

Expression level of *TBX3* gene in renal carcinoma and its clinical significance

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Abstract. The aim of the current study was to investigate and discuss the function of T-box 3 (*TBX3*) gene expression in the pathogenesis of renal carcinoma. The carcinoma, adjacent and normal renal tissues of 210 patients with renal carcinoma who presented to The Central Hospital of Wuhan, Tongji Medical College from March, 2006 to March, 2012 were collected to extract total RNAs. The total RNAs were reverse-transcribed into complementary DNA (cDNA), and quantitative polymerase chain reaction (qPCR) was applied to detect the expression of *TBX3* gene in these tissues, followed by its association with the prognosis of renal carcinoma as well as clinical features. A comparison of the renal carcinoma tissues with the adjacent tissues showed that *TBX3* gene was obviously highly expressed in renal carcinoma tissues ($P < 0.05$). In addition, compared with normal renal tissues, *TBX3* gene was obviously highly expressed in renal carcinoma tissues ($P < 0.05$). There was no significant difference in the expression levels of *TBX3* gene in normal renal tissues and adjacent tissues ($P = 0.15$). The expression of *TBX3* gene in renal carcinoma tissues was not associated with patient age, sex and tumor size ($P > 0.05$), but it was associated with tumor-node-metastasis (TNM) staging and lymph node metastasis ($P < 0.05$). The Kaplan-Meier survival analysis revealed that the median survival time of patients in the positive *TBX3* gene expression group (37.5 months) was shorter than that in the negative *TBX3* gene expression group (66 months), and there was a statistical difference ($P < 0.05$). The 3- and 5-year survival rates in the negative *TBX3* gene expression group were 74 and 62%, respectively, and the 3- and 5-year survival rates in the positive *TBX3* gene expression group were 52 and 32%, respectively, and the differences were significant ($P < 0.05$). The results

suggest that *TBX3* gene is highly expressed in renal carcinoma tissues, and it is associated with TNM staging, lymph node metastasis and distant metastasis, which may be involved in the occurrence and metastasis of renal carcinoma.

Introduction

Renal cell carcinoma (renal carcinoma for short) is a kind of tumor with a high malignancy in the urinary system, and it is one of the most common tumors. Also known as renal adenocarcinoma, it is a malignant tumor originated in the tubule epithelium in the renal parenchyma, accounting for 80-90% in renal malignant tumor (1). Its incidence and mortality rate are currently on the increase. Tumor metastasis has been identified in approximately half of the patients when they are examined, and a postoperative relapse rate as high as 90% is evident in more than half of the patients (2). Renal carcinoma exhibits special genetic and biological characteristics, heterogeneity and easy metastasis. Conventional chemoradiotherapy has no ideal effect on renal carcinoma with metastasis. Studies have found that satisfactory therapeutic effects have been obtained by applying molecular immunology, gene therapy and molecular-targeted therapy for tumor vascularization for advanced or metastatic renal carcinoma (3). The emergence of tumor-associated factors has a good application prospect for the diagnosis and treatment of renal carcinoma.

T-box (*TBX*) genes have the function of regulating transcription factors related to development, and *TBX3* gene plays its role mainly by means of its expression product *TBX3* protein, which is involved in each process of embryonic development in order to guarantee the normal differentiation and development of tissues and organs in the embryonic period (4). Previous findings showed that the expression of *TBX3* mRNA in some tumor tissues is markedly higher than that in adjacent tissues (5). It has been concluded from statistical analyses that several clinical features, including lymph node metastasis and tumor-node-metastasis (TNM) staging, have a significant correlation with the abnormal expression of *TBX3* gene (6). Some studies also indicate that *TBX3* gene is an oncogene (7), and *TBX3* protein is a major product of its function. Furthermore, *TBX3* protein is a kind of inhibitory factor associated with transcription, and the normal differentiation and development of organs and tissues are dependent on its expression to some extent (8,9). Therefore, this study was

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conducted to investigate the correlation of *TBX3* gene with the occurrence and metastasis of renal carcinoma by analyzing the expression level of *TBX3* gene in renal carcinoma tissues of patients with the disease.

