TXR1 and TSP1 expression varies by the molecular subtypes of breast cancer patients who received previous docetaxel-based first-line chemotherapy

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Abstract

The expression of taxol resistance gene 1 and thrombospondin 1 remains unknown in human breast cancer tissues. In the current study, we sought to measure the mRNA expression levels of taxol resistance gene 1 and thrombospondin 1 in breast cancer tissue and adjacent normal tissue specimens and further analyzed their expression according to the molecular subtypes and age of breast cancer patients who had received taxane-containing regimens. Archived breast cancer and adjacent non-tumor tissue specimens were obtained at Beijing Friendship Hospital, Beijing, China. The mRNA transcript levels of taxol resistance gene 1, thrombospondin 1 and multi-drug resistance 1 were determined by quantitative RT-PCR. Taxol resistance gene 1 and multi-drug resistance 1 protein levels were measured by immunoblotting assays. Forty-nine archived breast cancer tissue specimens were included. The majority of the specimens (65.3%) were of the molecular subtype A followed by triple negative breast cancer (14.3%). The mRNA transcript levels of taxol resistance gene 1, thrombospondin 1 and multi-drug resistance 1 in breast cancer tissues were higher than those of adjacent normal tissues. The mRNA expression of *TXR1* in the HER2 subtype (4.513 ± 0.810) was the highest and in the Luminal B subtype was the lowest (3.103 ± 0.417) among the four molecular subtypes. The HER2 subtype also had the highest mRNA expression of thrombospondin 1 (4.827 ± 0.927) and the Luminal B subtype had the lowest *TSP1* mRNA level (3.197 ± 0.565) among the four molecular subtypes. Our study represents the first attempt in delineating taxol resistance gene 1 and thrombospondin 1 expression in breast cancer and we demonstrate that taxol resistance gene 1 and thrombospondin 1 expression may vary according to the molecular subtypes of breast cancer.

Keywords: Breast cancer, taxane, thrombospondin 1, taxol resistance gene 1, RT-PCR, molecular subtype

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Introduction

Breast cancer remains the most prevalent type of cancer in women, with an estimated annual incidence of 1.6 million cases globally.¹ The incidence of breast cancer has been also rapidly increased over the previous two decades and now has become the most common form of cancer among women in China.^{2,3} Several classes of chemotherapeutic agents, including taxanes, are currently available to be used either singly or in combination. Adjuvant systemic chemotherapies have been shown to significantly reduce the risk of relapse and improve the overall survival (OS) of breast cancer patients. The taxanes such as paclitaxel and docetaxel represent an important class of anti-neoplastic agents that interfere with microtubule function, leading to altered mitosis and cellular death. Prior adjuvant taxane-containing chemotherapy has been

shown to be a prognostic factor for the OS and progression-free survival (PFS) breast cancer patients.⁴ However, patients with prior exposure to adjuvant taxanes may acquire drug resistance to taxanes, hampering the efficacy of this class of drugs.⁵

Chemoresistance is a major factor of poor response and reduced OS in breast cancer patients. The multi-drug resistance 1 (*MDR1*) gene, a member of the ABC family, encodes a membrane-bound phosphoglycoprotein (P-gp), which acts as an efflux pump and provides cell protection against cytotoxic agents. Increased P-gp expression has been demonstrated to be a major contributor of acquired chemotherapeutic resistance.⁶

Elucidating the mechanisms of chemoresistance is crucial to understand how to improve the use of taxanes, a class of anti-neoplastic agents that are widely used clinically.

