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High-expression of ZBP-89 correlates with distal metastasis and poor prognosis of patients in clear cell renal cell carcinoma

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ABSTRACT

ZBP-89, a Krüppel-type zinc-finger transcription factor, is found to participate in tumor development, invasion and metastasis. However, the expression status of ZBP-89 in clear cell renal cell carcinoma (CCRCC) remains elusive. Using quantitative real-time-PCR and Western Blot, we found that, in fresh cancer tissues, ZBP-89 was remarkably decreased in 79.2% (19/24) and 83.3% (5/6) of CCRCC at mRNA and protein level, respectively. Immunohistochemistry also revealed a significant decline of ZBP-89 expression in CCRCC, showing that low expression of ZBP-89 was present in 73.9% (105/142) of tumorous tissues but in 48.1% (52/108) of the corresponding adjacent kidney tissues. Furthermore, ZBP-89 expression in CCRCC was significantly correlated with several clinicopathological features, including TNM stage ($P = 0.005$) and distal metastasis ($P = 0.001$). Further study confirmed that ZBP-89 expression was markedly higher in metastatic CCRCC than that in non-metastatic tissue ($P = 0.002$). In addition, CCRCC patients with low ZBP-89 expression survived longer than those with high ZBP-89 expression, as indicated by the result of univariate analysis ($P < 0.0001$). More importantly, multivariate analysis revealed that ZBP-89 was an independent predictor of overall survival (HR, 2.871; 95% CI, 1.409–5.853; $P = 0.004$). Collectively, our study provides vigorous evidence that ZBP-89 was significantly downregulated in CCRCC and could be served as a promising biomarker for prediction of distal metastasis and prognosis of patient with CCRCC.

1. Introduction

Renal cell carcinoma (RCC), which accounts for 2–3% of adult malignancies, is the most common renal malignancy and its incidence continues to increase. There are 209,000 new cases per year worldwide and 102,000 death [1]. Despite the increased number of cases diagnosed at smaller size, RCC presents with metastases in up to 30% of cases, and nearly one third of patients undergoing nephrectomy for clinically localized disease eventually develop metastases [2,3]. For RCC patients, the 5 year survival is 69.4%. However, if the disease is diagnosed with metastasis, the percentage can be reduced to less than 10% [4]. The most important and valuable prognostic factors affecting survival of RCC patients are tumor grade, local extent of the primary tumor, presence of regional nodal metastases, and evidence of metastatic disease at presentation.

Clear cell renal cell carcinoma (CCRCC), the most prevalent subtype of RCC, represents approximately 75% of renal neoplasm. Although there are many promising studies searching biomarkers in CCRCC, after a decade of investigation, molecular markers have not yet made their way into clinical practice, as the results of many studies are sometimes contradictory [5]. With even small tumors having metastatic potential and the fact that the overall CCRCC mortality has not yet dropped [6], markers for the individual aggressiveness of this tumor are still desired.

ZBP-89 (BFCOL1, BERF1, ZNF-148 or Zfp-148), a Krüppel-type zinc-finger transcription factor that binds to GC-rich sequences, is universally expressed and conserved in mammals, and involved in many cellular functions related to cancer, including cell growth, differentiation, apoptosis and senescence [7]. ZBP-89 can regulate the expression of certain growth-related factors by activating or repressing transcription of the genes including *gastrin* [8] and *vimentin* [9]. Due to the ability of ZBP-89 to form direct protein complexes with well-known tumor suppressor factors, such as p53 [10] and p300 [11], ZBP-89 is thought to be involved in tumor development. ZBP-89 has been shown to be elevated in various human cancers, such as gastric [12], colorectal [13], breast [14] and

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liver cancers [15], but it disappears in about 70% of pancreatic adenocarcinomas [16]. However, the expression of ZBP-89 and its significance in CCRCC has not yet been elucidated.

In this study, we examined the mRNA and protein levels of ZBP-89 in CCRCC and determined the relationship between its expression and various clinicopathologic parameters in order to systematically investigate whether ZBP-89 was involved in CCRCC carcinogenesis and tumor development.

2. Materials and methods

2.1. Patients and samples

A total 142 tissue blocks prepared from CCRCC tissues and the adjacent non-tumorous kidney tissues were sectioned for immunohistochemistry (IHC) studies. Samples were collected by the surgical teams in Sun Yat-sen University Cancer Center, Guangzhou, China with prospective collection of clinico-pathological information from March 2002 to September 2006. In addition, 24 paired cases of CCRCC tissue along with the adjacent renal tissue were collected for quantitative real-time RT-PCR, 6 paired cases of CCRCC and normal kidney protein were analyzed for Western Blot and another 142 cases were used for IHC analysis (108 tumor tissues with adjacent normal kidney tissue). All the human specimens used in the study were approved by the Ethics Committees of Sun Yat-sen University Cancer Center and written informed consent was obtained from each patient.

