Original Article

Reduction of Tat-interacting Protein 30 Expression Could be a Prognostic Marker in Bladder Urothelial Cancer

Ye-Ping Li[1], Jian-Fang Zhu[2], Ka-Te Huang[3], Rong-Rong Wang[3], Bing Cai[1], Hui Xie[1], Hong-De Chen[1]

[1]Department of Urology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, China
[2]Department of Vascular Surgery, The Second Hospital of Shaoxing City, Shaoxing, Zhejiang 312000, China
[3]Department of Pathology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, China

Ye-Ping Li and Jian-Fang Zhu contributed equally to this study.

Abstract

Background: Tat-interacting protein 30 (*TIP30*) has been reported to be a tumor suppressor, with reduced or absent expression in various tumors. However, its role in bladder urothelial cancer (BUC) has not been investigated. Therefore, herein, we investigated the expression of TIP30 protein in BUC and normal bladder mucosa and the clinical significance of TIP30 expression in the prognosis of BUC.
Methods: We reviewed data from 79 cases of BUC and 15 adjacent tissue samples from 79 patients treated at our institution between 2004 and 2007. TIP30 expression was examined by immunohistochemistry. The relationship between TIP30 expression and tumor stage, histological grade, and survival was analyzed. Differences between groups were evaluated using the *t*-test or matched-pairs test, and differences in the survival rates were analyzed with the log-rank test.
Results: TIP30 protein expression was significantly reduced in BUC tissue ($t = -6.91$, $P < 0.05$) compared with normal tissue samples, and in invasive bladder cancer ($t = 10.89$, $P < 0.05$) compared with superficial bladder cancer. TIP30 protein expression differed significantly among different differentiated groups classified either according to the World Health Organization (2004, $F = 17.48$, $P < 0.01$) or World Health Organization (1973, $F = 10.68$, $P < 0.01$). TIP30 protein expression was significantly reduced in high-grade papillary urothelial carcinoma compared with papillary urothelial neoplasm of low malignant potential ($P < 0.05$) and low-grade papillary urothelial carcinoma ($P < 0.05$). Meanwhile, TIP30 protein expression was significantly reduced in Grade III BUC, compared with Grade I ($P < 0.05$) and Grade II ($P < 0.05$). Patients with low TIP30 expression showed a higher incidence of disease progression than those with high TIP30 expression ($t = 2.63$, $P < 0.05$). Kaplan-Meier survival analysis showed a strong positive relationship between TIP30 expression and overall survival (OS) ($\chi^2 = 17.29$, $P < 0.05$).
Conclusions: *TIP30* expression was associated with clinical tumor stage in BUC, suggesting that it might play an important role in disease progression. Furthermore, *TIP30* might predict postoperative OS. Thus, its evaluation might be useful for predicting prognosis.

Key words: Bladder Urothelial Cancer; Overall Survival Time; Tat-interacting Protein 30

Introduction

Bladder urothelial cancer (BUC) is among the most common malignancies worldwide. A total of 74% cases of bladder cancers are superficial at the time of diagnosis.[1] Approximately 50% of patients with superficial bladder cancers experience a recurrence within 6–12 months, and approximately 5–30% show progression to muscle-invasive cancer that has a 60–70% 5-year mortality.[2] Valuable predictors of recurrence are extremely limited for patients with bladder cancer, with the exception of tumor stage and grade, as well as the presence of carcinoma *in situ*. Therefore, the discovery of new and more effective biomarkers for bladder cancer is critical, not only for accurate evaluation of tumor recurrence and progression but also as a target for anticancer therapy.

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Address for correspondence: Dr. Hong-De Chen, Department of Urology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, China
E-Mail: 85404206@qq.com

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The human gene Tat-interacting protein 30 (*TIP30*), also known as *CC3* or *HITATIP2*, was first identified as a suppressor of variant small-cell lung carcinoma (vSCLC).[3] *TIP30* expression is downregulated in various tumors with poor prognosis such as vSCLC,[3] glioblastoma,[4-7] breast carcinoma,[8,9] gastric carcinoma,[10] hepatocellular cancer,[11-14] laryngeal carcinoma,[15] esophageal carcinoma,[16] colorectal cancer,[17] lung cancer,[18] and pancreatic cancer.[19] *TIP30* shows a positive effect in inhibiting cancer development and progression; however, its role in BUC has not previously been investigated.

