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Original Article

Expression of thyroid hormone responsive spot 14 homolog and thyroid hormone receptor β1 in human breast cancer tissues and its clinical significance

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Abstract: Aims: The present study is to investigate the expression of thyroid hormone responsive spot 14 homolog (Thrsp) and thyroid hormone receptor β1 (TRβ1) proteins in human breast cancer tissues and adjacent tissues, as well as its relationship with clinical pathological data of breast cancer patients. Methods: A total of 112 Uygur and Han patients with breast invasive ductal carcinoma and lobular carcinoma who were diagnosed by pathology and underwent radical surgery at the Fifth Affiliated Hospital or the Affiliated Tumor Hospital of Xinjiang Medical University between January 2012 and January 2015 were randomly selected into the present study. Expression of Thrsp and TRβ1 was determined using immunohistochemical staining. The correlation of the expression of Thrsp and TRβ1 with the clinical and pathological data of the patients was analyzed using χ^2 test. The correlation between Thrsp protein expression and TRβ1 protein expression was also investigated. Results: The positive expression rate of Thrsp in breast cancer tissues was higher than that in tumor-adjacent tissues, but the positive expression rate of TRβ1 in breast cancer tissues was lower than that in tumor-adjacent tissues. Thrsp and TRβ1 were mainly expressed in the nucleus, with only a little being expressed in the cytoplasm. Expression of Thrsp or TRβ1 was correlated with different clinical and pathological data of breast cancer patients. Thrsp protein expression was related with TRβ1 protein expression in breast cancer tissues. Conclusions: The present study demonstrates that TRβ1 and Thrsp are not independent prognostic factors for breast cancer. Thyroid hormone/TRβ1/Thrsp may be involved in energy and substance metabolisms in breast cancer cells, and affect their mitotic process.

Keywords: Breast cancer, thyroid hormone responsive spot 14 homolog, Thrsp, thyroid hormone receptor β1, TRβ1, clinical significance

Introduction

The incidence of breast cancer accounts for 29% of malignant tumors in women in 2015 [1]. Breast cancer shows increasing incidence, morbidity and mortality year by year, and has become the first killer of women's health [2]. Abnormal expression of signaling pathway plays important roles in the occurrence and development of malignant tumors [3]. In clinical practice, many breast cancer patients are found to have combined thyroid hormone (TH) abnormalities or thyroid cancer [4, 5]. It is found that thyroid dysfunction is connected with the occurrence and development of breast cancer [6], but the mechanism is still unclear. Ditsch et al. report that the risk of invasive breast cancer in patients with hypothyroidism is significantly higher than hyperthyroidism patients [7]. A study shows that triiodothyronine level is correlated with breast cancer development in a dose-dependent manner in premenopausal and postmenopausal women [8]. Another study indicates that TH is helpful for clinical monitoring and prognosis prediction [9]. Thyroid receptor (TR) is widely expressed in normal human breast tissues [10, 11], and plays a role in the development and differentiation of breast tissue cells [12]. There are three subtypes of TR, TRα1, TRα2 and TRβ1. TRα1 and TRα2 are encoded by TH receptor alpha (THRA) gene on chromosome 17, and TRβ1 is encoded by TH

receptor beta (THRB) gene on chromosome 3 [13]. Currently, the most studied is TRβ1 subtype. Most researchers believe that TRβ1 may act as a tumor suppressor gene in the occurrence and development of human breast cancer [14, 15]. In addition, abnormal expression of TH responsive spot 14 homolog (Thrsp) exists in human breast cancer tissues [16]. Thrsp is closely related with fat metabolism diseases and breast cancer, and is thought to control metabolism and growth [16]. However, there are few reports on the expression of Thrsp and TRβ1 proteins in human breast cancer. In the present study, we investigate the expression of Thrsp and TRβ1 proteins in human breast cancer tissues and adjacent tissues, as well as its relationship with clinical pathological data of breast cancer patients.

