TPX2 as a Novel Prognostic Indicator and Promising Therapeutic Target in Triple-negative Breast Cancer

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Abstract

The relationship between targeting protein for xenopus kinesin-like protein 2 (TPX2) expression and triple negative breast cancer (TNBC) has not yet been studied. Herein, patients with confirmed TNBC are evaluated by immunohistochemical staining of TPX2. Our study reveals that elevated TPX2 protein level is significantly associated with worse outcomes, including progression-free and overall survival, in patients with TNBC. In conclusion, we demonstrate that TPX2 could be a novel prognostic marker of progression-free and overall survival in TNBC.

Introduction: Triple-negative breast cancer (TNBC), which lacks endocrine therapies and targeted therapies, has the worst prognosis of all breast cancers which remain the most common malignancy in women worldwide. Targeting protein for xenopus kinesin-like protein 2 (TPX2) is a microtubule-associated protein that is strongly correlated with chromosomal instability, resulting in the development of different human tumors. Herein, we investigated the relationship between the clinical outcome of TNBC and the expression level of the TPX2 protein. **Materials and Methods:** Patients initially treated at Tongji Hospital for confirmed TNBC were evaluated by immunohistochemical staining and retrospectively recruited into our study. The immunohistochemical staining evaluation of TPX2 was based on the staining intensity and extent. STATA was used to analyze all the data. **Results:** In total, 97 patients with TNBC were recruited into our study. The TPX2 protein was overexpressed in almost all patients with TNBC. Our study demonstrated that an elevated TPX2 protein level was significantly associated with worse outcomes in the patients with TNBC, including worse progression-free survival (PFS) and overall survival (OS) (log-rank test, $P < .001$). Our model also indicated that TPX2 expression was an independent predictor of OS (hazard ratio, 2.20; 95% confidence interval, 1.13-4.28; $P = .020$) but not of PFS ($P = .639$). **Conclusion:** In conclusion, we demonstrated that TPX2 could be a novel prognostic marker of PFS and OS after the initial treatment of TNBC. We also revealed that TPX2 expression could serve as an independent predictor of OS but not of PFS and a promising therapeutic target in patients with TNBC.

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Introduction

Triple-negative breast cancer (TNBC), which has only rare expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2), accounts for approximately 15% to 20% of all breast cancer cases which remain the most common malignant tumor in women worldwide. In China, it is estimated that the incidence rate of new cases was 2686 per 1 million people and that the mortality rate was 695 per 1 million deaths in 2015.[1] The exact causes of breast cancer are still unclear; however, it is believed that tumor development is related to a high body mass index (BMI), hormone dysfunction, and genetic changes such as BRCA1 or BRCA2 mutation. Patients with positive expression of hormone receptors (including ER and/or PR) or overexpression of Her2 usually have a better prognosis than patients with TNBC, as well as having the potential to be treated with anti-hormone endocrine therapy (eg, tamoxifen) or anti-HER2 targeted therapy (eg, herceptin); however, patients with TNBC lack

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endocrine and targeted therapy options, which contributes to TNBC having the worst prognosis of all breast cancers. Moreover, through whole-genome expression profiling, different genes overexpressed in TNBC have been identified, showing that TNBC is a heterogenic disease with different subtypes, such as basal-like, mesenchymal-like, and luminal androgen-positive type.[2-5] However, the exact genetic predisposition for TNBC is still poorly understood. Only chemotherapy was thought to be effective and recommended for advanced-stage TNBC before immune checkpoint inhibitors were used in TNBC; fortunately, it was reported recently that chemotherapy with a regimen of nab-paclitaxel plus the immune checkpoint inhibitor atezolizumab could produce a better prognosis than chemotherapy alone as a first-line treatment for advanced-stage TNBC with a programmed cell death ligand-1 (PD-L1) expression rate over 1%.[6] However, most patients with TNBC have a PD-L1 expression rate of less than 1% or even no expression, which is not appropriate for immune checkpoint inhibitor therapy; therefore, new targets and approaches are still required to be investigated to improve the clinical outcome of patients with TNBC.

