total IHC score range from 7 to 9), tissues with AKIP1 high+++ expression (total IHC score ranging from 10 to 12).[14] In addition, according to AKIP1 expression in tumor tissues, all patients were grouped as patients with AKIP1 low expression (n = 98), patients with AKIP1 high expression (n = 112), patients with AKIP1 high+ expression (n = 60), patients with AKIP1 high ++ expression (n=37), and patients with AKIP1 high+++ expression (n=15).

2.4. Follow-up

Survival data of patients were collected from follow-up records, and all patients were followed up to December 31, 2018. The follow-up duration was ranging from 1.0 month to 119 months, and the median follow-up duration was 88.0 months. OS was defined as the duration from resection to death.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 22.0 software (IBM, Chicago, IL). Figures were plotted using GraphPad Prism 7.00 (GraphPad Software, La Jolla, CA). Between tumor tissues and adjacent tissues, comparison of AKIP1 IHC score was determined by Paired-samples t test; comparison of proportions was determined by McNemar test. Between tumor AKIP1 high expression patients and tumor AKIP1 low expression patients, comparison of age or tumor size was determined by Student *t* test; comparison of gender or tumor location was determined by Chi-square test; comparison of pathological grade, T stage, N stage, or TNM stage was determined by Wilcoxon rank sum test. The OS was displayed by Kaplan–Meier curve, and the difference of OS between/among groups was analyzed by log-rank test. Factors predicting OS were analyzed by univariate and multivariate Cox proportional hazard regression model. *P*-value <.05 was considered as significant.

3. Results

3.1. Clinical features

A total of 210 ccRCC patients were included in the present study (Table 1). The mean age of ccRCC patients was 58.8 ± 11.5 years, and there were 80 (38.1%) females and 130 (61.9%) males. As for tumor features, regarding tumor location, there were 101 (48.1%) patients with the tumor on the right kidney and 109 (51.9%) patients with tumor on the left kidney. In terms of pathological grade, there were 95 (45.2%), 89 (42.4%), and 26 (12.4%) patients with G1 (well differentiation), G2 (moderate differentiation), and G3 (poor differentiation), respectively. The mean tumor size was 5.8 ± 2.6 cm. The numbers of patients with TNM stage I, II, and III were 144 (68.6%), 43 (20.5%), and 23 (11.0%), respectively. More detailed information of ccRCC patients was listed in Table 1.

Table 1

Clinical features of ccRCC patients.

Items	ccRCC patients (N = 210)
Demographic characteristics	
Age (yr), mean ± SD	58.8 ± 11.5
Gender, No. (%)	
Female	80 (38.1)
Male	130 (61.9)
Tumor features	
Tumor location, No. (%)	
Right	101 (48.1)
Left	109 (51.9)
Pathological grade, No. (%)	
G1	95 (45.2)
G2	89 (42.4)
G3	26 (12.4)
Tumor size (cm), mean ± SD	5.8 ± 2.6
T stage, No. (%)	
T1	152 (72.4)
T2	46 (21.9)
T3	12 (4.7)
N stage, No. (%)	
N0	195 (92.9)
N1	15 (7.1)
TNM stage, No. (%)	
I	144 (68.6)
II	43 (20.5)
III	23 (11.0)

ccRCC = clear cell renal cell carcinoma, SD = standard deviation.

