Int J Clin Exp Med 2017;10(1):1643-1650
www.ijcem.com /ISSN:1940-5901/IJCEM0028166

Original Article

TROP2 is associated with the recurrence of patients with non-muscle invasive bladder cancer

Lianhua Zhang[1*], Guoliang Yang[1*], Haifeng Jiang[1], Mengyao Liu[2], Haige Chen[1], Yiran Huang[1], Zhiwei Wang[3], Juanjie Bo[1]

[1]Department of Urology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [2]Clinical Stem Cell Research Center, RenJi Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [3]Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA. [*]Equal contributors.

Received March 14, 2016; Accepted June 8, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: Human trophoblastic cell surface antigen 2 (TROP2), a single-transmembrane surface glycoprotein, has been demonstrated to play a critical role in tumorigenesis. Overexpression of TROP2 has been observed in a variety of human cancers. However, the clinical significance of TROP2 expression in non-muscle invasive bladder cancer (NMIBC) remains unclear. Therefore, in this study we aim to investigate the correlations between TROP2 expression and prognosis in patients with NMIBC. Immunohistochemistry was performed to detect the expression of TROP2 protein in 102 primary NMIBC tissue specimens. Moreover, whether TROP2 is associated with clinicopathologic factors and prognosis was also analyzed. We found high expression of TROP2 protein in NMIBC. High expression of TROP2 was significantly associated with tumor grade (P=0.001), stage (P<0.001), and recurrence (P=0.03). The Kaplan-Meier survival analysis demonstrated that high TROP2 expression was significantly correlated to shorter recurrence-free survival (P=0.0012). Multivariate analysis further suggested that TROP2 was an independent prognostic factor for NMIBC (P=0.043). Therefore, TROP2 might be a novel molecular marker for predicting the recurrence of patients with NMIBC.

Keywords: TROP2, bladder cancer, recurrence, prognosis, biomarker

Introduction

Bladder cancer is one of the most common malignancies in human populations, and it was estimated in 2013 that 72,570 new cases of cancer of the urinary bladder were diagnosed in the United States and 15,210 deaths were attributable to bladder cancer [1]. At the initial diagnosis, approximately 80% present as non-muscle invasive bladder cancer (NMIBC), which can be managed with a combination of transurethral resection (TUR) and intravesical therapy [2, 3]. Moreover, 50-70% of NMIBC patients will develop disease recurrence within two years of their initial diagnosis, and 20% to 30% of them have progression to muscle-invasive bladder cancer (MIBC) [4, 5]. Recurrence and progression are the main characteristics of NMIBC. To date, the well-established and routinely used clinical markers to predict recurrence and progression are pTNM stage and tumor differentiation [6]. One limitation of the current use of pTNM stage is the fact that tumors with the similar stage and grade can have a significantly different biology [7]. Therefore, it is necessary to identify new molecular markers for NMIBC recurrence.

Human trophoblastic cell surface antigen 2 (TROP2), also termed as GA733-1 or EGP-1, which is a single-transmembrane surface glycoprotein, plays a regulatory role in cell-cell adhesion [8-10]. It has been shown that TROP2-encoding gene is a member of tumor-associated calcium signal transducer (TACSTD) gene family [11]. Although the regulation of TROP2 gene is not fully understood, the phosphorylation sites of the cytoplasmic tail region and a conserved tyrosine and serine phosphorylation site are considered to play an important role in signal transduction [12]. Some studies have demonstrated that TROP2 behaved as a true oncogene, leading to the tumorigenesis and invasiveness [11, 13, 14]. It has been identified

Table 1. Correlation between TROP2 protein expression and clinicopathologic features of the patients with NMIBC

Parameter	Total	TROP2 expression		*P* value
		Low expression	High expression	
Gender				0.236
Female	35	15	20	
Male	67	37	30	
Age (yeas)				0.514
≤65	40	22	18	
>65	62	30	32	
Tumor size (cm)				0.114
≤3	63	36	27	
>3	39	16	23	
Tumor number				0.111
Unifocal	49	29	20	
Mutlifocal	53	23	30	
Grade				0.001
Low grade	59	38	21	
High grade	43	14	29	
T stage				<0.000
Ta	52	36	16	
T1	50	16	34	
Recurrence				0.03
Positive	44	17	27	
Negative	58	35	23	
Progression				0.896
Positive	23	12	11	
Negative	79	40	39	

that TROP2 contributed to tumor pathogenesis via activating the ERK and MAPK pathways [15].