Targeting protein for xenopus kinesin-like protein 2 (TPX2) is a microtubule-associated protein that activates the cell cycle kinase protein Aurora-A and then plays an essential role in the formation of the mitotic spindle.[7] Cells with a deficiency in TPX2 fail to form the TPX2-Aurora-A complex and thus develop short spindles, resulting in mitotic failure and cell apoptosis.[8] However, when overexpressed, TPX2 is strongly correlated with chromosomal instability, resulting in the development of different human tumors.[7,9] Although whole-genome expression profiling shows that TNBC is a heterogenic disease with different subtypes, TPX2 gene overexpression can be identified in almost all subtypes of TNBC.[2-5] Recently, it was reported in renal clear cell carcinoma that elevated mRNA and protein levels of TPX2 are associated with increased aggressiveness and poor outcomes.[10] It has also been reported in colon cancer that aberrant expression of TPX2 is significantly associated with unfavorable clinicopathological variables and that the overexpression of TPX2 plays a critical role in the progression and metastasis of colon cancer.[11] However, few studies have examined the relationship between the expression level of TPX2 and the outcome of TNBC.

Herein, we retrospectively investigated the protein expression level of TPX2 in patients with TNBC recruited in our hospital and demonstrated the relationship between the expression level of the TPX2 protein and clinical outcomes and the associations between the expression level and different clinical features.

Materials and Methods

Patients

Patients who underwent surgery or biopsy and had pathologically confirmed breast cancer that was immunohistochemically proven to be hormone receptor (both estrogen receptor and progesterone receptor)-negative and HER2-negative, less than 10% HER2-positive, or 10% to 30% HER2-positive but with a confirmed lack of amplification by fluorescence in situ hybridization (FISH) in Tongji Hospital between January 2008 and December 2015 were retrospectively recruited into our study. Clinical and pathologic variables, including tumor size (T stage), lymph node infiltration (N stage), distant tissue or organ metastasis (M stage) and differentiation grade, were evaluated by a pathologist and an oncologist at Tongji Hospital according to the National Comprehensive Cancer Network and World Health Organization (WHO) standards. Specifically, 5 nonconsecutive blocks with a thickness of 4 mm were collected for each patient. Written consent for the use of all clinical data was provided by patients or their relatives if the patient had passed away. This retrospective study was approved by the ethics committee of Tongji Hospital affiliated with Tongji Medical College of Huazhong University of Science and Technology.

Immunohistochemistry (IHC)

For each patient, hematoxylin-eosin staining was performed to confirm the diagnosis of breast cancer. Three sections per patient were stained with a mouse anti-TPX2 monoclonal antibody (1:200 dilution; Abcam, Shanghai) using a standardized procedure guided by instruction. Briefly, the sections were deparaffinized in xylene and rehydrated in a graded alcohol series. The slides were then incubated with the anti-TPX2 antibody or phosphate-buffered saline as a negative control overnight and then exposed to a biotinylated secondary antibody, followed by an incubation with DAB for 30 minutes. The IHC-stained sections were read by 2 independent pathologists (Y.L. and X.T.) in a blinded manner. Evaluation was based on the staining intensity and extent. The staining intensity was graded as follows: 0, no staining; 1+, weak staining; 2+, moderate staining; and 3+, strong staining. The staining area was scored using the following scale: 0, no stained cells; 1+, < 10% of the tissue stained positive; 2+, 10% to 30% stained positive; and 3+, > 30% stained positive. The sum that represented the staining score (intensity plus extent) index was designated as follows: 1 to 2, weak expression; 3 to 4, moderate expression; and 5 to 6, strong expression.[10-12]

Statistical Analysis

In this study, STATA (version 12.0, Stata Corporation, College Station, TX) was used to analyze all the data. Analysis of variance was carried out when comparing different clinical features among different groups based on a 2-way statistical analysis. Progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier curves, and the differences in PFS and OS among patients stratified by their TPX2 protein expression was evaluated using the log-rank test. The Cox proportional hazards regression model was used to calculate multivariate hazard ratios (HRs) for variables and to identify factors that independently predicted PFS and OS. A P value $\leq .05$ was considered statistically significant.