In the present study, we performed immunohistochemistry (IHC) on tissue microarrays (TMAs) that contained BUC and normal bladder mucosa to investigate TIP30 expression, and analyzed the relationship between TIP30 and clinicopathological features. We aimed to investigate the expression and clinical significance of TIP30 in BUC. In addition, the correlation between TIP30 expression and prognosis was also analyzed. TIP30 might be a prognostic marker for BUC and a valuable target for the treatment on patients with BUC.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and approved by the local ethics committee of the institute (No: 2016010). Written informed consent was obtained from all patients or their guardians for children, before study enrollment.

Patients and follow-up

Tissues from patients with BUC were retrospectively identified from the Department of Pathology of the First Affiliated Hospital of Wenzhou Medical University between 2004 and 2007. None of these patients received preoperative chemoradiotherapy within 3 months of surgery. All patients who were treated with transurethral resection (TUR) of the bladder tumor or with partial cystectomy and who were histopathologically confirmed to have BUC were monitored through cystoscopy and urine cytology every 3 months during the first 2 years. From the 3rd year, patients without recurring malignancy were evaluated once per year. All cases were classified both according to the World Health Organization (2004) and World Health Organization (1973) for grade. Normal bladder mucosal specimens were obtained via TUR or partial cystectomy and used as controls. Recurrence was defined as the diagnosis of a new pTa or pT1 tumor, while progression was defined in terms of the development of muscle invasive lesions (pT2 or higher) or metastasis, or both.

Tissue specimens and tissue microarray building

A total of 79 samples of BUC, along with 15 specimens of the normal bladder mucosa, were included in this study. TMAs were prepared as described previously by Kononen *et al*.[20] A fresh hematoxylin and eosin (H and E)-stained section was prepared from each donor tissue block and used as a guide to define the morphologically representative regions of the tumor or normal mucosa for subsequent sampling. The chosen regions of each donor block were punched with a 0.6-mm diameter tissue cylinder and transferred to the donor paraffin-embedded block (recipient block). A 4-mm section was stained with H and E to assess the presence of the target tissue through light microscopy.

Immunohistochemistry

We immunohistochemically processed 4-μm sections from the formalin-fixed, paraffin-embedded TMA. We deparaffinized the TMA sections in xylene, and re-hydrated them in descending dilutions of ethanol. Epitope retrieval was induced through heat treatment at 100°C for 15 min. We used the LabVision™ Autostainer 360 (Thermo Fisher Scientific, Inc., Fremont, CA, USA) to perform immunostaining. We then incubated the sections with 0.3% hydrogen peroxidase to block endogenous peroxidase activity (30 min at room temperature).

The slides were incubated overnight in the Autostainer with an antibody against TIP30 according to the manufacturer's recommendation (1:200; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Nuclei were counterstained with hematoxylin. The positive control sample was normal bladder mucosa, and the negative control was the same normal tissue without the antibody.

Evaluation of immunostaining

Image-Pro Plus 6.0 (IPP6.0, MediaCybernetics, Inc., Bethesda, MD, USA) was used to analyze the immunoexpression levels of TIP30. The measurement parameter was the integrated optical density (*A*). All images were verified by two pathologists who were blinded to the results of the previous assessments. In cases of disagreement, a consensus was reached by discussion.