Materials and methods

Patients

A total of 112 Uygur and Han patients with breast invasive ductal carcinoma and lobular carcinoma who were diagnosed by pathology and underwent radical surgery at the Fifth Affiliated Hospital or the Affiliated Tumor Hospital of Xinjiang Medical University between January 2012 and January 2015 were randomly selected into the present study. All of the 112 breast cancer patients (median age, 47 years; age range, 22-88 years) had been living in Xinjiang for more than 10 years, and received radical surgery for breast cancer. Among the 112 patients, 38 cases had tumor diameter ≤ 2 cm, and 74 cases had tumor diameter > 2 cm; 51 cases had lymphatic metastasis, and 61 cases had no lymphatic metastasis; 21 cases were at histological grade I, 55 cases were at grade II, and 36 cases were at grade III. According to the 9th TNM staging standards by International Union Against Cancer and American Joint Committee on Cancer, 67 patients were at grades I + II, and 45 were at grades III + IV. In addition, 85 patients had positive expression of estrogen receptor (ER), and 27 patients had negative expression of ER; 54 patients had positive expression of progesterone receptor (PR), and 58 patients had negative expression of PR; 50 patients had positive expression of human epidermal growth factor receptor 2 (Her-2), and 62 patients had negative expression of Her-2.

The inclusion criteria were: i) patients with surgical treatment, diagnosis by pathology and paraffin pathological specimens; ii) patients without history of radiotherapy, chemotherapy, malignant tumors or genetic diseases; iii) Karnofsky performance score > 85 before surgery; iv) patients with complete medical records. The exclusion criteria were: i) patients had no paraffin pathological specimens; ii) patients with history of radiotherapy, chemotherapy, malignant tumors or genetic disease; iii) Karnofsky performance score < 85 before surgery; iv) male breast cancer patients; v) patients without complete medical records. Invasive breast cancer tissue samples (n = 112) and normal breast tissue samples (n = 112) more than 6 cm away from tumor tissues were collected, fixed with 4% neutral formalin, and paraffin-embedded for slicing. All procedures were approved by the Ethics Committee of Xinjiang Medical University. Written informed consents were obtained from all patients or their families.

Immunohistochemical staining

The tissue slices were dewaxed, dehydrated and washed with phosphate-buffered saline (PBS). Then, the slices underwent antigen retrieval, followed by antigen blocking before washing with PBS. Afterwards, slices were incubated with polyclonal Thrsp first antibody (1:200; Santa Cruz Biotechnology, Dallas, TX, USA) and polyclonal TRβ1 first antibody (1:100; Santa Cruz Biotechnology, Dallas, TX, USA) overnight. After washing with PBS, the slices were incubated with biotin-streptavidin horseradish peroxidase secondary antibody (ZSGB-Bio, Beijing, China), followed by washing with PBS again. Then, the slices were colored with diaminobenzidine (Ekear Biotechnology, Shanghai, China) before washing with PBS. After being stained with hematoxylin (Bogoo Biotechnology, Shanghai, China), the slices were subjected to dehydration, transparency and mounting. The images were taken under a microscope (Carl Zeiss, Oberkochen, Germany), and analyzed using IWORKS software (Apple, Cupertino, CA, USA).

Positive staining of Thrsp and TRβ1 proteins in breast cancer tissues was indicated by light yellow or brown granules. The pathological slices of the 112 patients were independently