3.2. Comparison of AKIP1 between ccRCC tumor tissues and adjacent tissues

Expression of AKIP1 in ccRCC tumor tissues and adjacent tissues were detected by IHC, and all tissues were classified as AKIP1 high expression (total IHC score >3) and AKIP1 low expression (total IHC score ≤3). AKIP1 high expression tissues were further divided into AKIP1 high+ (total IHC score 4–6), AKIP1 high++ (total IHC score 7–9), and AKIP1 high+++ (total IHC score 10–12) expression. Representative IHC images illustrated AKIP1 low expression in adjacent tissues, AKIP1 low expression in tumor tissues, AKIP1 high+ expression in tumor tissues, AKIP1 high++ expression in tumor tissues, and AKIP1 high+++ expression in tumor tissues (Fig. 1A, Supplementary Fig. 1, http://links.lww.com/MD/E378). AKIP1 IHC score was 4.9 ± 3.0 in tumor tissue and 3.2 ± 2.2 in adjacent tissue; further comparison analysis indicated that AKIP1 expression was increased in tumor tissue compared with adjacent tissue ($P < .001$) (Fig. 1B). Furthermore, in tumor tissue, 112 (53.3%) cases and 98 (46.7%) cases showed tumor AKIP1 high expression and low expression, respectively; in adjacent tissue, 65 (31.0%) cases and 145 (69.0%) cases exhibited adjacent AKIP1 high expression and low expression, respectively; besides, the percentage of AKIP1 high expression was elevated in tumor tissue compared with adjacent tissue ($P < .001$) (Fig. 1C). Additionally, 15 (7.1%), 37 (17.6%), 60 (28.6%), and 98 (46.7%) tumor tissue exhibited tumor AKIP1 high+++, high++, high+, and low expression; meanwhile, 3 (1.5%), 12 (5.7%), 50 (23.8%), and 145 (69.0%) adjacent tissue presented with adjacent AKIP1 high+++, high++, high+, low expression; further comparison analysis revealed that AKIP1 expression was increased in tumor tissue compared with adjacent tissue ($P < .001$) (Fig. 1D).

3.3. Correlation of tumor AKIP1 expression with clinical features in ccRCC patients

Tumor AKIP1 expression was positively associated with T stage ($P = .019$), N stage ($P = .032$), TNM stage ($P = .005$), while there was no association of tumor AKIP1 expression with age ($P = .311$), gender ($P = .129$), tumor location ($P = .178$), pathological grade ($P = .818$), or tumor size ($P = .076$) in ccRCC patients (Table 2).

3.4. Correlation of tumor AKIP1 expression with OS in ccRCC patients

In order to explore the correlation of tumor AKIP1 expression with prognosis, we adopted 2 different classified methods to divide tumor AKIP1 expression and group patients according to the corresponding tumor AKIP1 expression. The first method was that tumor AKIP1 expression was classified as tumor AKIP1 high and tumor AKIP1 low. Based on the first method, tumor