Statistical analysis

Data analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). The differences between groups were evaluated using the *t*-test or matched-pairs test. All statistical tests were two-tailed. The curves for disease-free survival (DFS) and overall survival (OS) were drawn using the Kaplan-Meier method, and differences in the survival rates were analyzed using the log-rank test. Prognostic factors were evaluated through univariate and multivariate analyses (Cox proportional hazards regression model). Continuous variables with normal distribution were presented as means ± standard deviation (SD), while skewed distributed variables were expressed as median (range). A value of $P < 0.05$ was considered statistically significant. DFS was measured from the surgical resection day until either recurrence or death without recurrence, and it was censored only for patients who were alive without evidence of recurrence at the last follow-up. OS was counted from the day of surgical resection until death from any cause and was censored only for patients known to be alive at last follow-up.

Results

Patient characteristics

The clinicopathologic characteristics of the 79 patients are summarized in Table 1. Patients with tumors consisted of nine women and 70 men, and 15 of these also had normal mucosa (seven women and eight men). The mean age at presentation was 68.8 ± 11.1 years (range, 37–91 years). Tumor specimens were obtained through TUR (n = 75; 94.9%) or partial cystectomy (n = 4; 5.1%), and 15 samples of normal mucosal tissue were obtained using the same method during surgeries. The tumor group included 39 primary tumors and 40 recurrences. The series contained 9 pTa, 51 pT1, and 19 pT2–3 tumors, among which eight, 41, and 30 were classified as papillary urothelial neoplasm of low malignant potential carcinoma (PUNLMP), low-grade papillary urothelial carcinoma (LG), and high-grade papillary urothelial carcinoma (HG), respectively, and 25, 28, and 26 were classified as Grade I, II, and III, respectively. The median follow-up period for all patients was 60.7 ± 29.2 months (range, 6–159 months).

Table 1: Correlations between TIP30 expression and clinicopathological characteristics of patients with BUC

Characteristics	*n*	Mean density	*t*/*F*	*P*
Sex				
Male	70	0.3857 ± 0.1549	0.65*	0.52
Female	9	0.3496 ± 0.1770		
Age				
≤65 years	28	0.3692 ± 0.1329	−0.55*	0.58
>65 years	51	0.3884 ± 0.1693		
Tumor grade (WHO2004)				
PUNLMP	8	0.4911 ± 0.1300	17.48†	<0.01
LG	41	0.4408 ± 0.1237		
HG	30	0.2715 ± 0.1416		
Tumor grade (WHO1973)				
Grade I	25	0.4598 ± 0.1170	10.68†	<0.01
Grade II	28	0.4037 ± 0.1522		
Grade III	26	0.2828 ± 0.1472		
Tumor size				
≥3 cm	39	0.3616 ± 0.1751	1.12*	0.27
<3 cm	40	0.4011 ± 0.1359		
Treatment method				
TUR	75	0.3966 ± 0.1455	4.02*	<0.01
Partial cystectomy	4	0.1010 ± 0.0782		
Tumor multiplicity				
Single	32	0.3783 ± 0.1692	−0.15*	0.88
Multiple	47	0.3839 ± 0.1494		
Clinical tumor stage				
Superficial	60	0.4450 ± 0.1156	10.89*	<0.01
Muscle invasive	19	0.1814 ± 0.0831		
Recurrence				
No	39	0.4096 ± 0.1801	1.58*	0.12
Yes	40	0.3543 ± 0.1263		
Progression				
No	51	0.4107 ± 0.1733	2.63*	0.01
Yes	28	0.3286 ± 0.1040		

*t value; †F value. TIP30: Tat-interacting protein 30; BUC: Bladder urothelial cancer; PUNLMP: Papillary urothelial neoplasm of low malignant potential; LG: Low-grade papillary urothelial carcinoma; HG: High-grade papillary urothelial carcinoma; TUR: Transurethral resection.