Materials and methods

Research objects and materials. In total, 210 patients with renal carcinoma who were admitted and treated in The Central Hospital of Wuhan, Tongji Medical College (Wuhan, China) from March, 2006 to March, 2012 were selected, and their carcinoma, adjacent and normal renal tissues (renal tissues more than 3 cm away from the tumor) were collected. Of the 210 patients, 86 patients were aged <60 years and 124 were aged ≥60 years, and 140 cases were males and 70 cases were females. Concerning TNM staging, 146 patients were in stage I-II and 64 were in stage III-IV. Regarding pathological typing, there were 165 cases of clear cell carcinoma and 45 cases of non-clear cell carcinoma, of which 95 cases were at low grade, and 115 were at middle and high grade.

Inclusion criteria for the study were: Patients who were histopathologically confirmed as renal carcinoma; patients who did not undergo chemoradiotherapy; and patients who voluntarily accepted this research and signed the informed consent. Exclusion criteria for the study were: Patients complicated with other malignant tumors; patients with congenital malformation or a long history of nephritis; patients with severe hepatic or renal dysfunction and coagulation disorders; and patients unable to cooperate with the research due to various reasons. All the patients received a long-term follow-up of >5 years. The study was approved by the Ethics Committee of The Central Hospital of Wuhan.

Major reagents. The quantitative polymerase chain reaction (qPCR) reagent used was, EvaGreen fluorescence quantitative PCR reagent (Biotium, Inc., Hayward, CA, USA). RNA extraction reagent TRIzol, and reverse transcription kit (Invitrogen, Carlsbad, CA, USA) as well as DNA Marker (100 bp ladder) (Beijing Dingguo Center for Biotechnology Development, Beijing, China) were also used.

Reverse transcription-polymerase chain reaction (RT-PCR). Premier 6.0 software (Premier Biosoft International, Palo Alto, USA) was used as a reference for the primer sequences of *TBX3* (primers were produced by Shanghai Yingjun Biological Technology Co., Ltd., Shanghai, China). The upstream and downstream sequences of *TBX3* were: 5'-CCCGAAGAA GACGTAGAAGATGAC-3', and 5'-CCCGAAGAAGAGGTG GAGGACGAC-3'. β -actin was used as an internal reference primer, and the upstream and downstream sequences were 5'-CCTCCATCGTCCACCGCAAATG-3' and 5'-TGCTGT CACCTTCACCGTTCCA-3'.

Methods. SYBR-Green I Real-Time PCR kit was utilized to amplify target genes, of which the primers are listed above. The $2^{-\Delta\Delta C_t}$ method was applied to detect the relative expression levels of relevant genes. The RNAs of samples were extracted in accordance with the methods and principles of qPCR. Ultraviolet adsorption was used to measure the concentration and purity of the RNA solution. Complementary DNA

Table I. Expression levels of *TBX3* gene in renal carcinoma tissues, adjacent tissues and normal renal tissues.

Group	Renal carcinoma tissues	Adjacent tissues	Normal renal tissues
Expression level	1.139±0.453	0.495±0.336	0.412±0.298
P-value	P<0.05		P=0.15

The comparison of the renal carcinoma tissues with the adjacent tissues shows that *TBX3* gene is obviously highly expressed in renal carcinoma tissues (P<0.05). Compared with that in normal renal tissues, *TBX3* gene is obviously highly expressed in renal carcinoma tissues (P<0.05). There is no significant difference in the expression levels of *TBX3* gene in normal renal tissues and adjacent tissues (P=0.15).

(cDNA) was produced according to the conventional methods. The cDNA of renal carcinoma tissue was marked as group A, adjacent tissues as group B, and normal renal tissues as group C.

Statistical analysis. In the present study, Statistical Product and Service Solutions (SPSS) 18.0 software (Chicago, IL, USA) was used for statistical analyses on the data of this research. The χ^2 test was used for comparison between groups. Measurement data were presented as mean ± standard deviation. The t-test was used for comparison between groups. Cox regression model was used for multivariate analyses on factors influencing the prognosis of patients with renal carcinoma which were obtained from the univariate analyses. The Kaplan-Meier survival analysis was used to show the median survival time of patients in the two groups. P<0.05 was considered to indicate a statistically significant difference.