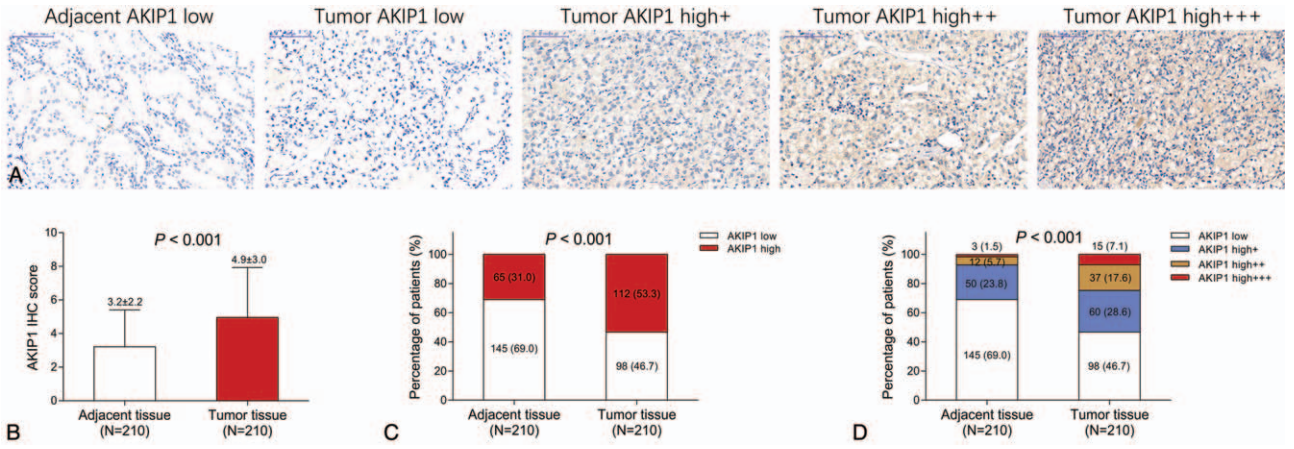

Figure 1. AKIP1 was upregulated in ccRCC tumor tissues compared with adjacent tissues. Adjacent AKIP1 low expression, tumor AKIP1 low expression, tumor AKIP1 high+ expression, tumor AKIP1 high++, tumor AKIP1 high+++ expression (A). Comparison of AKIP1 IHC score (B), percentage of patients with AKIP1 high and low expression (C), percentage of patients with AKIP1 low, high+, high++, high+++ expression (D) between adjacent tissues and tumor tissues. AKIP1 = A-kinase interacting protein 1, ccRCC = clear cell renal cell carcinoma, IHC = immunohistochemistry.

Table 2

Comparison of clinical features between tumor AKIP1 high expression patients and tumor AKIP1 low expression patients.

Items	AKIP1 low (n = 98)	AKIP1 high (n = 112)	*P*-value
Age (yr), mean ± SD	57.9 ± 11.2	59.5 ± 11.7	.311
Gender, No. (%)			.129
Female	32 (32.7)	48 (42.9)	
Male	66 (67.3)	64 (57.1)	
Tumor location, No. (%)			.178
Right	52 (53.1)	49 (43.8)	
Left	46 (46.9)	63 (56.2)	
Pathological grade, No. (%)			.818
G1	44 (44.9)	51 (45.5)	
G2	44 (44.9)	45 (40.2)	
G3	10 (10.2)	16 (14.3)	
Tumor size (cm), mean ± SD	5.5 ± 2.5	6.1 ± 2.7	.076
T stage, No. (%)			.019
T1	78 (79.6)	74 (66.1)	
T2	18 (18.4)	28 (25.0)	
T3	2 (2.0)	10 (8.9)	
N stage, No. (%)			.032
N0	95 (96.9)	100 (89.3)	
N1	3 (3.1)	12 (10.7)	
TNM stage, No. (%)			.005
I	76 (77.6)	68 (60.7)	
II	17 (17.3)	26 (23.2)	
III	5 (5.1)	18 (16.1)	

AKIP1 = A kinase-interacting protein 1, SD = standard deviation.

AKIP1 high expression was associated with worse OS ($P = .004$) (Fig. 2A). The second method was that tumor AKIP1 expression was classified as tumor AKIP1 high+++, high++, high+, low. According to the second method, increased grade of AKIP1 expression was correlated with unfavorable OS ($P < .001$) (Fig. 2B). These data suggested that tumor AKIP1 expression was negatively correlated with prognosis.

3.5. Factors predicting OS in ccRCC patients

Univariate Cox regression indicated that tumor AKIP1 high expression (hazard ratio [HR] = 2.085, $P = .005$), age (>60 years) (HR = 1.954, $P = .007$), pathological grade (G2/G3 vs G1) (HR = 2.568, $P < .001$), and TNM stage (II/III vs I) (HR = 4.145, $P < .001$) were correlated with decreased OS in ccRCC patients (Table 3). Further multivariate Cox regression analysis exhibited that tumor AKIP1 high expression (HR = 1.914, $P = .017$), age (>60 years) (HR = 1.724, $P = .030$), pathological grade (G2/G3 vs G1) (HR = 1.888, $P = .037$), and TNM stage (II/III vs I) (HR = 3.181, $P < .001$) could independently predict worse OS in ccRCC patients.

4. Discussion

In the present study, we found that

(1) AKIP1 was upregulated in ccRCC tumor tissues compared with adjacent tissues.
(2) Further clinical analysis suggested that tumor AKIP1 expression was positively associated with TNM stage in ccRCC patients.
(3) Additionally, tumor AKIP1 high expression was an independent predictive factor for decreased OS in ccRCC patients.