Results

Basic Characteristics of Recruited Patients

To validate our findings, 97 patients in total with evaluable pathologic specimens collected by surgery or biopsy and a diagnosis of TNBC by hematoxylin-eosin and IHC staining between January 2008 and December 2015 were involved in our analysis. The basic characteristics are summarized in Table 1. Specifically, the patients were all female, and the median age was 48.5 years (range, 25.0-76.0 years). The median follow-up time was 52.4 months (range, 5.1-120.0 months). Unlike in Western countries, there were few patients (4/97) with a high BMI in our study. More than one-half (52/97) of the patients recurred by the end of the follow-up time,

Table 1 Basal Characteristics of Patients

Clinical Information	N (%)
Age, y	
Mean	48.5
Range	25-76
BMI, kg/m^2	
<25	93 (96.0)
≥ 25	4 (4.0)
Stage	
I	10 (10.3)
II	37 (38.1)
III	29 (29.9)
IV	21 (21.6)
T stage	
T1	13 (13.4)
T2	36 (37.1)
T3	23 (23.7)
T4	24 (24.7)
N stage	
N0	32 (33.0)
N1	16 (16.5)
N2	22 (22.6)
N3	27 (27.8)
M stage	
M0	76 (78.4)
M1	21 (21.6)
Treatment received anthracene plus taxel	
Anthracene only	64 (66.0)
Taxel only	7 (7.2)
No or other regimen	16 (16.5)
Differentiation (WHO)	10 (10.3)
I	11 (11.3)
II	34 (35.1)
III	52 (53.6)
Disease recurrence	
Yes	52 (53.6)
No	45 (46.4)

Abbreviations: BMI = body mass index; WHO = World Health Organization.

indicating the aggressive biological behavior and poor prognosis of TNBC. Unlike patients with other types of breast cancer, most of the patients with TNBC were in an advanced or late stage at the time of diagnosis, specifically with high T and N stages. For example, 48.4% of the patients were graded as T3 or T4 initially, and more than one-half (50.4%) of the patients were graded as N2 or N3 at the time of diagnosis. Moreover, our study only included 11 (11.3%) of 97 patients with WHO grade I differentiation; most patients had WHO grade aggressive disease, and more than one-half (53.6%) were diagnosed with WHO III differentiation, indicating the intrinsic characteristic of this poorly differentiated malignancy. In terms of treatment, most (66.0%) patients received regimens of both anthracene and paclitaxel, which are recommended for TNBC, concurrently or sequentially.