2.2. Quantitative real-time PCR

mRNA transcripts were measured using a standard SYBR Green real-time assay. Total RNA was extracted from cells using the Trizol reagent (Invitrogen, CA, USA) according to the manufacturer's instruction. One microgram of RNA sample was reverse transcribed using the Suprescript III enzyme (Invitrogen, CA, USA) to obtain single-stranded cDNA. Real-time PCR was then performed on cDNA in an iQ Sybr Green Supermix (Bio-Rad) with gene-specific primers. The following primers were used: ZBP-89 forward, 5′-CGC TGT GAT GAA TGT GGT GAT GAG AC-3′; ZBP-89 reverse, 5′-CCC AGC TCT ATT ATC ATT TAC ATT C-3′; GAPDH forward, 5′-AAA TCC CAT CAC CAT CTT CC-3′; and GAPDH reverse, 5′-TCC ACC ACC CTG TTG CTG TA-3′. Amplicons were analyzed using the ΔΔCt method, and data are represented as the mean of three independent experiments ± SE.

2.3. Western Blot

Lysates were prepared from the tissues as described previously [17]. Forty microgram of proteins were boiled with 6× SDS loading buffer and then fractionated by SDS–PAGE. The protein was transferred onto PVDF membrane, which was then incubated with specific primary antibody to ZBP-89 and GAPDH in 5% milk, followed by a horse radish peroxidase (HRP)-conjugated anti-rabbit or anti-mouse antibodies and ECL detection reagent (Thermo Scientific).

2.4. Immunohistochemistry and evaluation

For immunohistochemical studies, paraffin embedded sections were dewaxed in xylene (3 × 5 min) and dehydrated in ethanol series (3 min in 100% ethanol, 1 min in each of 95% and 70% ethanol). Sections were washed in PBS and endogenous peroxidases were blocked with 3% H_2O_2 for 10 min. The tissue sections were subjected to antigen retrieval by pressured cooking in 10 mM citrate buffer for 3 min, and then incubated with serum blocking solution for 20 min to block nonspecific binding, followed by incu-

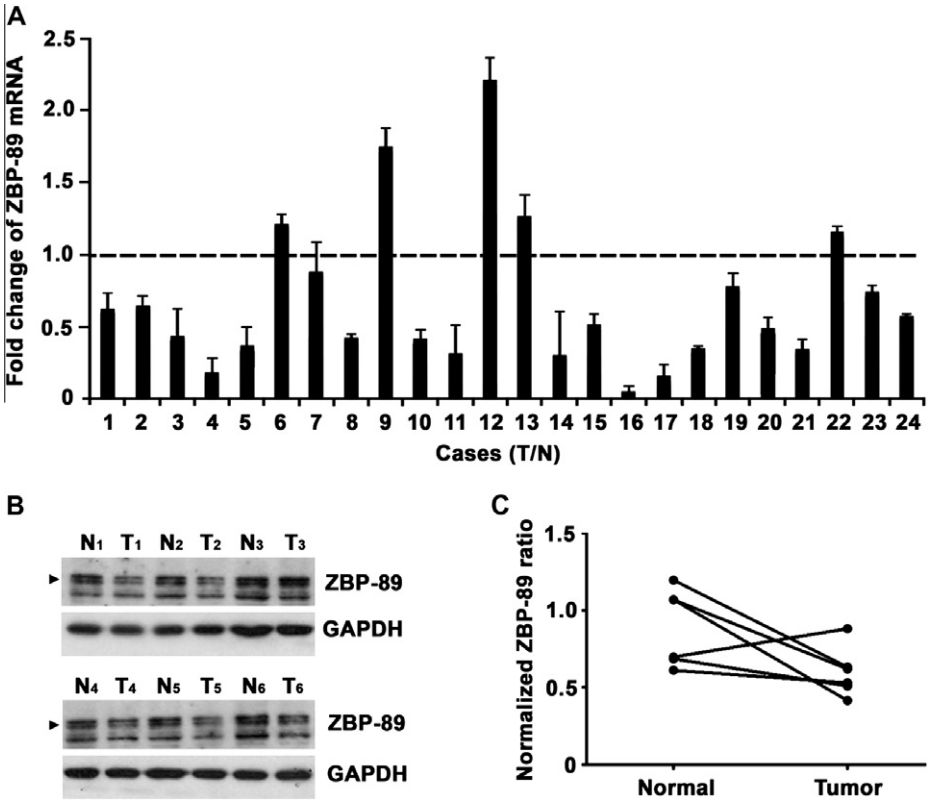

Fig. 1. The expression of ZBP-89 in CCRCC by qRT-PCR and Western Blot. (A) Fold change of ZBP-89 mRNA in CCRCC tissues (T) compared to the adjacent non-tumorous kidney tissues (N) ($n = 24$) was determined by qRT-PCR. (B) Expression of ZBP-89 protein in CCRCC tissues (T) and the adjacent non-tumorous kidney tissues (N) ($n = 6$) was examined by Western Blot. (C) The related expression of ZBP-89 in paired tissues was indicated.