Multiple studies have reported that low-level or no expression of TROP2 was found in normal human tissues, whereas overexpression of TROP2 was observed in various types of human malignant tumors [16, 17]. Moreover, high level of TROP2 was frequently associated with cancer progression and poor prognosis [18-21]. These findings indicate that TROP2 is not only a potential prognosis biomarker, but also a promising therapeutic target for cancer treatment [22]. However, TROP2 expression and its prognostic role in bladder cancer have not yet been determined. In the current study, we explored the expression of TROP2 in human bladder cancer and investigated whether TROP2 is associated with clinicopathological and prognostic significance in NMIBC.

Materials and methods

Patients and tissue samples

For immunohistochemical assay, a total of 102 paraffin-embedded samples of transitional cell bladder cancer and 23 specimens of normal bladder tissue were collected from Renji hospital (Shanghai, China) between January 2003 and December 2005. The criteria for enrollment were histopathological diagnosis of transitional cell carcinoma of the bladder, newly diagnosed and untreated, no history of other tumors, and the potential to follow up. The carcinoma in situ was excluded from our study. The clinical materials were only for research purposes, prior patient's consent and other ethical issues were approved by the Ethics Committee of Renji hospital. Clinical information about the samples is described in detail in **Table 1**. The patients included 67 males and 35 females from age 41 to 88 years (mean age, 66.1 years). All patients underwent transurethral resection of bladder tumor (TURBT). All patients with NMIBC received intravesical mitomycin C (MMC) or pirarubicin (THP) instillations once weekly for the first 8 weeks and then monthly up to 1 year. Cystoscopy and urine cytology were performed at 3-month intervals during the first 2-year and 6-month intervals after 2 years. The mean follow-up time for NMIBC patients was 47 months for patients at the time of analysis, and ranged from 6 to 103 months. We defined recurrence as the recurrence of primary NMIBC with a lower or the same pathologic stage and progression as confirmed by histologic muscle invasion (pathologic stage T2 or higher disease) or detectable distant metastases. The histopathological grade and clinical stage of bladder cancer in this study were defined according to the criteria of the World Health Organization (WHO, 2004) and the 6th edition of the pTNM classification of the International Union Against Cancer (UICC, 2002). All tumors were re-evaluated for histological type and grade by two senior pathologists (Qiang Liu and Zhao-Liang Wang) at the Renji Hospital.

Immunohistochemistry

Formalin-fixed and paraffin embedded tissue sections (5-μm) were deparaffinized and rehydrated. Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxide for 10