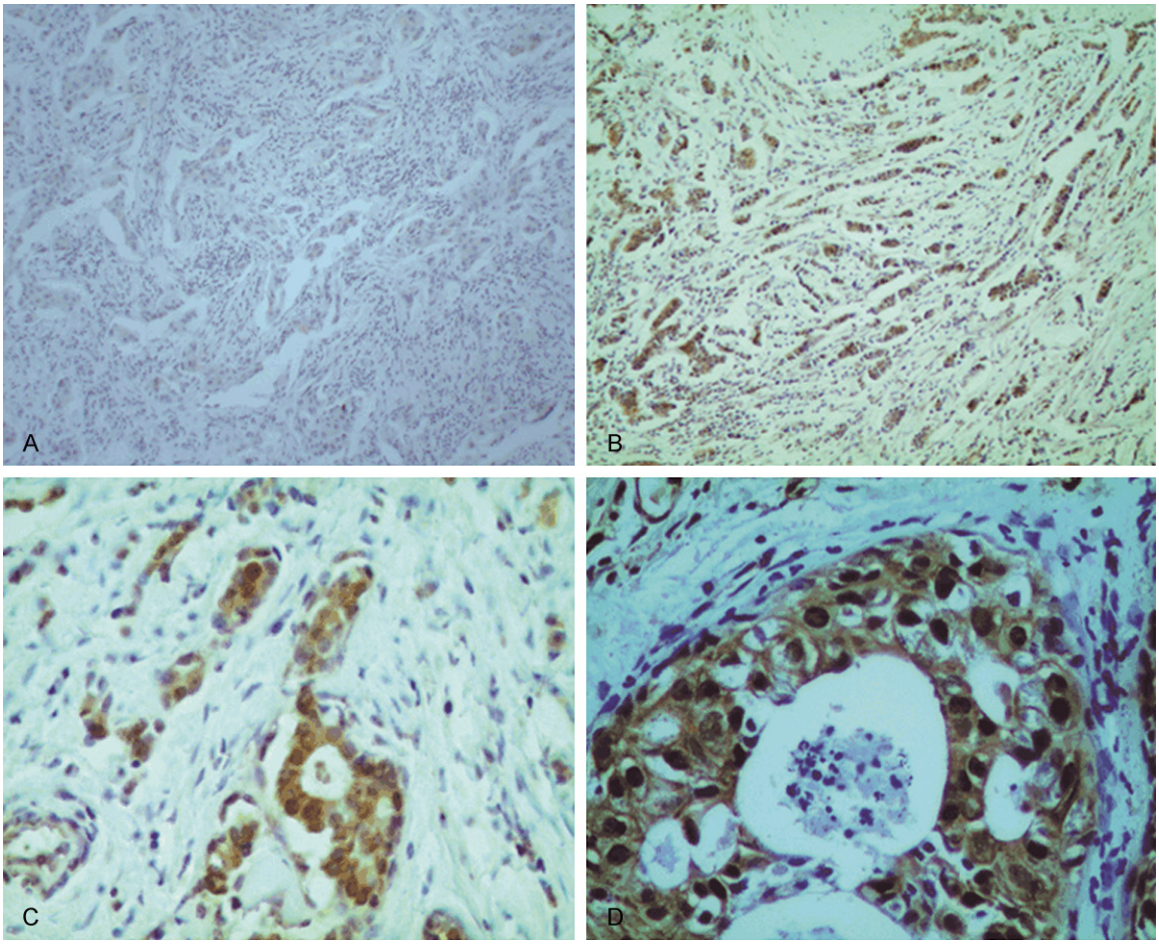

Figure 1. Expression of Thrsp detected using immunohistochemical staining. A. Breast cancer tissue with negative expression of Thrsp protein (×100); B. Breast cancer tissue with positive expression of Thrsp protein (×100); C. Thrsp expression in the nucleus (×400); D. Thrsp expression in the cytoplasm (×400).