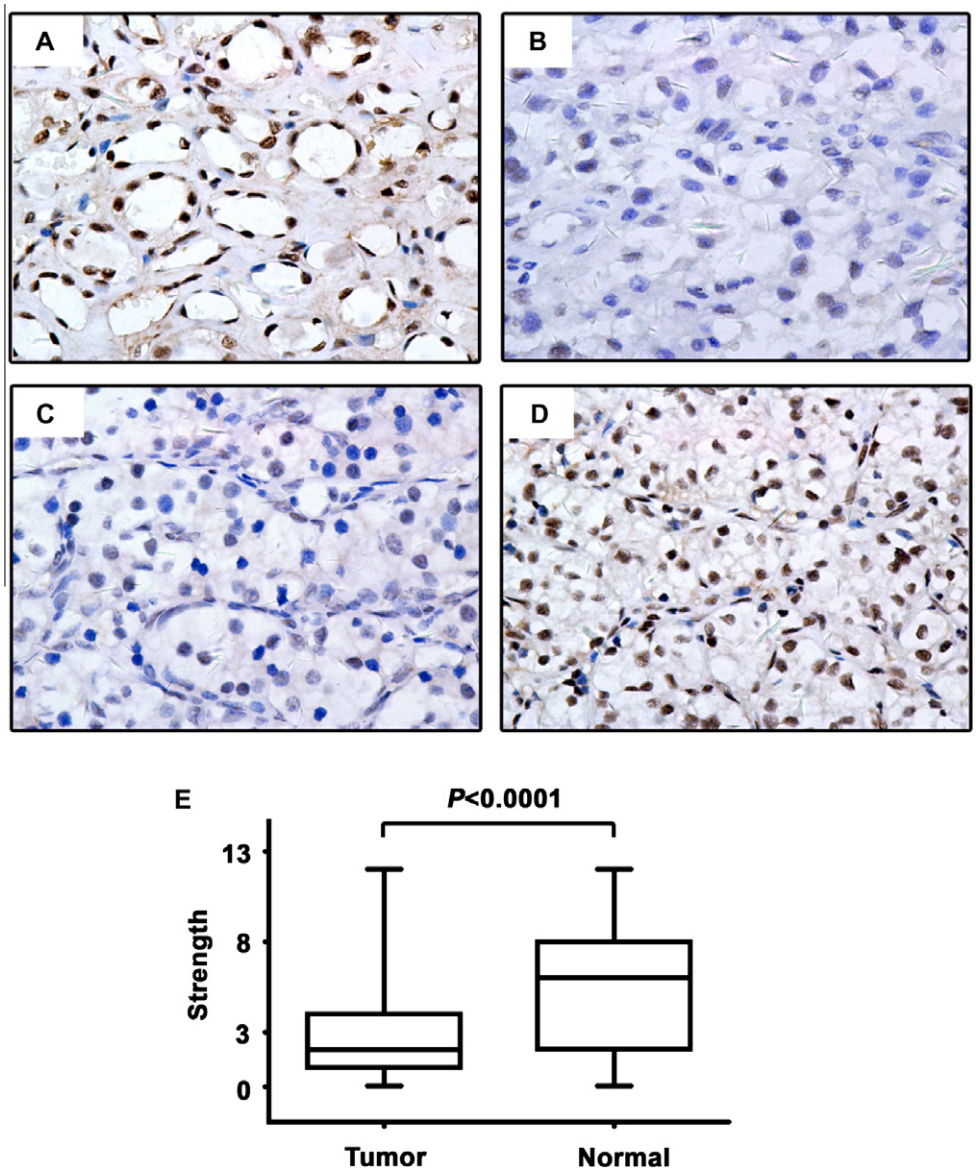

Fig. 2. The protein expression of ZBP-89 in CCRCC by immunohistochemistry. The immunoreactivity was primarily observed in the nucleus. (A) Strong staining of ZBP-89 was detected in normal kidney tissue. (B) Weak/negative expression of ZBP-89 was present in CCRCC tissue. (C) Moderate staining of ZBP-89 was observed in tumor tissue. (D) Strong staining of ZBP-89 was shown. (E) The box plot showed the mean staining score of ZBP-89 in CCRCC tissues and the adjacent non-tumorous kidney tissues.

bation with a primary antibody (polyclonal antibody, Rabbit anti-ZBP-89, Santa Cruz) for two hours at room temperature. After rinsing in PBS for 10 min, the sections were incubated with the biotinylated secondary antibody for 1 h and further incubation with the Streptavidin Biotin complex. Reactivity was developed in chromogen DAB (3,3-diaminobenzidine) solution. The signal was enhanced by applying the solution of $CuSO_4$ and NaCl for 5 min. Finally, the sections were counterstained with Mayer's hematoxylin, dehydrated, and mounted. All sections were observed under light microscopy and the staining intensities were assessed by two independent pathologists (L.R.Z. and C.M.Y.). Nucleus staining was graded for intensity (0-negative, 1-weak, 2-moderate, and 3-strong) and percentage of positive cells [0, 1 (1–24%), 2 (25–49%), 3 (50–74%), and 4 (75–100%)] with discrepancies resolved by consensus. The grades were multiplied to determine an *H*-score as described in a previous report [18]. The *H*-scores for tumors with multiple cores were averaged. Protein expression was then defined as negative (*H*-score = 0), weak (*H*-score = 1–3), or strong (*H*-score $\geqslant$ 4). We defined the negative and weak protein expression of ZBP-89 as low ZBP-89 group, and strong expression as high ZBP-89 group.