Tat-interacting protein 30 expression in tissue microarray sections

IHC staining for TIP30 protein was identified in the cytoplasm of both normal mucosa and BUC specimens [Figure 1]. Representative images of TIP30 IHC staining are shown in Figure 1. TIP30 expression in patients with BUC was significantly decreased compared with that in normal mucosa (0.549 ± 0.065 vs. 0.663 ± 0.066, t = −6.91, P < 0.01). These data suggest that decreased TIP30 expression might be involved in the carcinogenesis of BUC. TIP30 protein expression differed significantly among different differentiated groups classified according to the World Health Organization (2004) (F = 17.48, P < 0.01) or World Health Organization (1973) (F = 10.68, P < 0.01). TIP30 expression did not differ significantly between PUNLMP and LG BUC (P = 0.97), however, it was significantly reduced in HG BUC compared with PUNLMP (P < 0.05) and LG BUC (P < 0.05). Meanwhile, TIP30 expression did not differ significantly between Grade I and Grade II BUC (P = 0.45), however, it was significantly reduced in Grade III BUC, compared with Grade I (P < 0.05) and Grade II (P < 0.05). TIP30 expression in the muscle-invasive stage was significantly lower than that in the nonmuscle-invasive stage (t = 10.89, P < 0.01). Patients with low TIP30 expression showed a higher incidence of tumor progression compared with those with high TIP30 expression (t = 2.63, P < 0.05). This result indicates that reduced TIP30 expression might be correlated with the progression and prognosis of BUC. TIP30 expression in patients treated with TUR was significantly higher than that in those treated with partial cystectomy (t = 4.02, P < 0.01). Furthermore, no significant differences in TIP30 expression were observed with regard to age, sex, tumor number, or tumor size of patients with BUC (P > 0.05).

Correlation between Tat-interacting protein 30 expression and bladder urothelial cancer prognosis

In this study, the median A of patients with BUC was 0.372. All patients were assigned to either a high TIP30 expression group (A ≥0.372.) or a low TIP30 expression group (A <0.372).

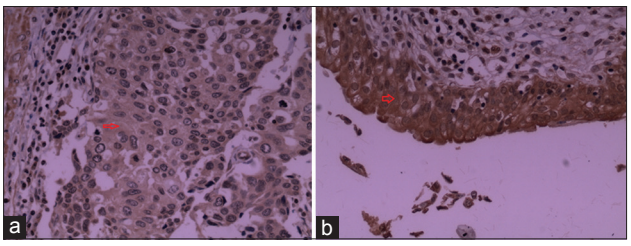

Figure 1: TIP30 expression in BUC and normal urothelium on IHC. (a) Weak TIP30 staining in the cytoplasm of high-grade BUC (×200). (b) Strong TIP30 staining in the cytoplasm of BUC with normal bladder mucosa (×200). TIP30: Tat-interacting protein 30; BUC: Bladder urothelial cancer; IHC: Immunohistochemistry.

Figures 2 and 3 show the Kaplan-Meier survival curves for patients with BUC tumors with high or low TIP30 expression. The OS of patients with low TIP30 expression was significantly lower than that of patients with high TIP30 protein expression ($\chi^2 = 17.29$, $P < 0.001$; Figure 2). However, the DFS of the two groups did not significantly differ ($\chi^2 = 0.15$; $P = 0.70$; Figure 3).

The results of univariate and multivariate analyses for the DFS of patients with BUC are shown in Table 2. Univariate analysis showed that TIP30 protein expression ($\chi^2 = 13.32$, $P < 0.01$), tumor grade ($\chi^2 = 15.48$, $P < 0.01$), and tumor stage ($\chi^2 = 8.60$, $P < 0.01$) were significant prognostic factors of OS. However, age, sex, size, and number of tumors had no prognostic significance ($P = 0.21$, 0.22, 0.97, and 0.12, respectively). Meanwhile, multivariate analyses showed that TIP30 protein expression ($\chi^2 = 5.55$, $P = 0.02$) and tumor grade ($\chi^2 = 15.18$, $P < 0.01$) were significant prognostic factors of OS.

