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Original contribution

Loss of DUSP2 predicts a poor prognosis in patients with bladder cancer☆,☆☆

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Summary Dual-specificity phosphatase 2 (DUSP2), a member of nuclear type I DUSP family, abolishes the activation of mitogen-activated protein kinases (MAPKs) and plays critical roles in the immune processes, inflammatory responses, and cancer progression. Currently, whether DUSP2 is involved in pathogenesis of bladder cancer remains unclear. In this study, we demonstrate that the expression level of DUSP2 was predominantly downregulated in bladder cancer tissues and cell lines as compared with that of paired normal tissues and benign urothelial cells. Besides, the expression of DUSP2 was significantly associated with pathological grade (P = .009), AJCC stage (P = .017), and subtype (P = .001) in The Cancer Genome Atlas cohort and mainly related to TNM stage (P = .016) in the tissue microarray cohort. Kaplan-Meier analysis suggested that patients with low DUSP2 expression had a shorter 5-year overall survival (P = .018 in The Cancer Genome Atlas; P = .012 in tissue microarray) and lower recurrence-free survival (P = .008). Cox regression analysis indicated that reduced DUSP2 was an independent high risk factor for survival prognosis in both cohorts. Taken together, our findings for the first time suggested DUSP2 as a progression and prognosis biomarker for bladder cancer. Whether DUSP2 functions as a tumor suppressor in bladder cancer deserves further studies.

1. Introduction

Bladder cancer is the 10th most common malignant tumors, with estimated 549 000 new cases emerged and 200 000 deaths worldwide in 2018 [1], which is a tremendous burden on health care systems. More than 70% of bladder cancer patients are diagnosed as having the non–muscle-invasive type that has a high rate of recurrence [2]. However, muscle-invasive (MIBC) or metastatic diseases are developed in 25% of patients at the time of initial diagnosis. The long-term survival of those patients is still unsatisfied with a 5-year survival rate of less than 60% [3]. Thus, a series of novel independent biomarkers based on integrated genomic analysis are urgently needed for bettering prediction of clinical outcomes in patients with bladder cancer.

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Dual-specificity phosphatase 2 (DUSP2), also known as phosphatase of activated cells 1 (PAC-1), is a member of the protein tyrosine phosphatase gene superfamily. The role of DUSP2 is to specifically dephosphorylate both phosphoserine/threonine and phosphotyrosine residues in mitogen-activated protein kinases (MAPKs) that consist of JNK, ERK, and p38, thereby modulating inflammatory response through inactivating MAPKs [4]. Inversely, ERK1/2 activation can induce DUSP2 expression, suggesting that a negative feedback loop is established between DUSP2 and MAPKs for mutual regulation [5]. DUSP2 was also shown as a p53 target gene in fibroblasts exposed to oxidative stress, and knockdown of DUSP2 with siRNA regained the activation of ERK and reduced apoptosis [6]. Recently, a growing number of studies have focused on the role of DUSP2 in various cancers. DUSP2 can act as a tumor suppressor in colon cancer [7,8], pancreatic ductal adenocarcinoma [9], ovarian carcinoma [10], and acute leukemia [11]. However, the expression and biological role of DUSP2 in bladder cancer remain obscure.

In this study, we first focused on the gene expression level of DUSP2 using publicly available databases, The Cancer Genome Atlas (TCGA) and Oncomine. Clinical bladder cancer samples and cell lines were used for further analysis on the differential expression of DUSP2. Clinical significance and prognostic value of DUSP2 were assessed with TCGA and tissue microarray (TMA) cohort. The results suggest DUSP2 as a progression and prognosis biomarker for bladder cancer.

2. Materials and methods

2.1. Patients and clinical specimens of bladder cancer

Sixteen cases of cancer specimens and paired adjacent noncancerous tissues were collected from patients diagnosed as having primary bladder cancer between September 2017 and August 2018 in the First Affiliated Hospital of Chongqing Medical University. The samples of TMA were collected from 56 patients (56 bladder cancer tissues and 10 adjacent nontumorous samples) with detailed clinical information who had undergone surgery between May 2007 and November 2011 at the National Engineering Center of Biochip in Shanghai. All patients were followed up until March 2014, and the follow-up period ranged from 2.3 to 7 years after surgery.

Ethics approval required was obtained from the ethic committees of local hospital and biobank center–related hospitals, and a written informed consent was signed by each participant before sample collection.

2.2. Cell lines and cell culture

Human bladder cancer cell lines (5637, UM-UC-3, TCCSUP, and T24) were purchased from the American Type Culture Collection (ATCC, Manassas, VA); RT4 was purchased from the Procell Life Technology Company (Wuhan, China); human ureteral epithelium immortalized cell, SV-HUC-1, was purchased from ATCC. Cells were cultured in complete medium and incubated in a humidified atmosphere with 5% CO_2 at 37°C.