Association Between TPX2 Expression and TNBC Clinical Prognosis

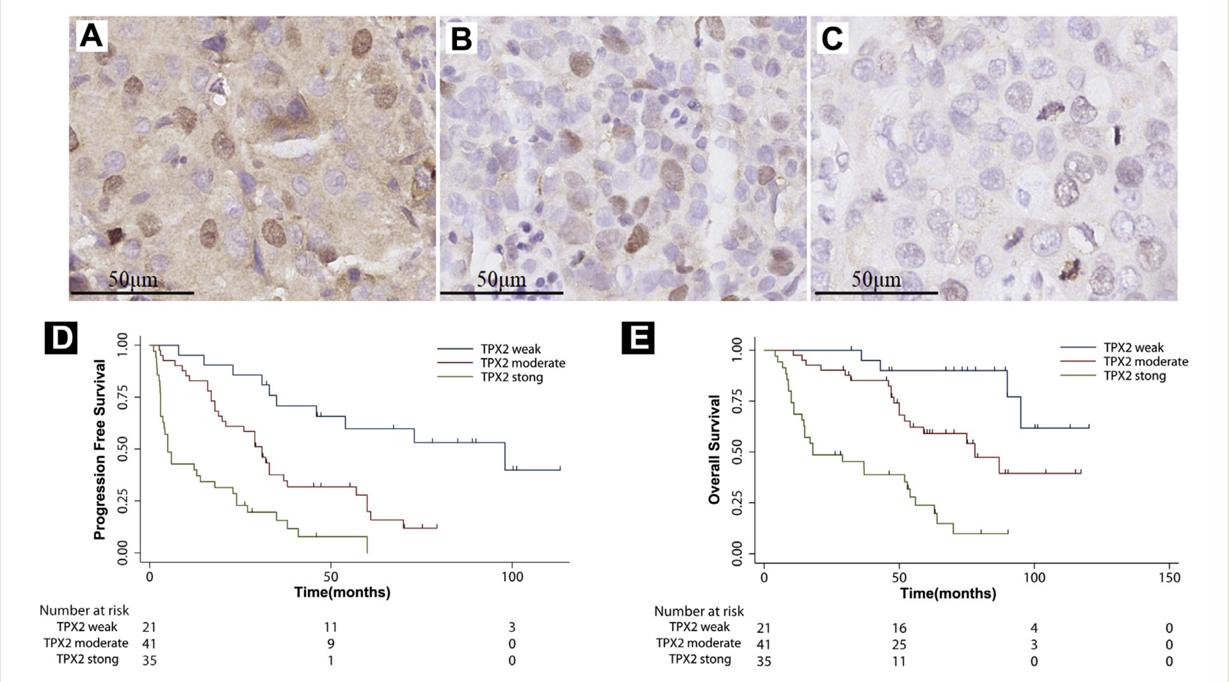
To determine whether TPX2 expression is associated with the clinical prognosis of TNBC, TPX2 expression was detected by IHC staining to calculate intensity and extent scores. We found that the TPX2 protein was overexpressed in almost all patients with TNBC. Representative staining images are shown in Figure 1A-C. In general, the TPX2 protein was expressed in both the cytoplasm and nucleus; according to the methods mentioned above, the TPX2 expression rate could be used to subdivide the patients into 3 groups: the weak, moderate, and strong expression groups, based on the staining intensity plus extent score.

Then, Kaplan-Meier analyses were performed for both PFS and OS. The proportions of patients who developed progression or recurrence after initial treatment were significantly different among the different TPX2 expression groups (Figure 1D). Specifically, the strong TPX2 expression group was associated with the worst median PFS, whereas the weak expression group was associated with the best median PFS (log-rank test, $P < .001$; TPX2 strong group, 35 (36.1%) of 97 patients, median PFS, 14.2 months [range, 1.7-60.4 months]; TPX2 moderate group, 41 (42.3%) of 97 patients, median PFS, 32.4 months [range, 3.4-78.9 months]; and TPX2 weak group, 21 (21.6%) of 97 patients, median PFS, 60.2 months [range, 8.1-113.0 months]) (Figure 1D). OS was also significantly different among the different groups (Figure 1E). This finding indicated that the expression level of TPX2 was substantially correlated with OS in the patients with TNBC in our study. The patients with weak expression of TPX2 had significantly longer median OS than those with strong TPX2 expression (log-rank test, $P < .001$; TPX2 strong group, median OS, 31.6 months [range, 5.6-89.4 months]; TPX2 moderate group, median OS, 57.6 months [range, 10.8-117.0 months]; and TPX2 weak group, median OS, 76.8 months [range, 32.5-120.0 months]). In conclusion, our analysis demonstrated that the TPX2 expression level could serve as a novel prognostic marker for both OS and PFS after the initial treatment of TNBC.

TPX2 expression was significantly associated with tumor stage and served as an independent predictor of OS in patients with TNBC.

To determine the associations between TPX2 expression and multiple clinical features, Analyses of variance were carried out to analyze our data (Table 2). In general, there were more patients with weak TPX2 expression with stage I TNBC (8/10) than with stage IV TNBC (0/21), whereas there were fewer patients with strong TPX2 expression with stage I TNBC (1/10) than with stage IV TNBC (18/21). The P value of the association between TPX2 expression and clinical stage was significant ($P < .001$). Specifically, a quantitative analysis showed that TPX2 expression was also associated with T, N, and M stages ($P < .001$ for all); in general, the earlier the stage was, the lower the expression of the TPX2 protein. Interestingly, TPX2 expression was also correlated with pathologic differentiation grade. There were more patients with WHO grade I differentiation in the weak TPX2 expression patient population (6/10) than in the moderate (9/34) or strong (6/52) patient populations, and the P value was .009. Collectively, these results revealed that TPX2 expression was significantly associated with tumor phase and pathologic differentiation grade, based on our data.