2.5. Statistical analysis

The correlations between the expression of ZBP-89 and clinicopathological parameters were analyzed with the chi-square test or Fisher's exact test. Overall survival was assessed by the Kaplan–Meier method, and log-rank test was used to analyze survival curves. Univariate and multivariate survival analyses were performed using the Cox proportional hazards regression model. Statistical significance was set at $P < 0.05$. All statistical analysis was performed by using the SPSS statistical software package (standard version 13.0; SPSS, Chicago, IL).

3. Results

3.1. The pattern of ZBP-89 expression in RCC by qRT-PCR and Western Blot

As determined by qRT-PCR, in 19 out of 24 cases, ZBP-89 mRNA expressions in CCRCC specimens were lower than those in the adjacent non-tumorous kidney tissues (Fig. 1A). A significant difference in the average level of ZBP-89 between tumor tissues and non-tumorous tissues ($P < 0.05$) was discerned. The protein levels of ZBP-89 in CCRCC tissues were detected (Fig. 1B and C). As depicted in Fig. 1B, ZBP-89 expression in tumorous tissues was on average 1.57-fold lower than that in the paired non-tumorous tissues.

3.2. The expression dynamics of ZBP-89 in RCC by immunohistochemistry

The protein level of ZBP-89 in CCRCC was further determined by IHC, using 142 pairs of tumor and adjacent non-tumorous kidney tissues. In our study, only 108 cases of RCC with adequate adjacent normal kidney tissue were used for IHC analysis. Expression of ZBP-89 was detected in 87.3% (124/142) of tumorous and 91.7% (99/108) of nontumorous tissues (Fig. 2A and D). Furthermore, low expression of ZBP-89 was detected 48.1% (52/108) in normal kidney compared with 73.9% (105/142) in cases. There is a significant difference of ZBP-89 expression in tumorous and paired non-tumorous kidney tissues (Fig. 2E, $P < 0.0001$).

3.3. The relationship between ZBP-89 expression and clinicopathological parameters

The relationship between the ZBP-89 expression and clinicopathological parameters including the patient's sex, age, tumor size, histological grade, TNM stage, T stage, node status and metastasis status was analyzed in 142 CCRCC cases that were further divided into two subgroups: 'Low ZBP-89 expression' and 'High ZBP-89 expression' as defined in the Immunohistochemistry section of Patients and Methods. A significant correlation was found between ZBP-89 expression and two clinicopathological parameters, including clinical TNM stage ($P = 0.005$) and distal metastasis ($P = 0.001$). Patients with advanced TNM stage appeared to be likely with high ZBP-89 expression in tumorous tissues than those with early TNM stage. On the other hand, patients with distal metastasis had higher ZBP-89 expression, compared to those without distal metastasis. There were no statistical association between ZBP-89 expression and the rest clinicopathological parameters ($P > 0.05$, Table 1).

We next intended to confirm the finding that ZBP-89 expression positively related to distal metastasis in CCRCC. To this end, we stratified and categorized our samples into three groups: normal, non-metastatic tumor and metastatic tumor. According to the IHC results, ZBP-89 expressions were denoted strong, weak/negative, moderate respectively in normal, non-metastatic and metastatic group (Fig. 3A and C). As expected, the expression of ZBP-89 in non-metastatic and metastatic CCRCC was significantly discrepant ($P = 0.002$, Fig. 3D).

Table 1
Correlation between ZBP-89 expression and clinicopathological parameters.

Variable	Cases ($n = 142$, %)	ZBP-89 expression		
		Low ($n = 105$)	High ($n = 37$)	P value[a]
Sex				0.226
Female	39 (27.5)	26	13	
Male	103 (72.5)	79	24	
Age[b]				0.612
⩽52	64 (45.1)	46	18	
>52	78 (54.9)	59	19	
Grade[c]				
I	21 (14.8)	17	6	0.802
II	67 (47.2)	46	15	
III	37 (26.1)	33	10	
IV	17 (11.9)	11	6	
Tumor diameter[d]				0.529
⩽6.7 cm	83 (58.5)	63	20	
>6.7 cm	59 (41.5)	42	17	
TNM stage				**0.005**
I	58 (40.8)	51	7	
II	38 (26.8)	26	12	
III	26 (18.3)	18	8	
IV	20 (14.1)	10	10	
Tumor stage				0.067
1	75 (52.8)	59	16	
2	38 (22.5)	22	16	
3	22 (15.5)	18	4	
4	7 (9.2)	6	1	
Lymph node metastasis				0.155
No	131 (92.3)	99	32	
Yes	11 (7.7)	6	5	
Distal metastasis				**0.001**
No	125 (88.0)	98	27	
Yes	17 (12.0)	7	10	

[a] Chi-square test.
[b] Mean age.
[c] Histological grade was with reference to World Health Organization (WHO) classification published in 2004.
[d] Mean diameter.