2.3. Immunohistochemistry

Immunohistochemial staining of formalin-fixed, paraffin-embedded was performed as previously described [12]. Briefly, deparaffinized sections were immersed in 0.01 mol/L sodium citrate buffer (pH 6.0; boiling temperature, 30 minutes) for antigen retrieval, incubated with 3% hydrogen peroxide for 10 minutes, blocked with 10% goat serum for 15 minutes at room temperature, incubated with primary antibodies (Abcam Inc., Cambridge, MA, USA, ab137640) at 4°C overnight, washed with phosphate-buffered saline (PBS) 3 times, and incubated with secondary antibody for 20 minutes at room temperature. Then the slides were stained by 3,3′-diaminobenzidine kit (ZSGB-BIO, Beijing, China) and counterstained using hematoxylin. Two experienced pathologists independently evaluated the results without any information on the samples based on the immunohistochemistry (IHC) score calculated according to the staining intensity and extent; the score criterion was described specifically in previous study [13]. An IHC score of >3 was defined as DUSP2 high, and ≤3 was regarded as DUSP2 low.

2.4. Quantitative real-time polymerase chain reaction

Total RNA was extracted from bladder cancer cell lines and specimens using Trizol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions. Complementary DNA was synthesized using the PrimeScript RT reagent kit (Takara, Osaka, Japan). Quantitative real-time polymerase chain reaction (qRT-PCR) was performed using SYBR Green assay (Takara) and executed by ABI 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Primer sequences used were shown as follows: DUSP2, forward primer: 5′-TGCCCCAACCACTTTGAGG-3′, reverse primer: 5′-AGTCAATGAAGCCTATGGCCT-3′; β-actin, forward primer: 5′-CATGTACGTTGCTATCCAGGC-3′, reverse primer: 5′-CTCCTTAATGTCACGCACGAT-3′. Relative quantification values of DUSP2 were calculated with the use of $2^{-\triangle\triangle CT}$ method.

2.5. Western blot

Total proteins of tissues and cells were extracted using RIPA lysis buffer (Beyotime, Haimen, China) and PMSF (Beyotime). Concentration of protein was measured by a bicinchoninic acid kit (Beyotime). Protein was separated by 8% to 12% sodium dodecyl sulfate–polyacrylamide gel electrophoresis and electrotransferred to polyvinylidene difluoride membranes (Merck

Millipore, Darmstadt, Germany). The membranes were blocked with 5% nonfat milk for 1 hour at room temperature and incubated with primary anti-DUSP2 (Abcam; ab137640) and anti–β-actin (Abcam; ab8226) overnight at 4°C. After washing with TBST, the bands were incubated with antirabbit IgG, horseradish peroxidase–linked antibody (Cell Signaling Technology, Inc., Danvers, MA, CST #7074) for 1.5 hours at room temperature and detected using electrochemiluminescence assay.

2.6. Immunofluorescence

5637 and T24 cells were fixed with 4% formaldehyde for 10 minutes and permeabilized with 0.5% Trition X-100 (Sigma, St Louis, MO) for 15 minutes at room temperature, blocked with goat serum for 20 minutes, and then incubated with anti-DUSP2 overnight at 4°C. After washing with PBS, samples were labeled with IgG H&L (Alexa Fluor 488;