Figure 1 Representative Immunohistochemical Staining Images and Outcomes of Different TPX2 Expression Groups of Patients With Triple-negative Breast Cancer. A-C, Representative Microscopic Images of Strong, Moderate, and Weak Staining for TPX2 (40×); D, E, Kaplan-Meier Curves for the Progression-free and Overall Survival of the Different TPX2 Expression Groups



Abbreviation: TPX2 = targeting protein for xenopus kinesin-like protein 2.

Furthermore, a multivariate analysis was performed to examine whether TPX2 expression serves as an independent predictor of PFS and OS (Table 3). Interestingly, after correcting for stage, T stage, N stage, M stage, BMI, and pathologic differentiation grade, our model indicated that TPX2 expression was an independent predictor of OS (HR, 2.20; 95% confidence interval, 1.13-4.28; $P = .020$) but not of PFS (HR, 1.13; 95% confidence interval, 0.70-1.81; $P = .639$).

Discussion

TNBC is the subtype of malignant breast carcinoma with the worst prognosis. Without targeted therapies or endocrine therapies, chemotherapy is thought to be the recommended treatment in the adjuvant therapy context after surgery and in the neoadjuvant context; it is also recommended as the first-line treatment in patients with advanced stage TNBC. However, most patients are diagnosed at an advanced stage or will experience recurrence or progression after initial chemotherapy, contributing to the poor prognosis of TNBC. Thus, a new approach and strategy is required for the treatment of TNBC.

In our study, TPX2 was found to be expressed in almost all patients with TNBC, and the expression level was correlated with the prognosis of TNBC, including both PFS and OS. Specifically, our data showed that increased protein expression of TPX2 was associated with more aggressive biological behavior and worse outcomes than low expression of TPX2. Furthermore, elevated expression of the TPX2 protein was associated with worse T, N, and M stages, a high pathologic differentiation grade, and worse PFS and OS. Similar to our study, other studies have reported that increased TPX2 protein expression is associated with a worse prognosis in renal clear-cell carcinoma, gastric cancer, and colon cancer.[10,11,13]

TPX2 is required and essential for microtubule formation and spindle assembly during mitosis. Cells lacking TPX2 have difficulties assembling their spindle, resulting in mitotic failure.[8] It has been reported that an increased level of TPX2 protein expression is found in several malignant tumors and that downregulation of TPX2 expression in colon cancer cells and glioma can suppress proliferation and inhibit migratory and invasive abilities through the PI3K/AKT/mTOR pathway in vivo and in vitro.[10,11,14,15] Our study also found that the TPX2 protein was overexpressed in almost all patients with TNBC and that the extent of this elevation correlated with the aggressiveness of the biological behavior of this malignancy. Thus, it is reasonable to suggest that TPX2 expression is not only a novel marker to identify disease severity but also a therapeutic target in TNBC and other types of malignant carcinomas, such as colon cancer. Interestingly, it has been reported that silencing TPX2 can substantially promote paclitaxel sensitivity in pancreatic cancer cells, suggesting that a TPX2 inhibitor combined with chemotherapy could be a potential approach for TNBC treatment, especially in patients with a PD-L1 expression rate of less than 1%.[14]

Overexpression of the TPX2 protein is strongly correlated with chromosomal instability, which serves as a potential mechanism of early tumorigenesis,[16] and this process was also recently reported to

Table 2 Correlation Between TPX2 Expression and Clinical Characteristics of TNBC

Clinical Information	TPX2 Expression			*P* Value
	Weak	Moderate	Strong	
Stage				<.001
I	8	1	1	
II	10	23	4	
III	3	14	12	
IV	0	3	18	
BMI, kg/m^2				
<25	20	39	34	.694
≥25	1	2	1	
T stage				<.001
T1	8	3	2	
T2	8	17	11	
T3	3	15	5	
T4	2	5	17	
N stage				<.001
N0	16	14	2	
N1	2	11	3	
N2	1	10	11	
N3	2	6	19	
M stage				<.001
M0	21	38	17	
M1	0	4	17	
Differentiation (WHO)				.009
I	6	4	1	
II	9	11	14	
III	6	26	20	

Abbreviations: BMI = body mass index; TNBC = triple-negative breast cancer; TPX2 = targeting protein for xenopus kinesin-like protein 2; WHO = World Health Organization.