Downregulation of thrombospondin 1 (*TSP1*) through the taxol resistance gene 1 (*TXR1*) overexpression has been recently proposed as a novel mechanism that modulates the cellular cytotoxicity of taxanes *in vitro*.⁷ *TSP1* is a secreted glycoprotein that is predominantly stored in platelets. It is also present in normal breast secretions and high levels of *TSP* are observed in malignant breast secretions and cytosols.^{8,9} *TSP1* can mediate tumor growth suppression via blocking angiogenesis.^{10,11} An earlier study showed that docetaxel induced expression of *TSP-1* in head and neck squamous cell carcinoma cells.¹² Lih *et al.*⁷ demonstrated that *TSP1* may be an effector of the apoptotic response to taxane treatment and *TXR1* may mediate taxane resistance by repressing *TSP1* levels. Furthermore, van Ark-Otte *et al.*¹³ and Papadaki *et al.*¹⁴ showed that overexpression of *TXR1* was significantly correlated with downregulation of *TSP1* expression and the expression of both genes was significantly correlated with treatment response in human lung and breast cancer cells. Papadaki *et al.*¹⁵ also demonstrated that low *TXR1* and high *TSP1* expression was an independent factor for increased PFS docetaxel-based first-line chemotherapy in patients with advanced/metastatic non-small-cell lung cancer. In breast cancer MCF-7 cells, Bai *et al.*¹⁶ showed that increased expression of *TXR1* was associated with a taxol-resistant phenotype.

However, the expression of *TXR1* and *TSP1* remains unknown in human breast cancer tissues. We hypothesize that *TXR1* and *TSP1* expression is dysregulated in breast cancer tissues and may be of prognostic significance for breast cancer patients who have received taxane-containing regimens. In the current study, we sought to measure the levels of *TXR1* and *TSP1* in breast cancer tissue and adjacent normal tissue specimens and further analyzed the expression of these molecules according to the molecular subtypes and age of breast cancer patients who had received taxane-containing regimens.

Materials and methods

Tissue acquisition

We obtained archived breast cancer and adjacent non-tumor tissue specimens at Beijing Friendship Hospital, Beijing, China. These specimens were snap frozen surgical samples of patients who were diagnosed with breast cancer between January 2012 and December 2014 at the Department of General Surgery, Beijing Friendship Hospital. A patient was included in the study (1) if she had a pathological diagnosis of adenocarcinoma of the breast; (2) if she was at least 18 years of age; (3) if she had received adjuvant taxane-based chemotherapeutic regimens. A subject was excluded (1) if she had lack of definite ER/PR status; (2) if she had received <2 cycles of chemotherapy as the first-line adjuvant chemotherapy; (3) if her medical records and follow-up data were incomplete; (4) if she had other primary tumors.

The study protocol was approved by the Ethics Committee of Beijing Friendship Hospital, and the study was performed in accordance with the institutional and state guidelines on the experimental use of human tissue specimens.

Quantitative RT-PCR

Total cellular RNA was prepared using TRIzol[®] reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. First strand cDNA synthesis was performed using the Reverse Transcription System (Promega, Madison, WI, USA) as instructed by the manufacturer in a 20 μ L volume containing 1 μ g total RNA, 0.5 μ g RT primer, 2 μ L 10 $\times$ reverse transcriptase buffer, 2 μ L 10 mM dNTPs, 0.5 μ L RNase inhibitor, 7.9 μ L nuclease-free water, 4 μ L 25 mM MgCl₂, and 15 U reverse transcriptase for 60 min at 42°C and 5 min at 95°C in triplicate. The mRNA transcript levels were analyzed by quantitative RT-PCR using a 7500 Real-Time PCR system (ABI, Oyster Bay, NY, USA). The following primers (Sangon Biotech, Shanghai, China) were used: *Txr1*, 5'-GCACACTGTTGATATGGAAGGG-3' (sense) and 5'-AGCTTTGGGAAGCGTGTGTA-3' (antisense); *TSP1*, 5'-AGTCATAGCAACATTCACAGTTTGT-3' (sense) and 5'-TCTTATGGGGGCCCTTGACT-3' (antisense); *MDR1*, 5'-AGAGTCAAGGAGCATGGCAC-3' (sense) and 5'-ACAGTCAGAGTTCAGTGGCG-3' (antisense). Relative expression was calculated using the comparative cycle threshold (Ct) method ($\Delta\Delta$ Ct), and β -actin was used for normalization. Each reaction was performed in triplicate. Cutoff points were calculated according to the median value for the mRNA expression of each gene. Tumor samples with mRNA expression above or equal to the median were considered as samples with high expression, whereas those with value below the median as samples with low expression.