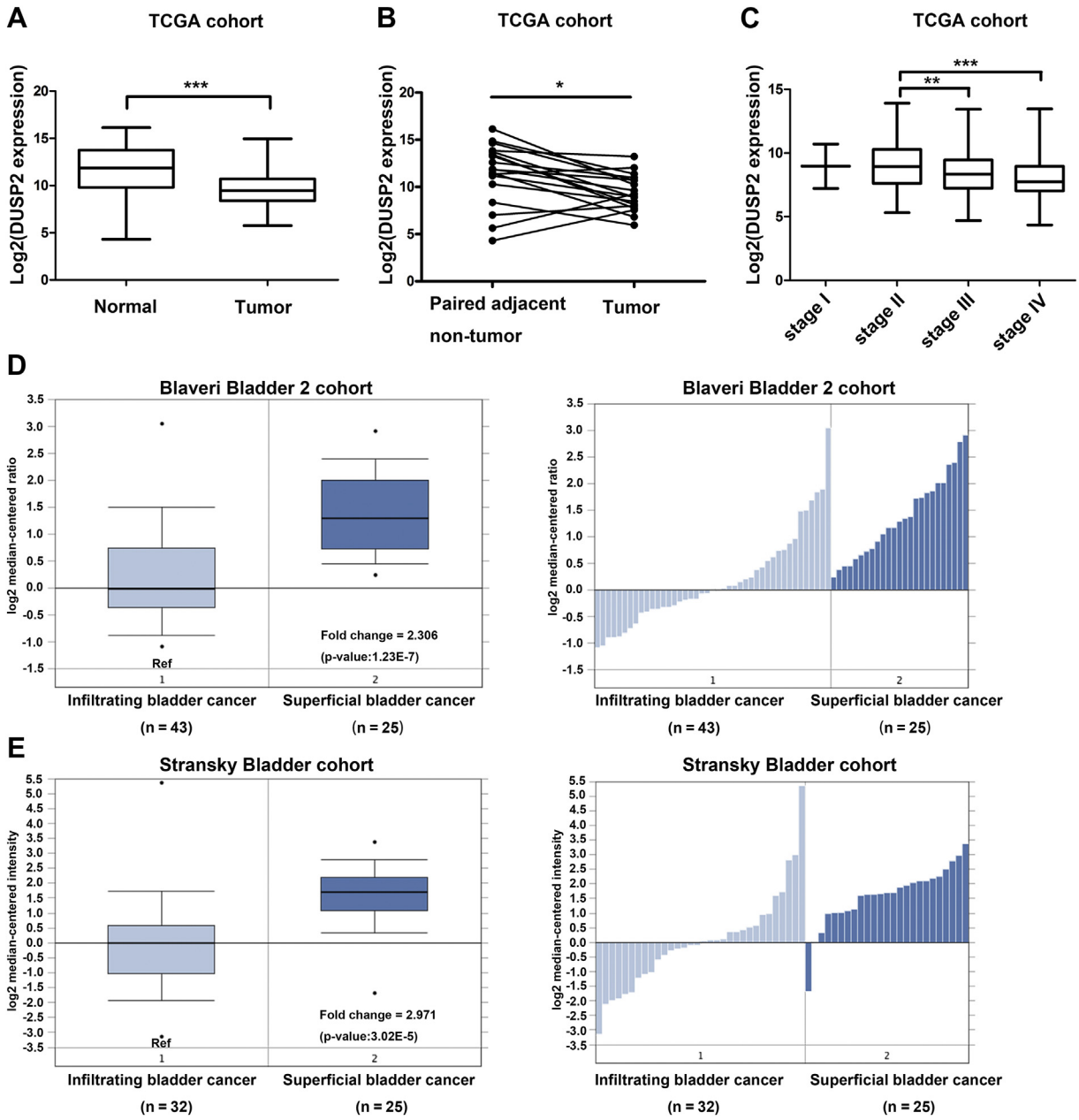

Fig. 1 The expression of DUSP2 in bladder cancer in TCGA and Oncomine databases. A, The mRNA level of DUSP2 was analyzed using TCGA cohort containing 414 bladder cancer samples and 18 normal samples. Median with interquartile range is marked. B, mRNA expression of DUSP2 was compared in 18 normal tissues and corresponding matched cancer tissues from TCGA cohort. C, The expression level of DUSP2 among different TNM stages in TCGA cohort. D and E, Comparison of the expression of DUSP2 between invasive and superficial subtypes in Blaveri bladder 2 (D) and Stransky bladder (E) data sets from Oncomine database. *$P < .05$, **$P < .01$, **$P < .001$.