Discussion

As a putative tumor suppressor gene, *TIP30* is decreased in several cancer cell types and is involved in the regulation of tumor cell growth and metastasis.[9] As a transcription cofactor, *TIP30* may suppress the expression of genes that are involved in proliferation, apoptosis, angiogenesis, and metastasis,[21-23] suggesting that *TIP30* may act as a cancer suppressor. For example, overexpression of *TIP30* has been shown to suppress tumor invasion through the extracellular matrix.[9] The restoration of *TIP30* expression resulted in reduced expression of cyclin D1, *Bcl*-2, and *Bcl-xl*, but also led to overexpression of *p*27, *Bax*, *p53*, and caspase 3 and 9; resulted in cell cycle G0/G1 arrest; induced apoptosis in human gastric cancer-derived cells; and led to significantly attenuated tumor growth and abrogation of metastasis in mouse models.[10] Moreover, previous studies showed similar results, demonstrating that *TIP30* overexpression in various cell lines resulted in increased expression of several proapoptotic genes and angiogenic inhibitors and reduced expression of angiogenic stimulators.[5,6,24]

Downregulation of *TIP30* has been found to lead to the expression of osteopontin, matrix metalloproteinase-2, and vascular endothelial growth factor, suggesting that downregulation of this protein promotes metastatic progression of lung cancer.[18] Chen and Shtivelman[25] found that inhibition of *TIP30* expression allowed tumor cells to evade apoptosis through glucose deprivation, and studies on animal models showed that *TIP30*-/- mice spontaneously developed tumors faster than wild-type mice.[26,27] Meanwhile, *TIP30* knockdown led to prolonged epidermal growth factor receptor (EGFR) signaling in early endosomes, along with delayed EGFR degradation and increased EGFR nuclear location, leading to increased expression of *pAKT* and *pERK1/2* in human lung adenocarcinoma cells.[27] *TIP30* deletion enhanced proliferation of primary mammary epithelial cells and resulted in rapid immortalization of mammary epithelial cells *in vitro* relative to wild-type cells.[28]

The role of *TIP30* in tumorigenesis is also evidenced by the reduced expression of TIP30 in human colorectal cancer.[17] The decreased TIP30 expression is associated with poor prognosis in patients with hepatocellular carcinoma.[12] Human hepatocellular carcinoma with methylated TIP30 has shown a tendency toward significantly high recurrence and mortality rates and low DFS.[25] *TIP30* can also induce apoptosis and mitochondrial dysfunction, probably through stabilization of *p53* mRNA, and this mechanism is blocked by inhibition of p53 expression.[6]

Comparison of the *TIP30* cDNA sequences in the National Center for Biotechnology Information databases revealed the presence of *TIP30* missense mutation in approximately 24% of various types of cancer cells.[26]

Therefore, *TIP30* might play important roles in both the suppression of tumorigenesis and tumor invasion. However,

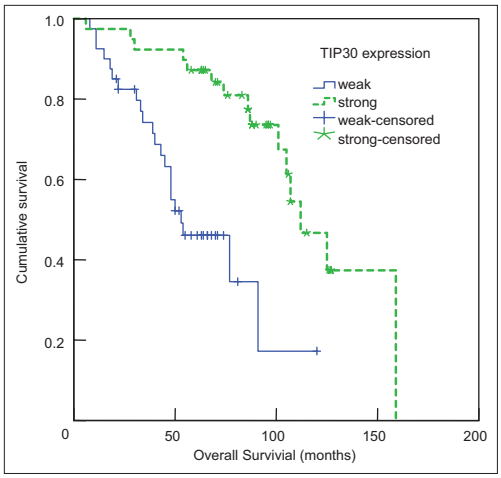

Figure 2: Patients with high TIP30 expression showed significantly lower overall survival rates than those with low TIP30 expression ($\chi^2 = 17.29$, $P < 0.001$). TIP30: Tat-interacting protein 30.

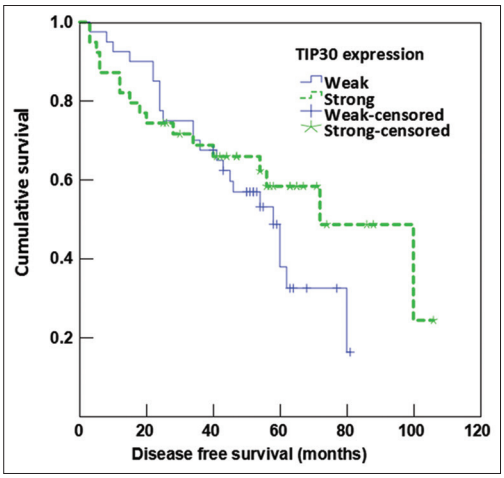

Figure 3: Disease-free survival was not significantly different between the group with high TIP30 expression and group with low TIP30 expression ($\chi^2 = 0.15$; $P = 0.70$). TIP30: Tat-interacting protein 30.