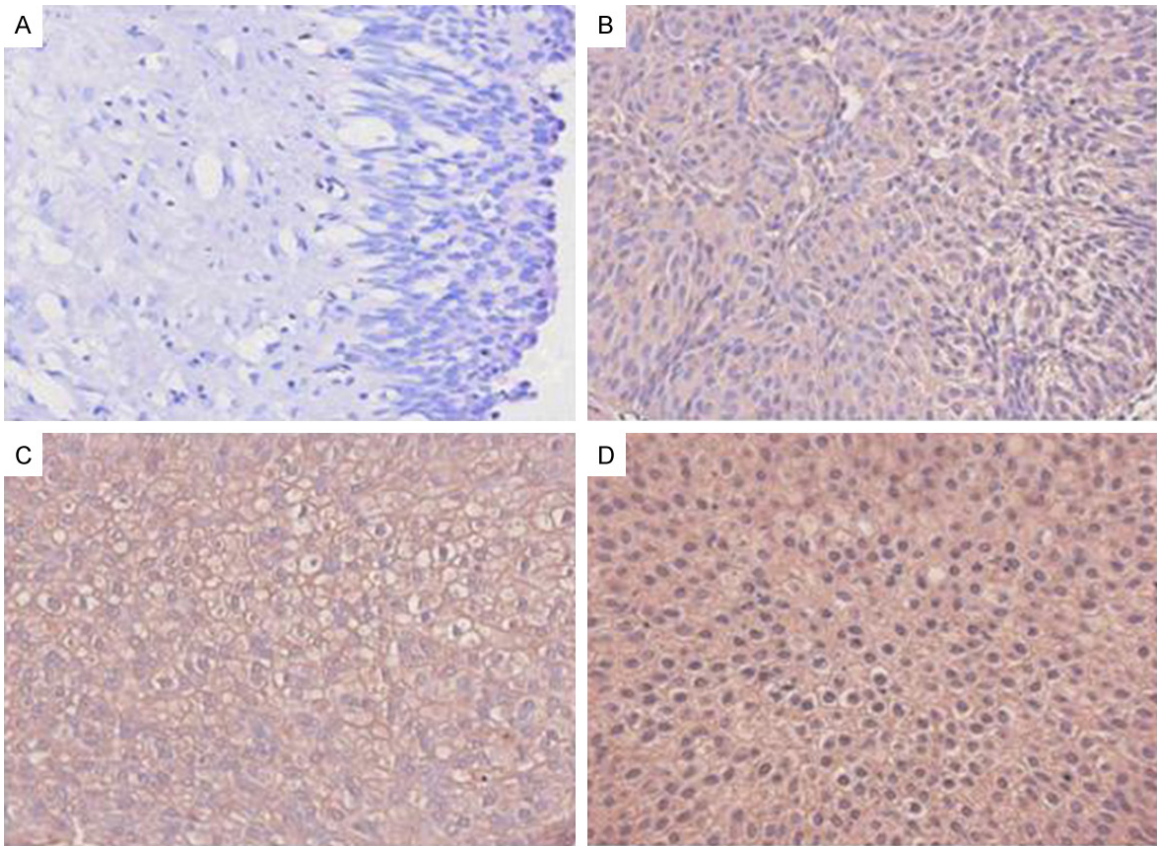

Figure 1. Immunohistochemical staining of TROP2 protein in bladder tissues. A. TROP2 staining was negative in normal bladder urothelium; B. Bladder cancer with moderate expression; C. Bladder cancer with strong membranous expression; D. Bladder cancer with strong cytoplasmic expression.

minutes. For antigen retrieval, sections were treated with a buffer (1 mmol/L EDTA/PBS [pH 9.0]) for 30 minutes in water bath at 96°C. Slides were incubated overnight at 4°C in a humidified chamber with goat polyclonal antibody anti-TROP2 (AF650, R&D Systems, Inc., Minneapolis, MN, USA) at the dilution of 1:50. Biotinylated anti-goat link was used as secondary antibody (30 min). Slides were then incubated with a streptavidin-horseradish peroxidase complex. Diaminobenzidine (DAB) was used as chromogen and the sections were counterstained with haematoxylin. Samples incubated with normal serum instead of primary antibodies were used as negative controls.

Evaluation of immunostaining

Two independent observers blinded to the clinical parameters evaluated five areas of each slide for correlation and confirmation. If they didn't agree with each other, they reevaluated the slides on a double lens microscope and discussed to get the final agreement. The staining intensity was scored as 0 (negative), 1 (weak), 2 (medium) and 3 (strong). The extent of staining was scored as 0 (0%), 1 (1-10%), 2 (11-50%), 3 (51-100%). The staining index (SI) was calculated as staining intensity score × proportion of positive tumor cells. Using this method of assessment, we evaluated the expression of TROP2 in normal bladder epithelium and malignant lesions by determining the SI, which scores as 0, 1, 2, 3, 4, 6, and 9. For the purpose of statistical evaluation, tumors with a final staining score of >1 were considered to high expression.

Statistical analysis

The significance of the relationships between TROP2 protein expression and clinicopathological parameters was evaluated using χ^2 tests. Recurrence-free survival and progression-free survival curves were calculated using the Kaplan-Meier method and compared by log-

Table 2. Univariate analysis of recurrence-free and progression-free survivals (months, Mean ± SE) in patients with NMIBC

Variable	Case	Recurrence-free survival			Progression-free survival		
		Mean ± SEM (months)	95% CI	*P* value	Mean ± SEM (months)	95% CI	*P* value
Gender				0.592			0.314
Female	35	68±7	(54-82)		85±6	(72-98)	
Male	67	62±5	(52-72)		76±5	(66-86)	
Age (yeas)				0.640			0.640
≤65	40	67±7	(54-81)		78±6	(65-90)	
>65	62	63±5	(53-73)		82±5	(72-92)	
Tumor size (cm)				0.787			0.639
≤3	63	64±5	(54-74)		78±5	(68-86)	
>3	39	66±7	(52-80)		82±7	(69-95)	
Tumor number				0.293			0.026
Unifocal	49	70±6	(57-82)		90±5	(80-99)	
Mutlifocal	53	60±6	(49-72)		71±6	(60-83)	
Grade				<0.001			<0.001
Low	59	79±5	(69-88)		89±4	(80-97)	
High	43	40±6	(28-52)		60±8	(56-82)	
T stage				0.025			0.015
Ta	52	72±6	(62-83)		86±5	(77-96)	
T1	50	55±6	(43-67)		69±6	(36-66)	
TROP2				0.0012			0.198
Low expression	52	77±5	(67-87)		84±5	(75-94)	
High expression	50	45±5	(34-55)		63±6	(51-75)	

rank test. The significance of various variables for recurrence-free survival and progression-free survival was analyzed by the Cox proportional hazards model in the multivariate analysis. SPSS 11.0 software (SPSS, Inc., Chicago, IL) was used for statistical analysis. A value of $P<0.05$ was considered statistically significant.