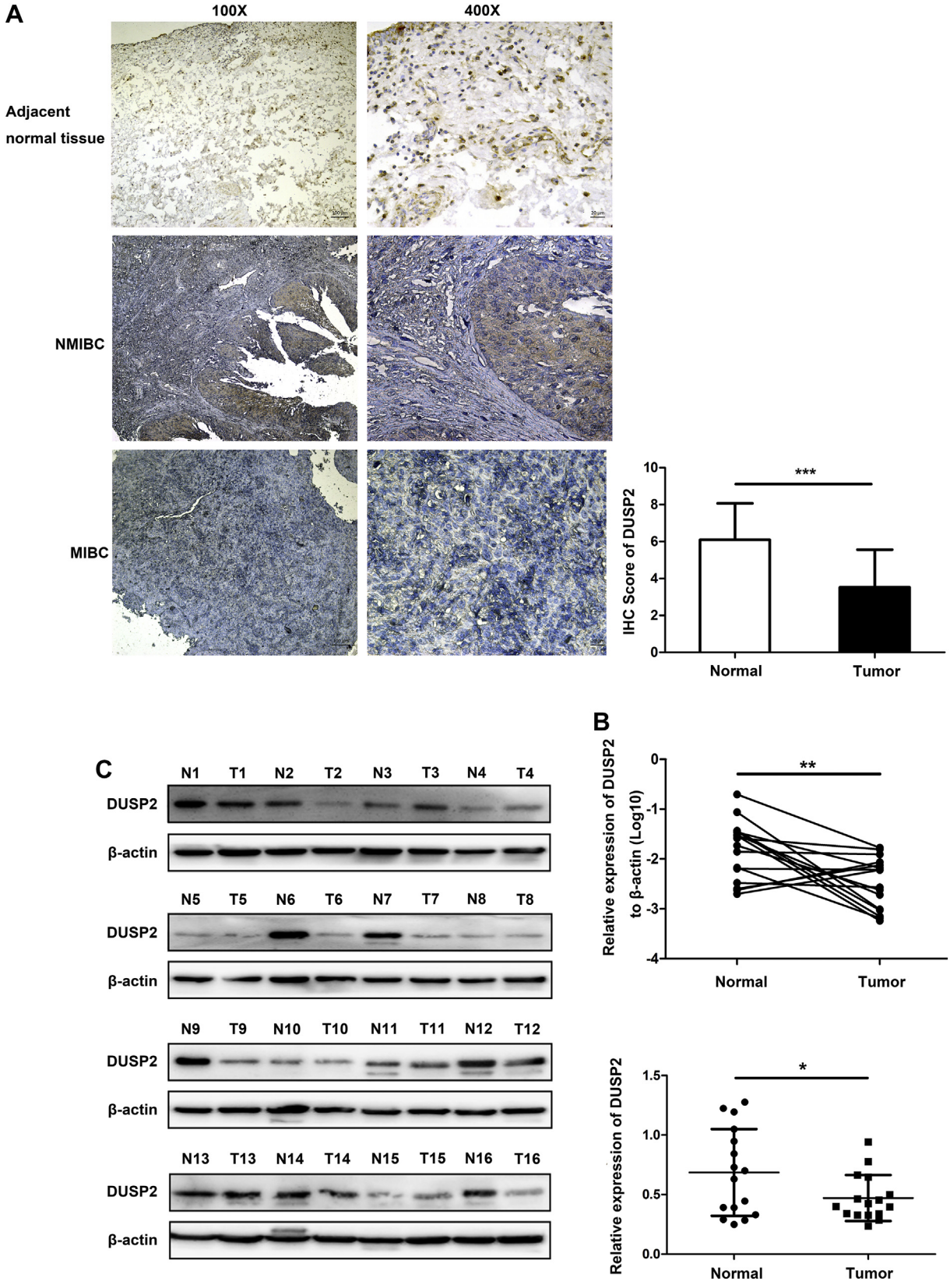

Fig. 2 Detection of DUSP2 expression in tissues by IHC staining, qRT-PCR, and Western blot. A, IHC analysis of DUSP2 protein expression in nontumorous samples, NIMBC and MIBC tissues. The difference of DUSP2 IHC score in normal and cancer tissues is shown. Scale bar, 100 μm. B and C, The mRNA and protein expression levels of DUSP2 were significantly reduced in 16 paired tumors than in adjacent normal tissues using qRT-PCR and Western blot. *$P < .05$, **$P < .01$, ***$P < .001$.

Abcam; ab150077) for 1 hour in a dark place, washed with PBS, and stained with DAPI for 10 minutes. Later, samples were visualized under a confocal laser scanning microscope (Olympus Fluoview 2000, Andor Belfast UK).

2.7. Bioinformatics analysis of Oncomine and TCGA database

DUSP2 expression in bladder cancer patients and their clinical information were obtained from TCGA database. Only when patients were recorded with complete RNAseq data and fully clinicopathological information including pathological grade, pathological stage, subtype, overall survival (OS), and recurrence-free survival (RFS) data were those individuals enrolled for further analysis. At last, 299 cases of bladder cancer patients were included for OS analysis and 274 for RFS analysis in our study.

To evaluate the messenger RNA (mRNA) expression level of DUSP2 in bladder cancer, we used the data sets in the Oncomine database. The threshold criterions were listed below: fold change ≥2, $P \leq 1E{-}4$. Collectively, Blaveri bladder 2 [14] and Stransky bladder data sets [15] were included in our study.

2.8. Statistical analysis

Statistical analyses were carried out by SPSS version 22.0 software (SPSS, Chicago, IL) and GraphPad 5.0 (GraphPad Software, San Diego, CA). The correlations between DUSP2 expression and clinicopathological parameters were evaluated using the χ^2 test. Univariate and multivariate analyses of prognosis were conducted using the Cox proportional hazard regression model. Survival curves were plotted using the Kaplan-Meier analysis and log-rank test. Comparisons between 2 groups were performed using the Student *t* test. A *P* value of <.05 was considered statistically significant.

3. Results

3.1. The expression of DUSP2 is downregulated in human bladder cancer

To explore whether DUSP2 expression differs between bladder cancer and normal bladder tissues, we first examined RNA sequencing data extracted from the TCGA database containing 414 cases of bladder cancer and 18 normal tissues. The