Results

Expression levels of *TBX3* gene in renal carcinoma tissues, adjacent tissues and normal renal tissues. The comparison of the renal carcinoma tissues with the adjacent tissues showed that *TBX3* gene was obviously highly expressed in renal carcinoma tissues (P<0.05). Compared with that in normal renal tissues, *TBX3* gene was obviously highly expressed in renal carcinoma tissues (P<0.05). There was no significant difference in the expression levels of *TBX3* gene in normal renal tissues and adjacent tissues (P=0.15) (Table I).

Relationship between the expression level of *TBX3* gene in renal carcinoma tissues and clinical features. According to the median expression level (0.769) of *TBX3* gene in renal carcinoma tissues, the patients were divided into the positive *TBX3* gene expression group (105 patients in total, of which the *TBX3* gene expression level was >0.769) and the negative *TBX3* gene expression group (105 patients in total, of which the *TBX3* gene expression level was <0.769). The *TBX3* gene expression level in the carcinoma tissues with lymph node metastasis was obviously elevated compared with that in carcinoma tissues without lymph node metastasis (P<0.05). The expression of *TBX3* gene in renal carcinoma tissues was

Table II. Relationship between expression level of *TBX3* gene in renal carcinoma tissues and clinicopathologic characteristics.

Clinicopathologic characteristics	<i>TBX3</i> gene expression		P-value
	Positive (n)	Negative (n)	
Age (years old)			0.198
<60	41	45	
≥60	64	60	
Sex			0.121
Male	69	71	
Female	36	34	
TNM staging			0.008 ^a
I+II	56	90	
III+IV	49	15	
Lymph node metastasis			0.012 ^a
Yes	74	11	
No	31	94	
Pathological grading			0.097
Middle and high	53	57	
Low	52	48	
Tumor size			0.061
<7	45	66	
≥7	60	39	
Pathological typing			0.135
Clear cell carcinoma	79	86	
Non-clear cell carcinoma	26	19	

^aP<0.05.

not related to the patients' age, sex and depth of tumor invasion (P>0.05), but it was associated with TNM staging and lymph node metastasis (P<0.05) (Table II).

Univariate analyses on factors influencing prognosis of renal carcinoma. The results showed that TNM staging, lymph node metastasis and 5-year survival rate of *TBX3* gene had statistical significance (P<0.05), indicating that the factors affecting the prognosis of renal carcinoma. However, sex, age, degree of differentiation and tumor size had no significant differences on the 5-year survival rate of patients (P>0.05) (Table III).

Multivariate analyses on factors influencing the prognosis of renal carcinoma. Cox regression model was used for multivariate analyses on factors influencing the prognosis of patients with renal carcinoma which were obtained from the univariate analyses (P<0.05). It was found that TNM staging, lymph node metastasis and *TBX3* gene expression level were the independent risk factors for renal carcinoma (P<0.05) (Table IV).

*Relationship between the expression of *TBX3* gene in renal carcinoma and prognosis.* The Kaplan-Meier survival

Table III. Clinicopathologic data of renal carcinoma and 5-year survival rate.

Clinicopathologic characteristics	Case	5-year survival rate (%)	χ^2 test	P-value
<60	86	50.1		
≥60	124	48.3		
Sex			4.14	0.121
Male	140	49.8		
Female	70	51.2		
TNM staging			12.35	0.000 ^a
I+II	146	80.5		
III+IV	64	40.7		
Lymph node metastasis			10.17	0.002 ^a
Yes	85	41.1		
No	125	84.2		
Pathological grading			7.56	0.189
Middle and high	110	52.9		
Low	100	43.7		
Tumor size			6.47	0.076
<7	111	78.6		
≥7	99	51.4		
Pathological typing			7.13	0.147
Clear cell carcinoma	165	61.2		
Non-clear cell carcinoma	45	49.8		
<i>TBX3</i> gene expression			10.21	0.006 ^a
Positive	105	62.0		
Negative	105	32.0		

^aP<0.05.