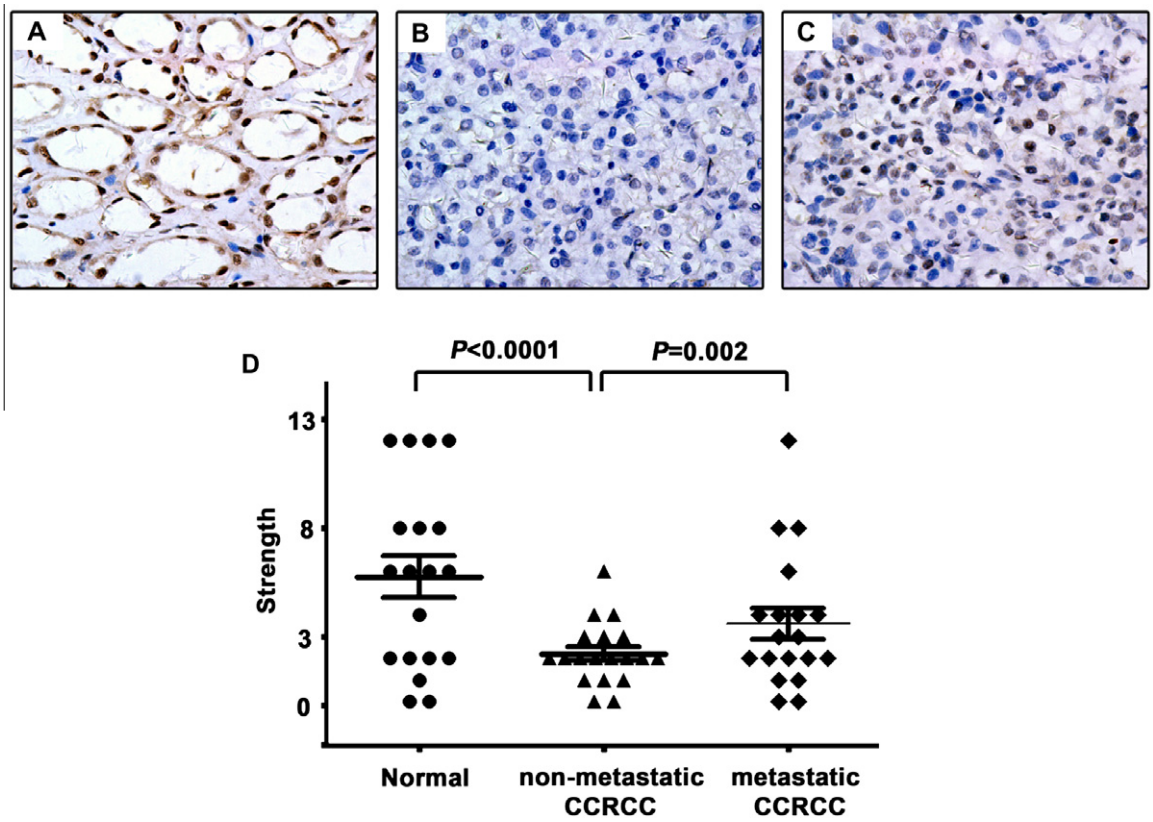

Fig. 3. ZBP-89 expression in metastatic and non-metastatic CCRCC. Representative image of ZBP-89 staining in normal kidney tissue (A), non-metastatic (B), metastatic (C) and CCRCC (D). A significant increase of ZBP-89 expression in metastatic CCRCC was shown.

3.4. The association of ZBP-89 expression in CCRCC with patient survival

The association between ZBP-89 expression in CCRCC and patient survival was analyzed by Kaplan–Meier methods (Fig. 4). Forty-one deaths were recorded in 142 patients. The mean survival time was 43.5 months, with a range of 2.9–95.2 months (Fig. 4A). The over-all survival in CCRCC patients with the high expression of ZBP-89 tended to be shorter than that of patients with low expression of ZBP-89 ($P < 0.001$, Fig. 4B).

In order to assess the prognostic value of ZBP-89 expression in CCRCC, we utilized univariate analysis to control for other prognostic factors. Results indicated that ZBP-89 ($P < 0.0001$), as well as clinical grade ($P = 0.001$), TNM stage ($P < 0.0001$), tumor stage ($P < 0.0001$), and distal metastasis ($P < 0.0001$), was responsible for efficacy of therapy in CCRCC patient, by showing that ZBP-89 expression was of significance in correlation to overall survival of CCRCC patients (Table 2).