Table 1. Thrsp and TRβ1 expression rates in human breast cancer tissue and adjacent tissues

Groups	No. of cases	Thrsp			TRβ1		
		(+)	(-)	Positive rate (%)	(+)	(-)	Positive rate (%)
Breast cancer tissues	112	64	48	57.14	57	55	42.31
Tumor-adjacent tissues	112	4	108	3.57	112	0	100

Note: For Thrsp, $\chi^2 = 76.018$, $P < 0.01$; for TRβ1, $\chi^2 = 72.899$, $P < 0.01$.

reviewed by two experienced pathologists. When the results were not consistent, consensus was reached through consultation. According to the standards reported previously [17], 10 fields were randomly selected from each slice (400×) and a total of 400 cells were counted. For the scoring of positive cell staining intensity, cells with no color scored 0 point, light yellow cells scored 1 point, brown cells scored 2 points, and dark brown cells scored 3 points. For the scoring of positive cell percentage, tissues with 0% positive cells scored 0 point, tissues with ≤ 10% positive cells scored 1 point, tissues with 11%-50% positive cells scored 2 points, tissues with 51%-75% positive cells scored 3 points, and tissues with ≥ 75% positive cells scored 4 points. After multiplying staining intensity and the percentage of positive cells, tissues with less than 2 points were negative, and tissues with ≥ 2 points were positive ("+", ≥ 2 points and < 3 points; "++", ≥ 3 points and < 4 points; "+++", ≥ 4 points).

Statistical analysis

All results were analyzed using SPSS v17.0 software (IBM, Armonk, NY, USA). Comparisons