Table IV. Multivariate analyses on prognosis of renal carcinoma.

Variables	Odds ratio (OR)	95% confidence interval (95% CI)	P-value
<i>TBX3</i> gene expression	4.24	1.87-5.35	0.016 ^a
Lymph node metastasis	3.19	2.18-8.56	0.023 ^a
TNM staging	3.67	2.47-7.62	0.004 ^a

^aP<0.05.

analysis revealed that the median survival time of patients in the positive *TBX3* gene expression group (37.5 months) was lower than that in the negative *TBX3* gene expression group (66 months), and there was a statistical difference (P<0.05). The 3- and 5-year survival rates in the negative *TBX3* gene expression group were 74 and 62%, respectively. The 3- and

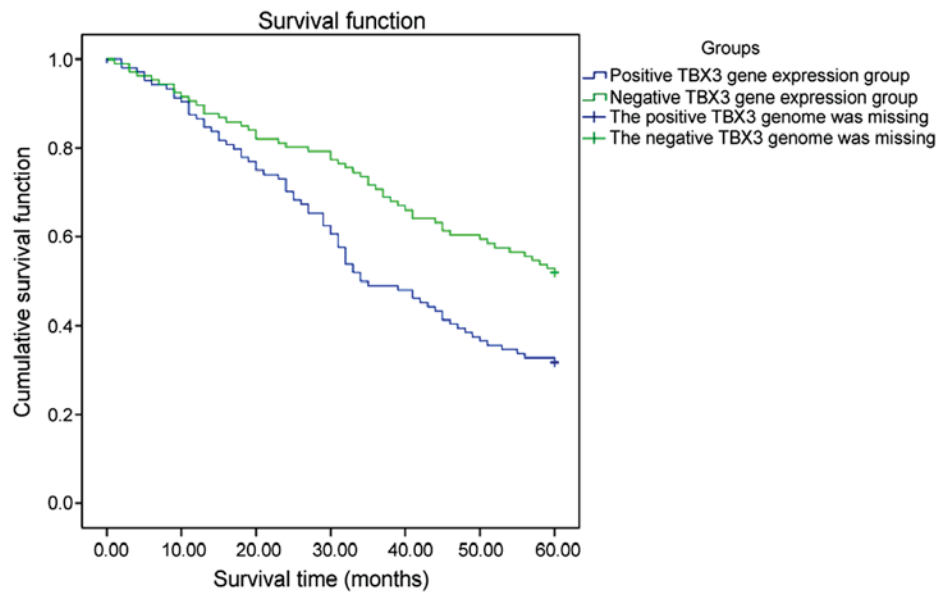


Figure 1. Survival curves of *TBX3* gene. The 3- and 5-year survival rates in the negative *TBX3* gene expression group are 74 and 62%, respectively. The 3- and 5-year survival rates in the positive *TBX3* gene expression group are 52 and 32%, respectively.

5-year survival rates in the positive *TBX3* gene expression group were 52 and 32%, respectively, and the differences were significant ($P < 0.05$) (Fig. 1).

Discussion

Studies in recent years have indicated that *TBX3* gene is highly expressed in multiple tumors, and studies have been conducted with regard to breast cancer, pancreatic cancer, colorectal cancer, lung cancer and melanoma (10-14). However, to the best of our knowledge, there is no detailed research on *TBX3* gene in renal carcinoma. Currently, the cause of renal carcinoma has yet to be elucidated, and most of the clinical manifestations of early renal carcinoma are not obvious. Most renal carcinomas are in advanced stage once they are identified, and the staging of the disease is closely associated with the 5-year survival rate (15,16). This experiment provided an important reference for early diagnosis, metastasis and other aspects of renal carcinoma by studying the expression level of *TBX3* gene in renal carcinoma tissues. It also offered a better basis for assisting clinicians to treat the disease. In the age of precision medicine (17), *TBX3* gene is to become a potentially effective therapeutic target and prognostic indicator in patients with renal carcinoma.