We further subjected the statistically significant parameters to Cox proportional hazards regression model to evaluate the significance of ZBP-89 expression in CCRCC prognosis. Results suggested that ZBP-89 was also an independent predictor for overall survival (HR: 2.871, 95% CI: 1.409–5.853, $P = 0.004$) (Table 3).

4. Discussion

The present study presents compelling evidence that the transcription factor ZBP-89 is decreased in CCRCC. According to our data, about 73.9% of CCRCC patients carried low-expressed ZBP-89. We also found that ZBP-89 expression in tumor tissues significantly correlated with two clinicopathological parameters, the TNM stage and distal metastasis. Furthermore, high ZBP-89 expression in tumor was associated with poor survival of CCRCC patients. Univariate and multivariate analysis also showed ZBP-89 was a potential prognostic factor of overall survival.

ZBP-89 has been shown to be increased in some cancers, including gastric cancer [12], colorectal cancer [14] and liver cancer [15], but reduced in pancreatic adenocarcinomas [16]. However, the role of ZBP-89 in human cancers is not well studied. Therefore, the expression of ZBP-89 in cancers may differ according to cell origin. In our study, we found the ZBP-89 expression was down regulated in CCRCC and high ZBP-89 expression in tumor was associated with poor clinicopathological parameters. We speculate that ZBP-89 might play different role in the development and/or progress of CCRCC in early and late stage, since patients with distal metastasis and poor survival appear to express higher levels of the protein. ZBP-89 was suggested to play a role at the early stage of gastric cancer development, as its level was elevated in pre-malignant states of gastric cancers [19]. The involvement of ZBP-89 in the gastric tumorigenesis was further supported by the finding that the Epstein–Barr virus (EBV) *BMRF1* gene increased the binding of ZBP-89 to the *gastrin* promoter [20]. It is known that EBV infection is an etiological cause for a subset of gastric cancer [21] and that gastrin is up-regulated in a variety of pre-malignant conditions and established gastric cancers [17]. These data indicate ZBP-89 may be involved in tumor development. Importantly, ZBP-89 has been reported to regulate the expression of various molecules that are involved in the tumor growth, invasion and metastasis [7]. For example, ZBP-89 up-regulates the expression of matrix metallopeptidase 3 (MMP-3) through activating its promoter [13]. The role of ZBP-89 in the regulation of MMP-3 is further supported by the fact that mutations in the polymorphic region of the MMP-3 promoter that includes ZBP-89's binding element impair its basal and induced transcriptional activity in high microsatellite instability (MSI-H) colorectal tumors [13]. Since MMP-3 is involved in tu-

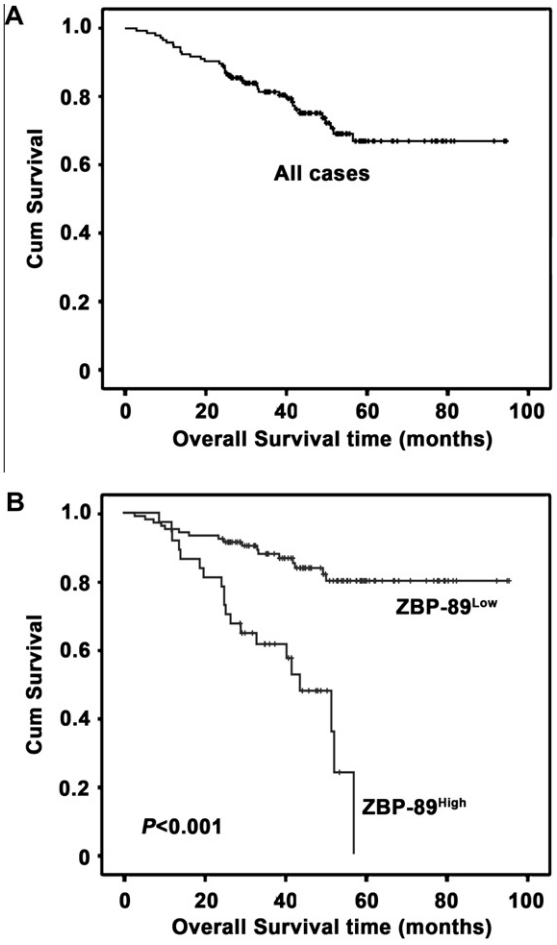

Fig. 4. Survival analysis of ZBP-89 expression in CCRCC. (A) Probability of overall survival of total CCRCC patients. (B) ZBP-89 protein level showed prognostic role in overall survival.

mor invasion and metastasis [22,23], it is plausible that ZBP-89 participates in tumor development and metastasis by regulating MMP-3. Although few literatures reported the association between MMP-3 expression and CCRCC's clinicopathological parameters, the mRNA and protein levels of MMP-3 were significantly higher in RCC tissue compared with the adjacent non-malignant renal tissue [24]. In this study, we found the high expression of ZBP-89 was related with advanced TNM stage and distal metastasis. Furthermore, ZBP-89 expressions were markedly higher in metastatic CCRCCs than those in non-metastatic ones. It is therefore reasonable to assume that high-expressed ZBP-89 upregulates MMP-3 expression in CCRCC to interweave with the invasion and metastasis of CCRCC.