Western blot analysis

Whole cell extracts were prepared using keyGEN Whole Cell Lysis Assay (KeyGEN BioTECH, NanJing, China). Western blotting assays were performed as previously depicted,¹⁷ and primary antibodies against β -actin (Santa Cruz Biotechnology, Santa Cruz, CA), *TXR1* and *MDR1* (both from Abcam) were used. The protein bands were visualized using Immobilon Western Chemiluminescent HRP Substrate (Merck Millipore, Darmstadt Germany). Densitometric analysis was performed using Image J. Protein expression was normalized against β -actin.

Statistical analysis

Data were expressed as mean $\pm$ SEM for normally distributed data and median and interquartile range (IQR) for non-normally distributed data. Differences between groups were analyzed by Wilcoxon rank sum test. *P* values less than 0.05 were considered statistically significant.

Results

Expression of *TXR1*, *TSP1*, and *MDR1* in breast cancer tissues

Forty-nine archived breast cancer tissue specimens were included in the current study. The majority of the specimens (65.3%) were of the molecular subtype A followed by triple negative breast cancer (14.3%). Only 10.2% of the patients each were of the HER2 and Luminal B subtype.

We examined the mRNA expression of *TXR1*, *TSP1*, and *MDR1* in breast cancer tissues and adjacent normal tissue

Table 1 Non-tumoral and tumoral mRNA expression of *TXR1*, *TSP1*, and *MDR1* determined by RT-PCR.^a

Group	Gene	N	ΔC_T	$\Delta\Delta C_T$ (T-N)	$2^{-\Delta\Delta C_T}$
Normal tissues	<i>TXR</i>	12	3.507 ± 0.367	0.000 ± 0.367	1.000 (0.776–1.289)
	<i>TSP1</i>	12	3.391 ± 0.412	0.000 ± 0.412	1.000 (0.753–1.330)
	<i>MDR1</i>	11	8.860 ± 1.488	0.000 ± 1.488	1.000 (0.357–2.805)
Tumor tissues	<i>TXR</i>	49	3.839 ± 0.231	0.332 ± 0.231	0.795 (0.677–0.933)
	<i>TSP1</i>	49	3.651 ± 0.333	0.260 ± 0.333	0.835 (0.663–1.052)
	<i>MDR1</i>	42	8.973 ± 0.600	0.112 ± 0.600	0.925 (0.663–1.402)

TXR1: taxol resistance gene 1; *TSP1*: thrombospondin; *MDR1*: multi-drug resistance 1.

^a ΔC_T represents the difference in C_T between target genes (*TXR*, *TSP1*, and *MDR1*) and the internal reference gene (β -actin). $\Delta\Delta C_T$ (T-N) represents the difference in C_T between tumor tissues and normal tissues. The $2^{-\Delta\Delta C_T}$ method is used to express the amount of each gene in tumor tissues relative to that of normal tissues.

tissues (Table 1). Our quantitative RT-PCR showed that the mRNA transcript levels of *TXR1* in breast cancer tissues (3.839 ± 0.231) were higher than those of adjacent normal tissues (3.507 ± 0.367). Furthermore, the mRNA transcript levels of *TSP1* in breast cancer tissues (3.651 ± 0.333) were also higher than those of adjacent normal tissues (3.391 ± 0.412). The mRNA transcript levels of *MDR1* in breast cancer tissues (8.973 ± 0.600) were higher than those of adjacent normal tissues (8.860 ± 1.488).

We further examined the protein expression of *MDR1* and *TXR1* by immunoblotting assays (Table 2). We found that the normal tissues had a noticeably higher median expression of *MDR1* (median, 3.300 (IQR, 1.166, 12.387)) than the paired tumor tissues (median, 1.286 (IQR, 1.046, 3.056)) (Wilcoxon rank sum test, $P = 0.010$). No apparent difference was observed in the expression of *PRR13* between normal tissues (median, 1.173 (IQR, 0.550, 2.667)) and the paired tumor tissues (median, 1.026 (IQR, 0.908, 1.574)) (Wilcoxon rank sum test, $P = 0.918$).