Table 2: Univariate and multivariate analyses of related factors for predicting the overall survival of patients with bladder cancer in a Cox proportional hazards model

Variables	Univariate analysis			Multivariate analysis		
	HR	95% *CI*	*P*	*HR*	95% *CI*	*P*
Sex						
Male/female	1.73	0.72–4.17	0.22	1.79	0.65–4.84	0.33
Age						
>65 years/≤65 years	1.60	0.77–3.34	0.21	1.34	0.63–2.88	0.45
Tumor grade						
G II + III/G I	8.58	2.94–25.03	<0.01	11.56	3.37–39.58	<0.01
Clinical tumor stage						
T2 + T3/Ta + T1	3.36	1.50–7.56	<0.01	1.23	0.42–3.60	0.70
Size						
<3 cm/≥3 cm	0.99	0.51–1.90	0.97	0.59	0.25–1.39	0.22
Multiplicity						
Multiple/single	0.59	0.30–1.14	0.12	0.63	0.31–1.29	0.21
Smoking						
Yes/no	1.09	0.55–2.14	0.81	0.95	0.33–2.74	0.93
Drinking						
Yes/no	0.88	0.43–1.83	0.74	0.77	0.27–2.25	0.64
TIP30 expression						
Strong/weak	0.25	0.12–0.53	<0.01	0.29	0.10–0.81	0.02

HR: Hazard ratio; *CI*: Confidence interval; TIP30: Tat-interacting protein 30.

the role of *TIP30* in BUC is largely unknown. In the present study, we evaluated TIP30 expression in bladder cancer and normal bladder mucosal tissues using TMA and IHC. The results showed significantly lower average expression levels of TIP30 in bladder cancer tissues than those in normal bladder mucosal tissues, suggesting that TIP30 expression might play an important role in bladder tumorigenesis. We also found that TIP30 expression was reduced significantly in invasive bladder cancer compared with superficial bladder cancer ($P < 0.05$). TIP30 expression did not differ significantly between PUNLMP and LG BUC ($P = 0.97$), however, it was significantly reduced in HG BUC compared with PUNLMP ($P < 0.05$) and LG BUC ($P < 0.05$). Meanwhile, TIP30 expression did not differ significantly between Grade I and Grade II BUC ($P = 0.45$), however, it was significantly reduced in Grade III BUC, compared with Grade I ($P < 0.05$) and Grade II ($P < 0.05$). TIP30 expression in patients treated with TUR was significantly higher than that in those treated with partial cystectomy ($P < 0.01$). However, this finding might be meaningless because of the small sample size, and because tumors with a broad base were always identified by cystoscopy before surgery in patients treated with partial cystectomy. Patients with low TIP30 expression showed a higher incidence of disease progression than those with high TIP30 expression ($P < 0.05$). Kaplan-Meier survival analysis showed a strong positive relationship between TIP30 expression and OS ($P < 0.05$).

Some limitations should be clarified. The normal bladder mucosa specimens in this study were insufficient in number to allow analysis and differentiation among BUC specimens. The mechanisms by which *TIP30* inhibits the development of BUC remain elusive and further studies should be designed to evaluate these issues.

In summary, loss of *TIP30* expression might be associated with BUC tumorigenesis and is an independent predictor for OS in patients with BUC. We believe that evaluation of *TIP30* might assist in the development of new criteria for determining the prognosis of patients with BUC. Moreover, *TIP30* might be a new and valuable target for the development of therapeutic strategies for patients with BUC.

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Conflicts of interest

There are no conflicts of interest.

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