Results

TROP2 is overexpressed in NMIBC. To analyze the difference in protein expression of TROP2 between bladder cancer tissues and normal tissues, we examined 102 bladder cancer tissue paraffin slices and 23 bladders normal tissue paraffin slices by immunohistochemistry. Normal bladder epithelial cells showed either no or weak staining (**Figure 1A**). By contrast, high expression of TROP2 protein was observed in 50 (49%) paraffin slices (P<0.001) in bladder cancer tissues. Notably, expression of TROP2 staining was mainly located in the cytomembrane and cytoplasm of bladder cancer cells (**Figure 1B-D**).

Correlation between TROP2 protein expression and clinicopathological features

The correlation between TROP2 protein expression and clinicopathological features of NMIBC was examined. As shown in **Table 1**, high expression of TROP2 was significantly associated with tumor grade ($P=0.001$), stage ($P<0.001$), and recurrence ($P=0.03$). However, TROP2 protein expression was not associated with other clinicopathological features such as age, sex, tumor size and tumor numbers.

Prognostic significance of TROP2 protein was observed in NMIBC

We evaluated the ability of TROP2 staining to predict tumor recurrence in NMIBC. In NMIBC specimens, TROP2 expression was higher in patients who experienced recurrence, compared with those with no recurrence ($P=0.03$). Using Kaplan-Meier analysis, we observed that the expression of TROP2 in bladder cancer was significantly correlated recurrence-free survival ($P=0.0012$) (**Table 2**). The log-rank test further

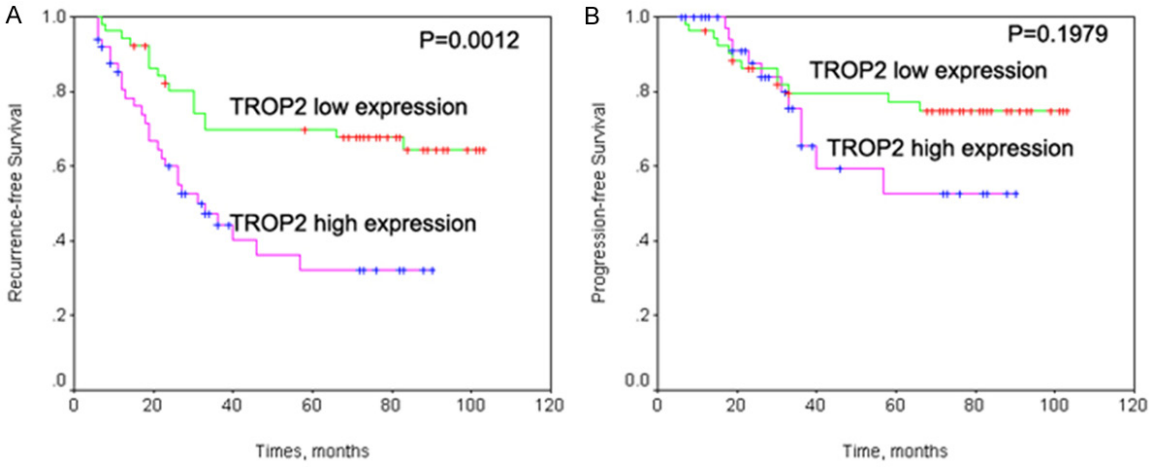

Figure 2. Kaplan-Meier survival analysis of recurrence-free survival and progression survival in NMIBC according to TROP2 expression.

Table 3. Multivariate Cox model analysis of recurrence-free survival and progression-free survival in patients with NMIBC

Variable	Recurrence-free survival		Progression-free survival	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Gender				
Female vs > Male	1.507 (0.794-2.86)	0.210	2.588 (0.969 -6.751)	0.058
Age (years)				
≤65 vs >65	1.002 (0.523-1.919)	0.995	0.857 (0.336-2.185)	0.746
Tumor number				
Unifocal vs mutlifocal	1.135 (0.570-2.259)	0.720	2.053 (0.673-6.265)	0.206
Tumor size (cm)				
≤3 vs >3	0.768 (0.400-1.473)	0.382	0.565 (0.209-1.524)	0.259
Grade				
Low vs High	3.387 (1.692-6.780)	0.001	8.327 (2.940-23.587)	<0.000
T stage				
Ta vs T1	1.092 (0.498-2.395)	0.827	1247 (0.381-4.083)	0.715
TROP2 expression				
Low vs High	2.041 (1.023-4.072)	0.043	1.009 (0.377-2.702)	0.985