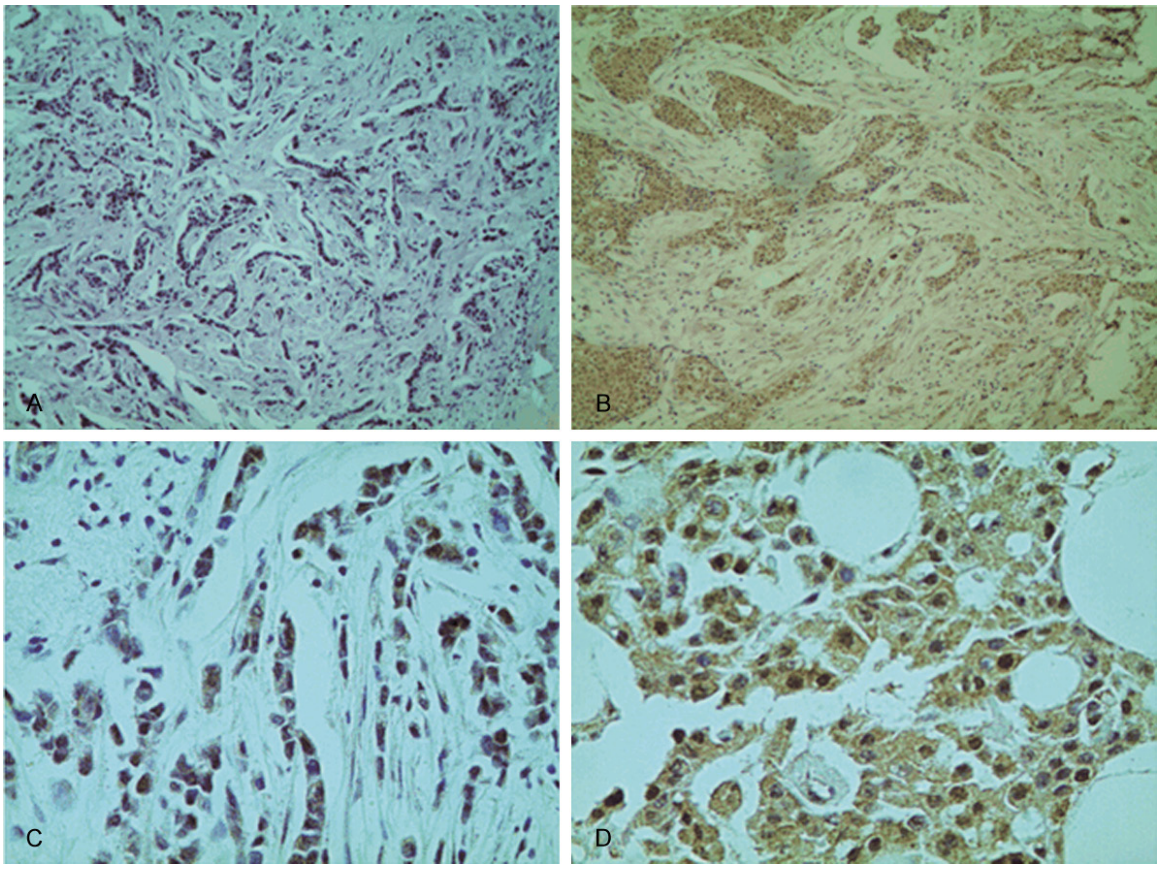

Figure 2. Expression of TRβ1 detected using immunohistochemical staining. A. Breast cancer tissue with negative expression of TRβ1 protein (×100); B. Breast cancer tissue with positive expression of TRβ1 protein (×100); C. TRβ1 expression in the nucleus (×400); D. TRβ1 expression in the cytoplasm (×400).

Table 2. Locations of positive expression of Thrsp and TRβ1 in human breast cancer cells (%)

Locations of positive expression	Thrsp		TRβ1	
	No. of cases	Percentage (%)	No. of cases	Percentage (%)
Cell nucleus	46	71.88	17	29.82
Both nucleus and membrane	12	18.74	11	19.30
Cell membrane	3	4.69	6	10.53
Cytoplasm	2	3.13	9	15.79
Both membrane and cytoplasm	1	1.56	0	0
Both cytoplasm and nucleus	0	0	14	24.56
Total	64	100.00	57	100.00

of measurement data between two groups or among multiple groups were performed using Chi-square test. The correlation degree between two categorical variables was described by Pearson contingency coefficient. Test standard was $\alpha = 0.05$. $P < 0.05$ was considered statistically significant.

Results

The positive expression rate of Thrsp in breast cancer tissues is higher than that in tumor-adjacent tissues, but the positive expression rate of TRβ1 in breast cancer tissues is lower than that in tumor-adjacent tissues

To measure the expression of Thrsp and TRβ1 in breast cancer tissues and tumor-adjacent tissues, immunohistochemical staining was performed. Positive expression of Thrsp protein was mainly detected in the cell nucleus in breast cancer tissues, but only a little was detected in the cytoplasm (**Figure 1**). The positive expression rate of Thrsp in breast cancer tissues (57.14%, 64/112) was significantly higher than that in tumor-adjacent

tissues (3.57%, 4/112) (**Table 1**). In addition, TRβ1 protein was expressed in breast cancer tissues, both at cell nucleus or cytoplasm (**Figure 2**). The positive expression rate of TRβ1 in breast cancer tissues (50.89%, 57/112) was significantly lower than that in tumor adjacent tissues (100%, 112/112) (**Table 1**). These results suggest that the expression of Thrsp in breast cancer tissues is higher than that in tumor-adjacent tissues, but the expression of TRβ1 in breast cancer tissues is lower than that in tumor-adjacent tissues.

Thrsp and TRβ1 are mainly expressed in the nucleus, with only a little being expressed in the cytoplasm

To identify the exact locations of Thrsp and TRβ1 expression, positive expression rates in the cells from breast cancer tissues were calculated. The positive expression rate of Thrsp in cell nucleus was 90.62%, with that only in the nucleus being 71.88% and that in both nucleus and cell membrane being 18.74%. The positive expression rate of Thrsp in cytoplasm was 4.69%, with that only in the cytoplasm being 3.13% and that in both cytoplasm and cell membrane being 1.56%. The positive expression rate of Thrsp in cell membrane was 4.69% (**Table 2**). Moreover, the positive expression rate of TRβ1 in cell nucleus was 73.68%, with that only in the nucleus being 29.82%, that in both cytoplasm and nucleus being 24.56%, and that in both nucleus and cell membrane being 19.30%. The positive expression rate of TRβ1 in cytoplasm was 45.61%, with that only in cytoplasm being 15.79% and that in both cytoplasm and nucleus being 29.82%. The positive expression rate of TRβ1 in cell membrane was 10.53% (**Table 2**). The result indicates that Thrsp and TRβ1 are mainly expressed in the nucleus, with only a little being expressed in the cytoplasm.