AKIP1, as a binding partner of NF-κB p65 subunit, is known to interact with the catalytic subunit of PKA and enhance the expressions of NF-κB-related genes, and existing researches exhibit that AKIP1 functions as a potent oncogenic protein, which is involved in tumorigenesis and progression of several cancers.[8,10–12,15,16] For example, 1 functional and molecular experiment exhibits that AKIP1 knockdown suppresses cell proliferation, invasion, and metastasis via regulating slug-induced EMT in gastric cancer.[12] Another study demonstrates that AKIP1 transactivates the expression of Zinc Finger E-box Binding homeobox 1, which contributes to the repression of E-cadherin (epithelial marker) and further results in activation of EMT, promotion of cell migration as well as invasion in NSCLC.[8] Since previous studies showed that EMT was associated with the invasive and metastatic properties of various tumors and presents ability in triggering the carcinogenesis features of cancer cells, including renal cell, we speculated that AKIP1 might be abnormally expressed in ccRCC tumor tissues as well, and further investigated the correlation of tumor AKIP1

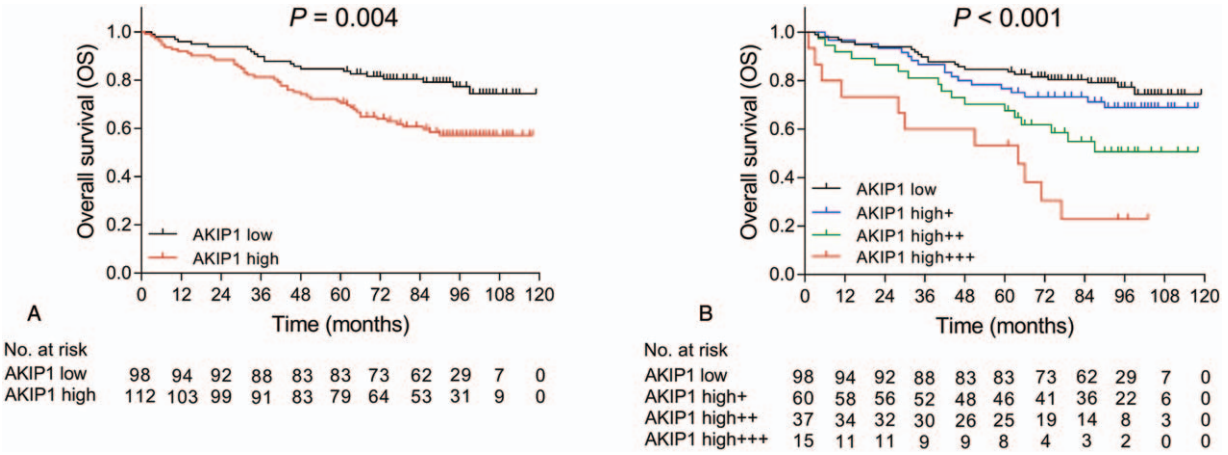

Figure 2. Tumor AKIP1 high expression was associated with poor OS in ccRCC patients. Comparison of OS between patients with AKIP1 high expression and those with AKIP1 low expression (A). Comparison of OS among patients with AKIP1 low expression, patients with AKIP1 high+ expression, patients with AKIP1 high ++ expression and patients with AKIP1 high+++ expression (B). AKIP1 = A-kinase interacting protein 1, ccRCC = clear cell renal cell carcinoma, OS = overall survival.

Table 3

Analysis of factors predicting OS.

Items	Univariate Cox regression		Multivariate Cox regression	
	P-value	HR (95% CI)	*P*-value	HR (95% CI)
AKIP1 high expression	.005	2.085 (1.254–3.467)	.017	1.914 (1.120–3.270)
Age (>60 yr)	.007	1.954 (1.205–3.169)	.030	1.724 (1.054–2.821)
Male	.963	0.988 (0.606–1.612)	.408	1.234 (0.750–2.030)
Tumor location (left)	.476	1.190 (0.737–1.921)	.406	0.805 (0.483–1.343)
Pathological grade (G2/G3 vs G1)	<.001	2.568 (1.511–4.364)	.037	1.888 (1.038–3.432)
TNM stage (II/III vs I)	<.001	4.145 (2.555–6.723)	<.001	3.181 (1.877–5.391)

AKIP1 = A kinase-interacting protein 1, CI = confidence interval, HR = hazard ratio, OS = overall survival.