demonstrated that the survival time was significantly different between groups with high and low expression of TROP2 protein, indicating that high level of TROP2 was tightly correlated with a shorter survival (**Figure 2**). Multivariate analysis was also performed with the Cox proportional hazards model including gender, age, tumor size, tumor numbers, grade, stage and TROP2 expression. The results showed that high expression of TROP2 protein had a significant correlation with bladder cancer recurrence, suggesting that TROP2 could be an independent prognostic factor for recurrence in patients with NMIBC (*P*=0.043) (**Table 3**).

Discussion

In present study, we demonstrated that TROP2 was highly expressed in bladder cancer tissues, compared with normal tissues. These results are consistent to previous studies in other types of human cancers [13, 23]. Moreover, the data of present study showed that the expression of TROP2 was tightly related with tumor grade, stage and recurrence. Patients with TROP2 overexpression exhibited a significantly decreased recurrence-free survival, indicating that TROP2 could be an independent prognostic predictor for NMIBC patient recur-

rence. Taken together, our results implies that over-expression of TROP2 could be involved in the progression of bladder cancer and may represent an independent prognostic factor for the outcomes in NMIBC patients.

Emerging evidence has uncovered that TROP2 plays an essential role in the development and progression of human cancers [24-29]. For instance, depletion of TROP2 suppressed the proliferation and invasion in lung adenocarcinoma cells [30]. Consistently, overexpression of TROP2 enhanced cell proliferation, migration, and invasion, whereas downregulation of TROP2 triggered apoptosis and impaired proliferation in the lung cancer cells [31]. Similarly, overexpression of TROP2 promoted the proliferation and invasion via regulation of ERK pathway in cervical cancer cells [23]. Moreover, TROP2 controlled epithelial hyperplasia and stem cell self-renewal through beta-catenin signaling [32]. In line with these findings, upregulation of TROP2 stimulated tumor growth, while tumor cell growth was abrogated by depletion of TROP2 expression [33]. However, it has been reported that TROP2 could be a tumor suppressor in several types of human cancers. For example, one study found that TROP2 was overexpressed in normal bile duct epithelia, but down-regulated in cholangiocarcinoma (CCA) cells [34]. Knockdown of TROP2 enhanced the proliferation and migration in CCA cells through regulation of MARCK, EMP1, and FILIP1L [34]. These reports suggest that further investigation is required to dissect the function of TROP2 in human malignancies.

Accumulated evidence has discovered the mechanism of TROP2-mediated tumorigenesis. Loss of TROP2 caused autocrine activation of the EGFR family member ErbB3 through neuregulin-1 in the mesenchymal subtype of head and neck squamous cell cancer (HNSCC) [35]. Moreover, loss of TROp2 induced sensitivity to anti-ErbB3 antibodies, leading to reduced proliferation and tumorigenic growth in HNSCC cells [35]. Due to the critical role of TROP2 in tumorigenesis, inhibition of TROP2 could be a novel therapeutic strategy for the treatment of human cancers [36, 37]. Indeed, the human Fab anti-TROP2 antibody inhibited cell growth and migration, and induced apoptosis in breast cancer cells [38]. Interestingly, Epigallocatechin-3-gallate (EGCG), green tea catechins, was found to inhibit the expression of TROP2 in human colorectal cancer cells. In summary, our study demonstrated that TROP2 was highly expressed in NMIBC and that TROP2 overexpression was correlated with shorter recurrence-free survival in NMIBC patients. Without a doubt, a large patients' cohort is required to validate our conclusion. If further exploration confirms our concept, the detection of TROP2 in tissue samples after TURBT could be used as a prognostic marker for determining the risk of recurrence in patients with NMIBC. It is also important to develop the inhibitors of TROP2 for the treatment of human cancers with high expression of TROP2.

Acknowledgements

This work is supported by grant from Science and Technology Committee of Shanghai Municipal (Grant No. 12ZR1417700), and Shanghai Municipal Health Bureau (Grant No. 20134387), China. We thank the two senior pathologists (Qiang Liu and Zhao-Liang Wang) at the Renji Hospital for their kind help.

Disclosure of conflict of interest

None.

Address correspondence to: Juanjie Bo, Department of Urology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China. E-mail: bojuanjie@sina.com; Zhiwei Wang, Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA. E-mail: zwang6@bidmc.harvard.edu

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