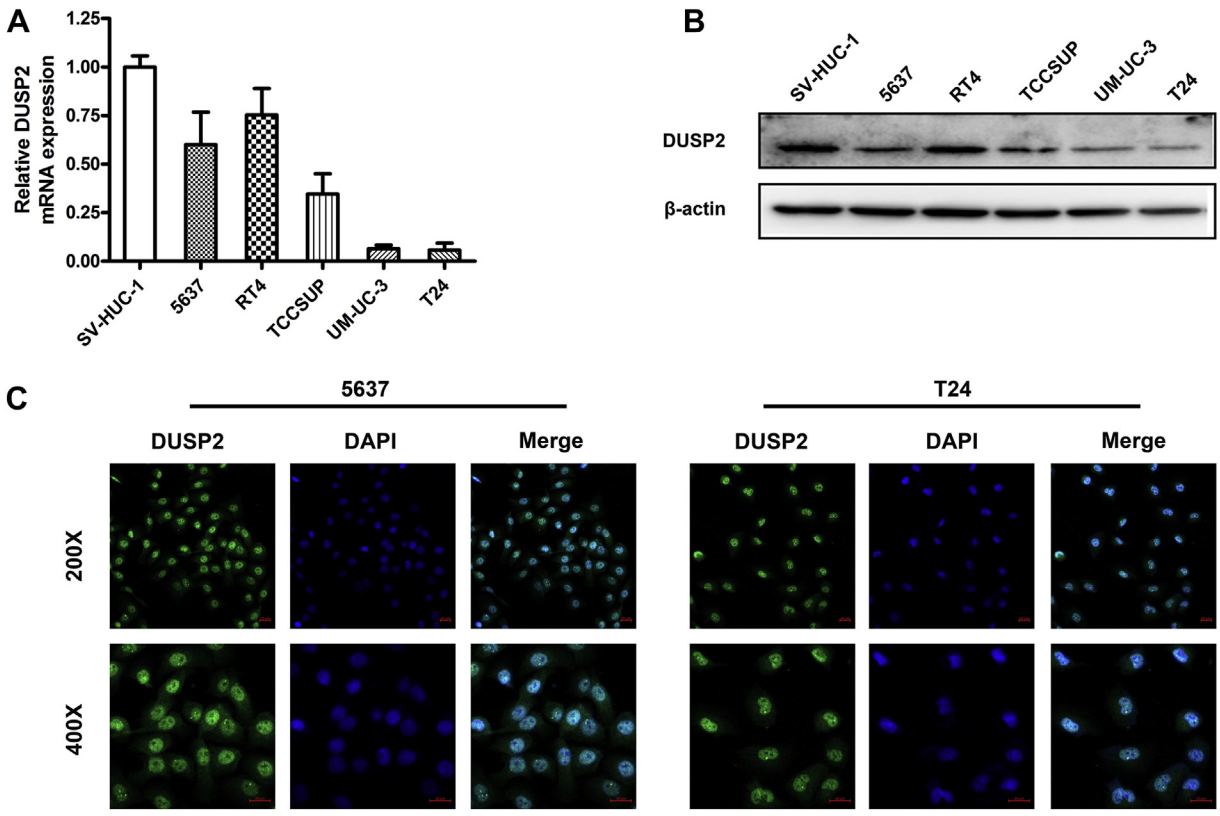

Fig. 3 The expression of DUSP2 in bladder cancer cell lines. A and B, The mRNA and protein expressions of DUSP2 detected by qRT-PCR and Western blot were decreased in several bladder cancer cell lines compared with normal urothelial cell line SV-HUC-1. C, Immunofluorescence showed that DUSP2 protein was mainly localized in the nucleus and some scattered across the cytoplasm in 5637 and T24 cells. Scale bar, 20 μm. $^{**}P < .01$, $^{**}P < .001$.

expression of DUSP2 was significantly higher in normal tissues than that in tumors (Fig. 1A). Similar result was obtained when 18 normal tissues were chosen to make a comparison with their matched cancer tissues (Fig. 1B). The mRNA expression of DUSP2 was gradually decreased with tumor progression when the cancer cases were grouped by pathological stages (Fig. 1C). Furthermore, analysis of representative data sets of Blaveri bladder 2 and Stransky bladder from the Oncomine database revealed that DUSP2 mRNA was significantly lower in invasive malignant bladder cancer compared with that of noninvasive superficial bladder cancer (Fig. 1D and E).

3.2. DUSP2 mRNA and protein expression level of in bladder cancers

To confirm DUSP2 expression suppression in bladder cancer, TMA containing 56 cases of bladder cancer tissues and 10 paired adjacent nontumorous tissues was used as a validation cohort. As shown in Fig. 2A, high DUSP2 expression was predominantly observed in most of the normal tissues (8/10) while in part of noninvasive tumors (7/16) and in the minority of MIBC tissues (11/40). DUSP2 localization was mainly in the cytoplasm and nucleus. IHC score revealed that DUSP2 staining was weaker in tumors than in normal tissues. We then analyzed expression of DUSP2 mRNA in 16 paired bladder cancer and normal tissues by qRT-PCR and found that DUSP2 was downregulated in bladder tumors in comparison with that in normal tissues (Fig. 2B), which was consistent with the trend seen in the TCGA and Oncomine databases. Next, the protein expression of DUSP2 in tissue samples was determined by Western blot. The result showed that the protein level of DUSP2 was also lower in tumors than that in normal tissues (Fig. 2C).

3.3. The expression of DUSP2 is decreased in bladder cancer cell lines

To further confirm DUSP2 expression suppression in bladder cancer, we measured DUSP2 mRNA and protein expression in human bladder cancer cell lines (5637, RT4, TCCSUP, UM-UC-3, and T24) and a human normal urothelial cell line (SV-HUC-1). qRT-PCR and Western blot results showed that bladder cancer cells had a lower mRNA and protein expression of DUSP2 compared with the normal SV-HUC-1 cells (Fig. 3A and B). Moreover, DUSP2 expression was much lower in cancer cells (5637, UM-UC-3, T24, and TCCSUP) that have high malignancy than in RT4 that has a lower histologic grade. In 5637 and T24 cells, DUSP2 protein was detected by immunofluorescence assay, and the results showed that DUSP2 protein was mainly localized to the nucleus and partially distributed to the cytoplasm (Fig. 3C).