Current studies have revealed that *TBX3* gene is closely associated with the occurrence and development of many kinds of malignant tumors. *TBX3* gene has multiple oncogenic mechanisms, and studies have found that this gene can inhibit the expression of cancer suppressive factor p19ARF (human p19ARF) of inhibitor of CDK4/alternative reading frame (INK4a/ARF), in order to suppress cell growth (18). As a result, there is a small amount of *TBX3* gene expression in normal cells, which is consistent with Smith *et al* (18). Some scholars have found that *TBX3* gene can directly inhibit the cells by suppressing the promoters of cyclin p21 (Cip1/WAF1) (19). In addition, *TBX3* gene can act on the transcriptional activation of p21 by attenuating p53 (20). In breast cancer, for example, it

can also be observed that *TBX3* gene is upregulated. Previous findings have revealed that *TBX3* gene is associated with the Wnt/ β -catenin signaling pathway for tumor formation, and the overexpression of *TBX3* gene can inhibit the expression levels of suppressor genes in normal cells, thus accelerating the formation and development of malignant tumors (19,20). Other studies have found that *TBX3* gene can strengthen the invasiveness of tumors by suppressing E-cadherin on the surface of cell membrane and upregulating β -catenin (21,22), thus leading to the invasion and metastasis of malignant tumors. In the present study, the *TBX3* gene expression level in tumor tissues with lymph node metastasis of patients with renal carcinoma was obviously elevated, which may be associated with the fact that *TBX3* gene can trigger tumor metastasis. Scholars have found that *TBX3* gene can exert its carcinogenic effect by virtue of transforming growth factor- β 1 (TGF- β 1) (23-25). Therefore, *TBX3* gene can promote migration and invasion, playing a vital role in the migration of malignant tumors (26).

In this study, the expression levels of *TBX3* gene in renal carcinoma, adjacent and normal tissues were investigated using a large sample size. The specimens were collected in our hospital and the samples were strictly controlled in accordance with the inclusion and exclusion methods, to guarantee the reliability of the samples. The limitation of this study was that it was a single-center study, which had a certain sampling bias in terms of population and region. qPCR was applied in this experiment to reverse transcribe cDNA, in order to reversely infer the expression level of *TBX3* gene. As a result, it had decided that this experiment has shortcomings such as money and time consumption. However, it was fully demonstrated in this research that compared with that in the adjacent tissues, *TBX3* gene was obviously highly expressed in renal carcinoma tissues ($P < 0.05$). There was no significant difference in the expression levels of *TBX3* gene in normal renal and adjacent tissues ($P = 0.15$). Findings of the present study were consistent with results of the studies conducted by Wang *et al* (27) and Shan *et al* (28), which revealed that *TBX3* gene was highly

expressed in tumors. It was shown in the present study that the expression of *TBX3* gene in renal carcinoma tissues was not related to the patients' age, sex and tumor size ($P>0.05$), but it was associated with TNM staging and lymph node metastasis ($P<0.05$). The high expression of *TBX3* gene may be associated with tumor metastasis, results obtained by Li and Varelas (20,21). The results of the presents study showed that the median survival time of patients in the positive *TBX3* gene expression group (37.5 months) was lower than that in the negative *TBX3* gene expression group (66 months), and there was a statistical difference ($P<0.05$). The 3- and 5-year survival rates in the negative *TBX3* gene expression group were 74 and 62%, respectively. The 3- and 5-year survival rates in the positive *TBX3* gene expression group were 52 and 32%, respectively, and the differences were significant ($P<0.05$).

In conclusion, *TBX3* gene is highly expressed in renal carcinoma tissues, and is associated with TNM staging, lymph node metastasis and distant metastasis, and may be involved in the occurrence and metastasis of renal carcinoma.

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Availability of data and materials

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

Authors' contributions

YW researched the literature, designed the study, analyzed and interpreted the patient data.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The Central Hospital of Wuhan. Patients voluntarily accepted this research and signed the informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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