expression with clinical tumor features in ccRCC patients.[17,18] We applied IHC detection, and observed that AKIP1 was upregulated in ccRCC tumor tissues compared with adjacent tissues. And further analysis found that tumor AKIP1 expression was positively associated with T stage, N stage, and TNM stage in ccRCC patients. The possible reasons might include that:

(1) Considering the close association of EMT with epithelial and carcinoma stem cell properties, AKIP1 high expression might increase the population of self-renewing tumor initiating cells, further generating tumors; therefore, AKIP1 was upregulated in ccRCC tumor tissues compared with adjacent tissues.[8,17]
(2) Moreover, when AKIP1 was highly expressed, PKA-promotor agents might enhance NF-κB transcriptional activity, further driving EMT and strengthening the ccRCC cell proliferation, invasion, and migration, thereby leading to promoted angiogenesis and lymph-angiogenesis in ccRCC patients.[7,8]

Therefore, tumor AKIP1 high expression was associated with advanced TNM stage in ccRCC patients. However, further mechanisms underlying AKIP1 mediated-EMT activation in ccRCC needed cellular experiments to exploration.

Regarding the correlation of AKIP1 with prognosis in cancer patients, several studies has linked the AKIP1 high expression with poor prognosis.[8,13,15] For example, NSCLC patients whose tumor tissues presents high level of AKIP1 have worse 5-year survival and disease-free survival.[8] Another study suggests that AKIP1 expression is correlated with cancer progression and shorter survival time in patients with esophageal squamous cell carcinoma.[13] Consistent with these previous studies, we also found that tumor AKIP1 high expression was correlated with decreased OS, and tumor AKIP1 high expression could independently predict poor OS in ccRCC patients. The possible reason might consist of that:

(1) According to the previous observation in our study, AKIP1 high expression was associated with advanced T stage, N stage, and TNM stage in ccRCC patients. Besides, TNM stage was observed to be a predictive factor for unfavorable prognosis in ccRCC patients; therefore, patients with tumor AKPI1 high expression were more likely to have undesirable prognosis.
(2) Several previous studies exhibit that enhanced EMT plays an important role in regulating the phenotype of cancer stem cell, thereby possessing cancer stem cell-mediated clinical significance, including: tumor relapse and increased drug resistance.[19,20]

According to these prior evidence, AKIP1 high expression might upregulate the expression of mesenchymal markers, but downregulate the expression of epithelial marker, which might activate EMT program and introduce the anti-apoptotic as well as drug-tolerant properties of ccRCC cells, hence, ccRCC patients with tumor AKIP1 high expression might have poor response to anticancer therapy and unfavorable prognosis.

There were still some limitations in our study.

(1) We excluded the ccRCC patients with distant metastases; therefore, the results of our study might not be suitable for all ccRCC patients.
(2) As our study retrospectively reviewed the medical records of 210 ccRCC patients, while most of patients were from remote regions, which made it hard to get precise information of DFS (Disease-free survival) data. Therefore, we only assessed the OS, and further study exploring the correlation of AKIP1 with DFS was needed.
(3) The underlying mechanism of AKIP1 in pathophysiologic process of ccRCC needed to be explored by further cellular experiments.
(4) Further cellular experiments were needed to explore the effect of AKIP1 on ccRCC cell proliferation, invasion, and migration.
(5) Further western blotting was needed to validate the results in the present study.

In conclusion, AKIP1 is upregulated in ccRCC, and its overexpression is associated with advanced TNM stage and poor prognosis in ccRCC patients, which provides evidence that AKIP1 presents potency to be a novel biomarker for tumor progression and prognosis surveillance in ccRCC.

Author contributions

Conceptualization: Rong Zhang, Hao Zhang.
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Formal analysis: Huimin Peng.
Investigation: Huimin Peng.
Methodology: Huimin Peng.
Resources: Rong Zhang, Hao Zhang.
Supervision: Rong Zhang, Hao Zhang.
Validation: Hao Zhang.
Writing – original draft: Huimin Peng.
Writing – review & editing: Rong Zhang, Hao Zhang.

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