TXR1, TSP1, and MDR1 expression according to molecular subtypes of breast cancer

We further analyzed the mRNA expression of *TXR1*, *TSP1*, and *MDR1* in breast cancer tissues according to the molecular subtypes (Table 3). We found that the mRNA expression of *TXR1* in the HER2 subtype (4.513 ± 0.810) was the highest and in the Luminal B subtype was the lowest (3.103 ± 0.417) among the four molecular subtypes. The HER2 subtype also had the highest mRNA expression of *TSP1* (4.827 ± 0.927) and the Luminal B subtype had the lowest *TSP1* mRNA level (3.197 ± 0.565) among the four molecular subtypes. Furthermore, the HER2 subtype had the highest mRNA expression of *MDR1* (10.432 ± 1.997) among the four molecular subtypes, while *MDR1* mRNA levels were comparable among the other three molecular subtypes ($P < 0.05$). These findings indicated that the mRNA expression of *TXR1*, *TSP1*, and *MDR1* in breast cancer tissues may vary according to their molecular subtypes.

TXR1, TSP1, and MDR1 expression according to the age of breast cancer patients

We were interested in whether breast cancer patients of different age differed in the mRNA expression of *TXR1*, *TSP1*,

Table 2 Relative protein expression of *TXR1* and *MDR1* in tumoral and non-tumoral tissues of breast cancer patients determined by Western blotting assays.^a

Protein	Relative expression, median (IQR)		Statistical volume	P^*
	Normal tissues, $n = 16$	Tumor tissues, $n = 16$		
PRR13	1.173 (0.550, 2.667)	1.026 (0.908, 1.574)	−0.103	0.918
MDR1	3.300 (1.166, 12.387)	1.286 (1.046, 3.056)	−2.585	0.010

TXR1: taxol resistance gene 1; *TSP1*: thrombospondin; *MDR1*: multi-drug resistance 1.

^aDensitometric analysis was performed using Image J. Protein expression was normalized against β -actin.

*Wilcoxon rank sum test.

and *MDR1* in breast cancer tissues. We found that the mRNA expression of *TXR1* was comparable among patients < 60 years (4.475 ± 0.268) and those ≥ 60 years (4.413 ± 0.394). The mRNA expression of *TSP1* was higher in patients < 60 years (3.768 ± 0.474) and those ≥ 60 years (3.466 ± 0.433) and the mRNA expression of *MDR1* was higher in patients < 60 years (9.294 ± 0.813) and those ≥ 60 years (8.500 ± 0.892) (Table 4).

Discussion

Currently, the expression of *TXR1* and *TSP1* in breast cancer tissues remains undefined. In the present study, we determined the levels of *TXR1* and *TSP1* in breast cancer tissues and adjacent normal tissues. We found that the mRNA transcript levels of *TXR1*, *TSP1*, and *MDR1* in breast cancer tissues were higher than those of normal adjacent tissues. When the mRNA expression of *TXR1*, *TSP1* and *MDR1* in breast cancer tissues was stratified according to the molecular subtypes of breast cancer, the HER2 subtype had the highest mRNA expression of *TXR1*, *TSP1*, and *MDR1* among the four molecular subtypes. On the other hand, the Luminal B subtype had the lowest mRNA expression of *TXR1*, and *TSP1*. Our findings indicate that *TXR1* and *TSP1* expression may vary according to the molecular subtypes of breast cancer.

Table 3 TXR1, TSP1, and MDR1 expression according to molecular subtypes of breast cancer determined by RT-PCR.^a

Molecular subtypes	Gene	n	ΔC_T	$\Delta\Delta C_T$	$2^{-\Delta\Delta C_T}$
HER-2	TXR1	5	4.513 ± 0.810	0.000 ± 0.810	1.000 (0.570–1.753)
	TSP1	5	4.827 ± 0.927	0.000 ± 0.927	1.000 (0.526–1.901)
	MDR1	4	10.432 ± 1.997	0.000 ± 1.997	1.000 (0.254–3.935)
Luminal A	TXR1	32	3.793 ± 0.292	−0.720 ± 0.292	1.648 (1.345–2.017)
	TSP1	31	3.548 ± 0.468	−1.279 ± 0.468	2.427 (1.755–3.358)
	MDR1	26	8.763 ± 0.810	−1.669 ± 0.810	3.180 (1.814–5.574)
Luminal B	TXR1	5	3.103 ± 0.417	−1.410 ± 0.417	2.657 (1.989–3.548)
	TSP1	6	3.197 ± 0.565	−1.631 ± 0.565	3.096 (2.093–4.581)
	MDR1	6	8.978 ± 1.933	−1.454 ± 1.933	2.739 (0.717–10.463)
Triple negative	TXR1	7	4.093 ± 0.677	−0.420 ± 0.677	1.338 (0.837–2.138)
	TSP1	7	3.657 ± 0.711	−1.170 ± 0.711	2.250 (1.374–3.684)
	MDR1	6	8.904 ± 0.910	−1.528 ± 0.910	2.885 (1.535–5.421)