3.4. The correlations of DUSP2 expression to clinicopathological characteristics and survival prognosis of bladder cancer patients

Two hundred ninety-nine cases of bladder cancer patients from TCGA cohort and 56 participants from TMA cohort with

Table 1 The relationship between DUSP2 and clinicopathological characteristics in patients with bladder cancer from TCGA cohort

Parameter	TCGA cohort			
	n	Low (n = 144)	High (n = 155)	*P*
Age (y)				.961
≤65	120	58	62	
>65	179	86	93	
Sex				.338
Female	76	33	43	
Male	223	111	112	
Grade				.009 **
Low	14	2	12	
High	285	142	143	
AJCC stage				.017 *
II	99	38	61	
III-IV	200	106	94	
Subtype				.001 **
Papillary	89	30	59	
Nonpapillary	210	114	96	
Recurrence				.093
No	205	92	113	
Yes	94	52	42	

NOTE. *P* values were calculated using the χ^2 test.
* $P < .05$.
** $P < .01$.

Table 2 The relationship between DUSP2 and clinicopathological characteristics in patients with bladder cancer from TMA cohort

Parameter	TMA cohort			
	n	Low (n = 28)	High (n = 28)	*P*
Age (y)				.265 [a]
≤65	20	8	12	
>65	36	20	16	
Sex				.467 [b]
Female	9	6	3	
Male	47	22	25	
Grade				1.000 [b]
Low	3	1	2	
High	53	27	26	
TNM stage				.016 *, [a]
I-II	27	9	18	
III-IV	29	19	10	
Subtype				.342 [a]
Papillary	13	8	5	
Non-Papillary	43	20	23	

[a] *P* values were calculated using the χ^2 test.
[b] *P* values were calculated using the corrected χ^2 test.
* $P < .05$.