One of the main findings in present study is that the high expression of ZBP-89 in CCRCC was significantly related to poor survival. To our best knowledge, this is the first report of association of ZBP-89 expression and survival in CCRCC patients. Surgical resection of the primary tumor for CCRCC patients with localized disease remains the mainstay of therapy. However, CCRCC is characterized by a lack of early warning signs, resulting in a high proportion of patients with metastases at diagnosis or relapse following nephrectomy. The prognosis for patients with distant metastases is poor, with a 5 year survival rate of less than 10% for those presenting stage IV disease [4,25]. In our study, high expression of ZBP-89 in CCRCC appeared to be a promising marker to predict distal metastasis and poor survival. It could be helpful to refine individual risk stratification and could be useful for recommendation of more aggressive therapy, according to the different expression of ZBP-89.

Table 2
Univariate analysis of ZBP-89 expression and clinicopathologic variables in CCRCC patients (log-rank test).

Variables	All cases	Mean survival (months)	Median survival (months)	*P* value
Age (years)				0.892
⩽52[a]	64	63.99	NR[b]	
>52	78	73.16	NR	
Sex				0.570
Male	103	63.15	NR	
Female	39	76.22	NR	
Grade[c]				**0.001**
I	21	88.44	NR	
II	67	72.31	NR	
III	37	61.92	NR	
IV	17	36.51	18.97	
Tumor diameter[d]				0.580
⩽6.7 cm	83	75.90	NR	
>6.7 cm	59	71.01	NR	
TNM stage				**0.000**
I	58	86.20	NR	
II	38	77.05	NR	
III	26	63.38	NR	
IV	20	29.65	25.00	
Tumor stage				**0.000**
1	75	83.75	NR	
2	38	75.41	NR	
3	22	45.17	42.47	
4	7	32.81	24.87	
Lymph node metastasis				0.272
No	131	75.14	NR	
Yes	11	56.24	NR	
Distal metastasis				**0.000**
No	125	81.91	NR	
Yes	17	23.65	24.33	
ZBP-89				**0.000**
Low expression	105	82.06	NR	
High expression	37	39.76	43.67	

[a] Mean age.
[b] NR, not reached.
[c] Histological grade was with reference to World Health Organization (WHO) classification published in 2004.
[d] Mean diameter.

Table 3
COX multivariate analysis of clinicopathological parameters and overall survival.

Variables	Hazard ratio (95% confidence interval)	*P* value
Grade	1.104 (0.700–1.742)	0.670
TNM stage	1.655 (1.035–2.645)	**0.035**
Tumor stage	1.044 (0.657–1.658)	0.856
Metastasis	6.468 (2.314–18.078)	**0.000**
ZBP-89	2.871 (1.409–5.853)	**0.004**

In conclusion, we have demonstrated in this study that ZBP-89 is down-regulated in CCRCC. High expression of ZBP-89 in CCRCC tissue associates with metastasis and advanced TNM stage. Additionally, high ZBP-89 expression in kidney cancer connects to poor overall survival. Taken together, ZBP-89 could be used as a promising metastatic and prognostic marker in CCRCC. On the other hand, further investigations are required to disclose the mechanism via which ZBP-89 is involved in the progression of CCRCC.