TXR1: taxol resistance gene 1; TSP1: thrombospondin; MDR1: multi-drug resistance 1.

^a ΔC_T represents the difference in C_T between target genes (TXR, TSP1, and MDR1) and the internal reference gene (β -actin). $\Delta\Delta C_T$ (T-N) represents the difference in C_T between tumor tissues and normal tissues. The $2^{-\Delta\Delta C_T}$ method is used to express the amount of each gene in tumor tissues relative to that of normal tissues.

Table 4 TXR1, TSP1, and MDR1 expression according to the age of breast cancer patients determined by RT-PCR.^a

Age, years	Gene	N	ΔC_T	$\Delta\Delta C_T$	$2^{-\Delta\Delta C_T}$
<60	TXR1	30	4.475 ± 0.268	0.000 ± 0.268	1.000 (0.830–1.205)
	TSP1	30	3.768 ± 0.474	0.000 ± 0.474	1.000 (0.720–1.389)
	MDR1	25	9.294 ± 0.813	0.000 ± 0.813	1.000 (0.569–1.757)
≥60	TXR1	19	4.413 ± 0.394	0.937 ± 0.394	0.522 (0.174–1.898)
	TSP1	19	3.466 ± 0.433	−0.302 ± 0.433	1.233 (0.914–1.664)
	MDR1	17	8.500 ± 0.892	−0.795 ± 0.892	1.735 (.935–3.218)

^a ΔC_T represents the difference in C_T between target genes (TXR, TSP1, and MDR1) and the internal reference gene (β -actin).

$\Delta\Delta C_T$ (T-N) represents the difference in C_T between tumor tissues and normal tissues. The $2^{-\Delta\Delta C_T}$ method is used to express the amount of each gene in tumor tissues relative to that of normal tissues.

Interestingly, van Ark-Otte *et al.*¹³ have shown an inverse relationship between TXR1 expression and TSP1 expression in human lung and breast cancer cells. Lih *et al.*⁷ have demonstrated that increase in TXR1 and decrease in TSP1 expression was highly correlated with taxane resistance in cancer cells. Bai *et al.*¹⁶ showed that TXR1 expression was associated with a resistant phenotype of breast cancer cells *in vitro*. However, it remains unknown whether TXR1 and TSP1 expression correlates with the outcome of breast cancer patients who receive taxane-based chemotherapy. However, because of the low number of patients in each molecular subtype, we were unable to investigate the significance of TXR1 and TSP1 expression for the therapeutic outcome of each individual molecular subtype.

The study has several limitations. The study lacks a non-taxane treated control arm and we cannot determine whether TXR1 and TSP1 expression is a specific predictor of therapeutic response to taxane-based regimens. The results of this study should be also interpreted with caution because of its retrospective nature and the limited sample

size. Nevertheless, it remains clinically important to evaluate the significance of TXR1 and TSP1 expression in breast cancer patients because taxanes are commonly used in this group of patients. Our study represents the first attempt in delineating TXR1 and TSP1 expression in breast cancer and we demonstrate that TXR1 and TSP1 expression may vary according to the molecular subtypes of breast cancer. The clinical relevance of the TXR1 and TSP1 expression should be further examined in prospective controlled clinical studies with an adequate population size.

Authors' contributions: ZW contributed to the conception of the study, HZ, XQ, XM, and TW contributed significantly to conducting experiments, YY, ZG, and ZZ contributed significantly to data analysis, ZB, YG, and ZY wrote the manuscript.

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DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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