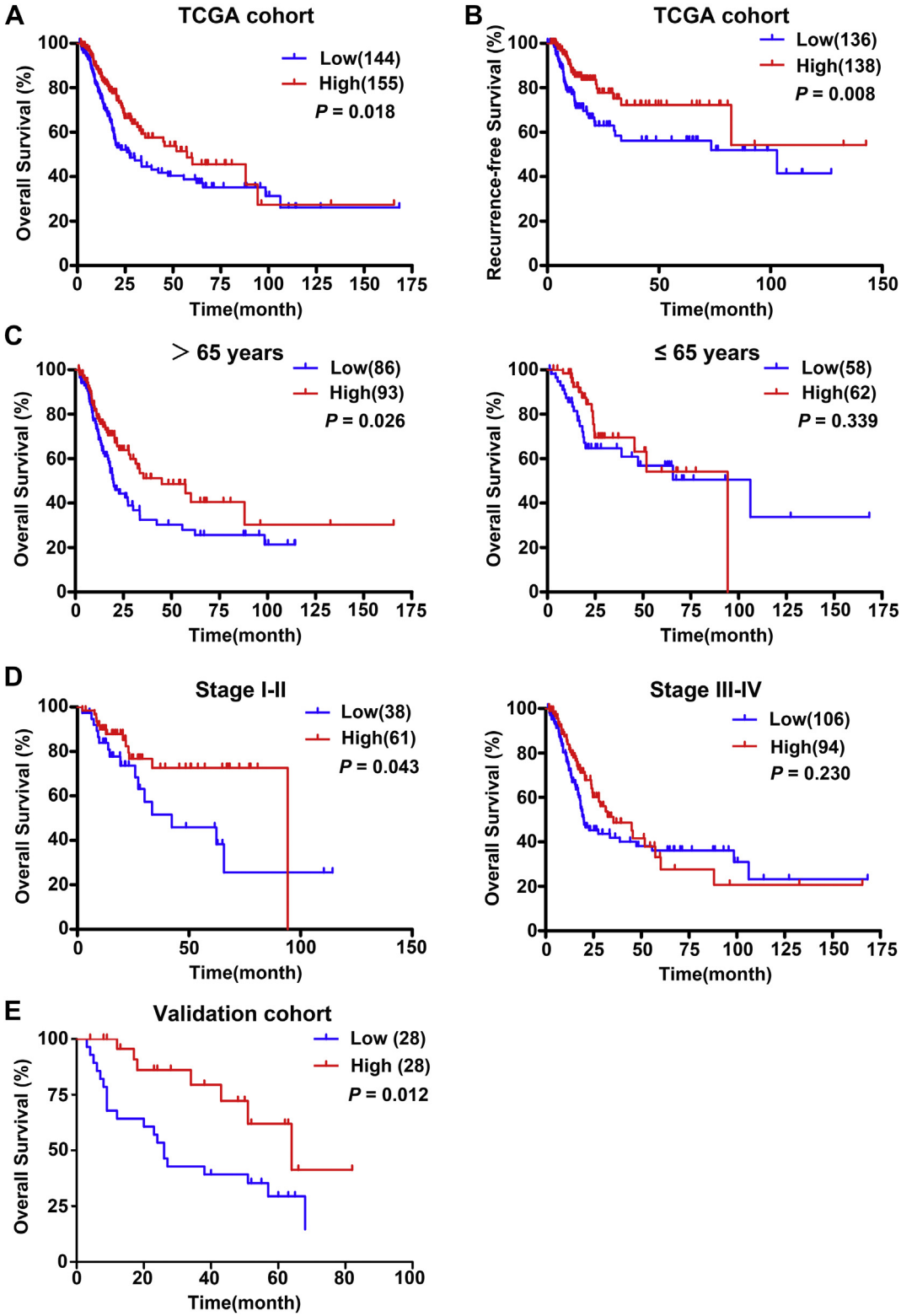

Fig. 4 Kaplan-Meier plots of survival according to DUSP2 expression. A and B, Kaplan-Meier estimates of OS (A) and RFS (B) in the DUSP2-high group and DUSP2-low group from TCGA cohort. C and D, Kaplan-Meier curves of OS in different subgroups stratified by age (C) and TNM stage (D) and classified into DUSP2 high and DUSP2 low. E, Kaplan-Meier survival curve shows that low expression of DUSP2 predicted worse prognosis in patients with bladder cancer in validation cohort. *P* value was calculated by log-rank test.

detailed clinicopathological information and follow-up records were divided into high- and low-expression groups according to the cutoff value of normalized mRNA expression of DUSP2 and median value of IHC score, respectively. The correlation of DUSP2 expression with clinical parameters was analyzed and summarized in Tables 1 and 2. The expression of DUSP2 was mainly associated with TNM stage ($P = .016$) in the TMA cohort and was closely associated with pathological grade ($P = .009$), AJCC stage ($P = .017$), and cancer subtypes ($P = .001$) in the TCGA cohort. Kaplan-Meier analysis showed that bladder cancer patients with low DUSP2 expression had shorter OS ($P = .018$, Fig. 4A) and RFS time ($P = .008$, Fig. 4B) than did those with high DUSP2 expression In addition, univariate Cox regression analysis revealed that reduced DUSP2 expression was significantly correlated with a poor OS both in the TCGA group (hazard ratio [HR], 0.656; 95% confidence interval [CI], 0.461-0.934; $P = .019$) and in the TMA group (HR, 0.297; 95% CI, 0.125-0.702; $P = .006$; Table 3). Multivariate analysis performed using the Cox proportional hazards model indicated that DUSP2 expression was an independent prognostic factor for OS in patients with bladder cancer, with an HR of 0.698 in TCGA (95% CI, 0.489-0.995; $P = .047$) and 0.321 in TMA (95% CI, 0.135-0.764; $P = .010$), along with age (HR, 1.974; 95% CI, 1.338-2.913; $P = .001$), pathological stage (in TCGA: HR, 1.555; 95% CI, 1.023-2.364, $P = .039$; in TMA: HR, 2.637; 95% CI, 1.160-5.995; $P = .021$) and recurrence status (HR, 2.353; 95% CI, 1.655-3.346 0.;; $P < .001$; Table 3). These results suggested that low expression of DUSP2, advanced age, high TNM stage, and recurrence led to unfavorable clinical outcome in bladder cancer patients. We therefore stratified the subjects originated from TCGA into several subgroups according to age (> 65 years versus ≤65 years) and TNM stage (stages I-II versus stages III-IV). Low DUSP2 expression was correlated with a poor prognosis for OS in elder subgroup ($P = .026$) but not in young group (Fig. 4C). Lows DUSP2 predicted an unfavorable outcome in the stage II subgroup ($P = .043$) but not in the stage III-IV group (Fig. 4D). Furthermore, patients with bladder cancer were categorized into high and low subgroups in validation

Table 3 Univariate and multivariate Cox regression analysis for OS of patients with bladder cancer

Variates	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
TCGA cohort				
Age (>65 y *vs* ≤65 y)	1.880 (1.278-2.765)	.001 **	1.974 (1.338-2.913)	.001 **
Sex (male *vs* female)	0.996 (0.673-1.476)	.986	–	–
Grade (high *vs* low)	2.155 (0.531-8.745)	.282	–	–
AJCC stage (III-IV *vs* II)	1.902 (1.257-2.879)	.002 **	1.555 (1.023-2.364)	.039 *
Subtype (nonpapillary *vs* papillary)	1.579 (1.024-2.433)	.038 *	1.363 (0.881-2.108)	.164
Recurrence (yes *vs* no)	2.465 (1.741-3.492)	<.001 ***	2.353 (1.655-3.346)	<.001 ***
DUSP2 (high *vs* low)	0.656 (0.461-0.934)	.019 *	0.698 (0.489-0.995)	.047 *
TMA cohort				
Age (>65 y *vs* ≤65 y)	1.080 (0.485–2.405)	.851	–	–
Sex (male *vs* female)	0.607 (0.243–1.518)	.286	–	–
Grade (high *vs* low)	0.655 (0.154–2.796)	.568	–	–
TNM stage (III-IV *vs* I-II)	2.864 (1.277–6.422)	.011 *	2.637 (1.160–5.995)	.021 *
Subtype (nonpapillary *vs* papillary)	1.571 (0.594–4.160)	.363	–	–
DUSP2 (high *vs* low)	0.297 (0.125–0.702)	.006 **	0.321 (0.135–0.764)	.010 *

NOTE. "–" indicates that there is no information of patients in this cohort.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

cohort from TMA samples, and the cases in the DUSP2-low group had a significantly shorter OS time than did those in the DUSP2-high group ($P = .012$, Fig. 4E).