Table 3 Multivariate Analysis by Cox Proportional Hazards Ratio to Evaluate TPX2 Expression in PFS and OS

Variable	HR	95% CI	*P*
PFS			
TPX2 expression	1.13	0.70-1.81	.639
Stage	2.88	1.05-7.92	.040
T stage	1.60	0.97-2.63	.066
N stage	2.63	1.59-4.34	.001
Metastasis	6.15	1.26-30.05	.025
WHO differentiation	1.09	0.72-1.65	.673
BMI	1.55	0.46-5.21	.479
OS			
TPX2 expression	2.20	1.13-4.28	.020
Stage	1.53	0.38-6.12	.548
T stage	3.20	1.67-6.13	.001
N stage	2.30	1.23-4.30	.009
Metastasis	6.51	0.76-56.07	.088
WHO differentiation	1.12	0.60-2.09	.714
BMI	1.02	0.22-4.69	.983

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; TPX2 = targeting protein for xenopus kinesin-like protein 2; WHO = World Health Organization.

drive metastasis through a cytosolic DNA response by driving tumor cells to imitate a myeloid-derived naive immune cell phenotype to escape type I interferon-dependent antitumor immunity.[7,17,18] It is reasonable to speculate that radiotherapy might not be helpful in patients with TPX2-overexpressing TNBC because radiotherapy-induced cytosolic DNA release can activate the cGAS-sting pathway but does not activate the downstream classical NF-κB pathway instead of the nonclassical NF-κB pathway.[19] In our study, we revealed that high TPX2 protein expression was strongly associated with more aggressive local lymph node infiltration and distant organ metastasis in patients with TNBC, suggesting that high expression of TPX2 might drive local and distant metastasis because high TPX2 protein expression promotes increased chromosomal instability, resulting in more tumor cells easily migrating. Interestingly, it has been reported that targeting TPX2 with specific peptides is a favorable approach to improve the effects of cytotoxic T lymphocytes in T cell-mediated immunotherapy in primary hepatic carcinoma.[20] It is worth noting that targeting TPX2 could be a promising approach to restore type I immune reactions and thus suppress local lymph node infiltration and distant organ metastasis.

However, our work does not demonstrate associations between the TPX2 expression level and the subtypes of TNBC, such as basal-like, mesenchymal-like, and luminal androgen-positive type, through genomic analysis. Although TPX2 was overexpressed in almost all patients with TNBC in our study, the details of the correlations between each subtype of TNBC and TPX2 expression should be given further study. Additionally, as this was a retrospective study, we did not discuss the mechanism of TPX2 overexpression associated with the outcome of TNBC. More work should be performed to further investigate this association in a prospective study.

Conclusion

In conclusion, we retrospectively analyzed 97 patients with TNBC in our study. We demonstrated that TPX2 was overexpressed in almost all patients with TNBC and could be a novel prognostic marker of PFS and OS after the initial treatment of TNBC. Moreover, we also revealed that TPX2 expression was significantly associated with tumor phase and pathologic differentiation grade and could serve as an independent predictor of OS but not of PFS in the patients with TNBC in our analysis. TPX2 could be a promising therapeutic target when combined with chemotherapy or radiotherapy, and targeting TPX2 could be a promising approach to restore type I immune reactions, thus inhibiting tumorigenesis and suppressing local lymph node infiltration and distant organ metastasis.

Clinical Practice Points

- Overexpression of TPX2 has been reported in many types of carcinoma; however, the relationship between TPX2 expression and TNBC is still unknown.
- In our study, an elevated TPX2 protein level was found to be significantly associated with worse outcome, including PFS and OS, in TNBC.
- Forwardly, TPX2 could serve as a prognostic indicator of TNBC. Thus, there is potential that TPX2 could be a new therapeutic target for the treatment of TNBC.

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Disclosure

The authors have stated that they have no conflicts of interest.

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