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References

[1] B.I. Rini, S.C. Campbell, B. Escudier, Renal cell carcinoma, Lancet 373 (2009) 1119–1132.
[2] N.K. Janzen, H.L. Kim, R.A. Figlin, A.S. Belldegrun, Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease, Urol. Clin. North. Am. 30 (2003) 843–852.
[3] A. Jemal, R. Siegel, E. Ward, T. Murray, J. Xu, M.J. Thun, Cancer statistics, CA Cancer J. Clin. 57 (2007) 43–66.
[4] R.J. Motzer, P. Russo, Systemic therapy for renal cell carcinoma, J. Urol. 163 (2000) 408–417.
[5] C. Eichelberg, K. Junker, B. Ljungberg, H. Moch, Diagnostic and prognostic molecular markers for renal cell carcinoma: a critical appraisal of the current state of research and clinical applicability, Eur. Urol. 55 (2009) 851–863.
[6] J.M. Hollingsworth, D.C. Miller, S. Daignault, B.K. Hollenbeck, Rising incidence of small renal masses: a need to reassess treatment effect, J. Nat. Cancer Inst. 98 (2006) 1331–1334.
[7] C.Z. Zhang, G.G. Chen, P.B. Lai, Transcription factor ZBP-89 in cancer growth and apoptosis, Biochim. Biophys. Acta 2010 (1806) 36–41.
[8] G.L. Law, H. Itoh, D.J. Law, G.J. Mize, J.L. Merchant, D.R. Morris, Transcription factor ZBP-89 regulates the activity of the ornithine decarboxylase promoter, J. Biol. Chem. 273 (1998) 19955–19964.
[9] Y. Wu, X. Zhang, M. Salmon, Z.E. Zehner, The zinc finger repressor, ZBP-89, recruits histone deacetylase 1 to repress vimentin gene expression, Genes Cells 12 (2007) 905–918.
[10] A.C. Keates, S. Keates, J.H. Kwon, K.O. Arseneau, D.J. Law, L. Bai, J.L. Merchant, T.C. Wang, C.P. Kelly, ZBP-89, Sp1, and nuclear factor-kappa B regulate epithelial neutrophil-activating peptide-78 gene expression in Caco-2 human colonic epithelial cells, J. Biol. Chem. 276 (2001) 43713–43722.
[11] L. Bai, J.L. Merchant, Transcription factor ZBP-89 cooperates with histone acetyltransferase p300 during butyrate activation of p21waf1 transcription in human cells, J. Biol. Chem. 275 (2000) 30725–30733.
[12] K. Vesely, M. Jurajda, R. Nenutil, M. Vesela, Expression of p53, cyclin D1 and EGFR correlates with histological grade of adult soft tissue sarcomas: a study on tissue microarrays, Neoplasma 56 (2009) 239–244.
[13] A. Moran, P. Iniesta, C. de Juan, C. Garcia-Aranda, A. Diaz-Lopez, M. Benito, Impairment of stromelysin-1 transcriptional activity by promoter mutations in high microsatellite instability colorectal tumors, Cancer Res. 65 (2005) 3811–3814.
[14] T. Frensing, C. Kaltschmidt, T. Schmitt-John, Characterization of a neuregulin-1 gene promoter: positive regulation of type I isoforms by NF-kappaB, Biochim. Biophys. Acta 1779 (2008) 139–144.
[15] C.Z. Zhang, Y. Cao, J.P. Yun, G.G. Chen, P.B. Lai, Increased expression of ZBP-89 and its prognostic significance in hepatocellular carcinoma, Histopathology, 2012.
[16] L. Bai, C. Logsdon, J.L. Merchant, Regulation of epithelial cell growth by ZBP-89: potential relevance in pancreatic cancer, Int. J. Gastrointest. Cancer 31 (2002) 79–88.
[17] C. Chao, M.R. Hellmich, Gastrin, inflammation, and carcinogenesis, Curr. Opin. Endocrinol. Diabetes Obes. 17 (2010) 33–39.
[18] M.T. Galgano, G.M. Hampton, H.F. Frierson Jr., Comprehensive analysis of HE4 expression in normal and malignant human tissues, Mod. Pathol. 19 (2006) 847–853.
[19] T. Taniuchi, E.R. Mortensen, A. Ferguson, J. Greenson, J.L. Merchant, Overexpression of ZBP-89, a zinc finger DNA binding protein, in gastric cancer, Biochem. Biophys. Res. Commun. 233 (1997) 154–160.
[20] E.A. Holley-Guthrie, W.T. Seaman, P. Bhende, J.L. Merchant, S.C. Kenney, The Epstein–Barr virus protein BMRF1 activates gastrin transcription, J. Virol. 79 (2005) 745–755.
[21] M. Fukayama, R. Hino, H. Uozaki, Epstein–Barr virus and gastric carcinoma: virus–host interactions leading to carcinoma, Cancer Sci. 99 (2008) 1726–1733.
[22] A. Juncker-Jensen, J. Romer, C.J. Pennington, L.R. Lund, K. Almholt, Spontaneous metastasis in matrix metalloproteinase 3-deficient mice, Mol. Carcinog. 48 (2009) 618–625.
[23] C.H. Tang, A. Yamamoto, Y.T. Lin, Y.C. Fong, T.W. Tan, Involvement of matrix metalloproteinase-3 in CCL5/CCR5 pathway of chondrosarcomas metastasis, Biochem. Pharmacol. 79 (2010) 209–217.
[24] V. Bhuvarahamurthy, G.O. Kristiansen, M. Johannsen, S.A. Loening, D. Schnorr, K. Jung, A. Staack, In situ gene expression and localization of metalloproteinases MMP1, MMP2, MMP3, MMP9, and their inhibitors TIMP1 and TIMP2 in human renal cell carcinoma, Oncol. Rep. 15 (2006) 1379–1384.
[25] A.S. Belldegrun, T. Klatte, B. Shuch, J.C. LaRochelle, D.C. Miller, J.W. Said, S.B. Riggs, N. Zomorodian, F.F. Kabbinavar, J.B. Dekernion, A.J. Pantuck, Cancer-specific survival outcomes among patients treated during the cytokine era of kidney cancer (1989–2005): a benchmark for emerging targeted cancer therapies, Cancer 113 (2008) 2457–2463.