4. Discussion

DUSPs can negatively regulate MAPKs activity through the Thr-Xaa-Tyr motif dephosphorylation, act as particularly key negative regulators, and modulate MAPKs subcellular localization [16-19]. Emerging evidence has shown that these specific phosphatases may be aberrantly regulated in many cancers. DUSP2 is generally involved in multiple biological processes through modulation of ERK1/2 and p38 in immune response and inflammatory diseases, as well as multiple cancers. However, the expression level of DUSP2 and its role in bladder cancer have been still elusive.

Previous research suggested that the transcript level of DUSP2 was downregulated in several cancers and their corresponding cancer cell lines [20]. Decreased expression of DUSP2 promoted angiogenesis and metastasis via facilitating interleukin-8 release in colon cancer, which was mediated by ERK1/2 and C/EBPα-dependent axis in hypoxia [8]. As a direct target of miR-361-3p, DUSP2 inversely regulated EMT-related proteins through facilitating inactivation of ERK1/2 in pancreatic ductal adenocarcinoma, and miR-361-3p–induced DUSP2 mRNA degradation was enhanced by Argonaute 2, an intrinsic endonuclease that acts as a "Slicer" [9]. DUSP2 also plays an essential role in cell survival and apoptosis. Tumor-suppressor factor p53, frequent mutation, and deletion in bladder cancer can transcriptionally activate DUSP2 through binding to a palindromic site in the DUSP2 promotor region in the cells stimulated by oxidative stress, and p53-mediated cell growth suppression and apoptosis depended on DUSP2 expression [6,21]. In this study, we extracted RNA sequencing data from TCGA and Oncomine data sets and found that the expression of DUSP2 was downregulated in bladder cancer specimens, particularly in the infiltrating type. We next detected its expression in 16 pairs of bladder cancer tissues and paired normal tissues using qRT-PCR and Western blot. The results confirmed that DUSP2 expression was reduced in cancer samples at mRNA and protein levels.

The clinical significance of DUSP2 in cancers has been controversial. Recently, some studies have demonstrated that decreased expression of DUSP2 was correlated with worse OS and distant metastasis-free survival in colon cancer [22]. In addition, colon cancer patients with the rs1724120 variant allele of DUSP2 had reduced risk [23], whereas DUSP2 mRNA level increased in metastatic ovarian carcinoma cells in effusions, and overexpression of DUSP2 predicted much poorer prognosis [10]. In the present study, Kaplan-Meier curves and Cox regression analysis suggested that the prognosis of bladder cancer patients with low DUSP2 expression was significantly worse than those with DUSP2-high in both the TCGA and TMA validation cohorts.

DUSP2 staining by IHC was evident in normal cervical epithelial layer and colon cells, while remarkably reduced in most cancer samples. Although the subcellular localization of DUSP2 protein was almost in the nucleus in cervical cells, half of the protein was in the cytoplasm in colon cells [20]. Similar result was obtained in our study that DUSP2 protein observed in the cytoplasm and nucleus was reduced in bladder cancer tissues in comparison with that in normal tissues. Immunofluorescence result also showed the similar cellular localization of DUSP2 in 5637 and T24 cells. It is reasonable to speculate that a slight variation on localization of DUSP2 protein in cervical, bladder, and colon cells might be attributed to different histologic components. Intriguingly, Han et al [24] performed RNA-Seq with T1 and T2 bladder cancer samples, and the result showed that DUSP2 expression was lower in T2 than in T1 patients. Further verification with various cell lines manifested that DUSP2 was upregulated in RT4 and 5637 cells with low pathological grade, whereas it was downregulated in T24, UM-UC-3, and UM-UC-13 cells with greater invasive potential. This observation is consistent with our finding: the DUSP2 mRNA and protein expression was apparently reduced in TCCSUP, UM-UC-3, and T24 cells, as compared with normal urothelial SV-HUC-1 cells, 5637, and RT4 cells. These results suggest that DUSP2 may be implicated in mediating invasive phenotype of bladder cancer and used as a potential molecular biomarker for identification of MIBC and non-MIBC.

In summary, we for the first time comprehensively investigated that DUSP2 expression was markedly decreased in bladder cancer tissues and cell lines compared with that in normal controls. DUSP2 was associated with TNM stage, pathological grade, and subtype. Kaplan-Meier and Cox regression analysis revealed that loss of DUSP2 predicted a shorter survival time and was an independent prognostic factor for bladder cancer patients. Collectively, our findings suggest DUSP2 as a potential biomarker for predicting prognosis and classification of subtypes in bladder cancer, which may be a promising strategy for diagnosis and treatment for patients with bladder cancer. Whether DUSP2 functions as a tumor suppressor in bladder cancer deserves further studies.

Ethics approval and consent to participate

All procedures performed in studies were in accordance with the ethical standards of the ethics committee of the institutional ethical review board of the First Affiliated Hospital of Chongqing Medical University.

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