Expression of Thrsp or TRβ1 is correlated with different clinical and pathological data of breast cancer patients

To identify the correlation of the expression of Thrsp and TRβ1 with the clinical and pathological data of breast cancer patients, χ^2 test was performed. The data showed that at $\alpha = 0.05$ level, Thrsp protein expression at different histological grades was significantly different from each other ($P < 0.05$), but its expression in patients with different ages, ethnic groups, primary tumor diameters, tumor markers, lymph node metastasis, molecular typing, or clinical grading was not significantly different from each other ($P > 0.05$) (**Table 3**). In addition, TRβ1 protein expression was related to Her-2, lymph node metastasis, histological grading and clinical grading ($P < 0.05$), but its expression in patients with different ages, ethnic groups, primary tumor diameters, ER, PR or molecular typing was not significantly different from each other ($P > 0.05$) (**Table 3**). These results suggest that the expression of Thrsp or TRβ1 is correlated with different clinical and pathological data of breast cancer patients.

Thrsp protein expression is closely correlated with TRβ1 protein expression in breast cancer tissues

To test whether Thrsp is related with TRβ1, we analyzed the correlation between Thrsp protein expression and TRβ1 protein expression. The data showed that the expression of TRβ1 protein in tissues with positive expression of Thrsp protein was significantly different from that in tissues with negative expression of Thrsp protein ($\chi^2 = 16.789$, $P < 0.001$) (**Table 4**). The result indicates that Thrsp protein expression is related with TRβ1 protein expression in breast cancer tissues.

Discussion

Breast cancer is a heterogeneous disease that involves a variety of molecules and mechanisms. As a TH binding element, TR plays important roles in the body development, tissue differentiation and substance metabolism. It is shown that the expression of TRβ1 is varied in various tumors such as thyroid cancer, breast cancer, gastric cancer, renal cell carcinoma, and nervous system tumor [18], and that TRβ1 acts as a tumor suppressor gene in the occurrence and development of breast cancer [14]. The present study shows that the positive expression rate of TRβ1 protein in breast cancer tissues is significantly lower than that in tumor-adjacent tissues, and the expression of TRβ1 is closely correlated with lymph node metastasis, histological grading Her-2 status, and clinical grading, suggesting that TRβ1 gene may participate in the occurrence and development of breast cancer. It is reported that TRβ1 gene methylation is the main reason for the reduced TRβ1 mRNA level in breast cancer tissues [19, 20].

Table 3. Relationship of the expression of Thrsp and TRβ1 proteins in breast cancer tissues with the clinical and pathological data of patients

Clinical pathological features		No. of cases	Thrsp				TRβ1			
			(+)	(-)	χ^2	*P*	(+)	(-)	χ^2	*P*
Age (years)										
< 50		49	26	23	0.593	0.441	24	25	0.096	0.757
≥ 50		63	38	25			29	34		
Ethnic groups										
Han		78	42	36	1.140	0.286	38	40	0.201	0.652
Uygur		34	22	12			15	19		
Primary tumor diameter										
≤ 2 cm		38	21	17	0.648	0.421	17	21	0.154	0.695
> 2 cm		74	43	25			36	38		
Tumor markers										
ER	(+)	85	49	36	0.037	0.848	41	44	0.463	0.495
	(-)	27	15	12			11	16		
PR	(+)	54	31	23	0.003	0.956	38	16	3.386	0.066
	(-)	58	33	25			31	27		
Her-2	(+)	50	28	22	0.048	0.826	23	27	4.579	0.032*
	(-)	62	36	26			41	21		
Lymph node metastasis										
Yes		51	27	24	1.564	0.211	14	37	14.831	0.000*
No		61	37	24			39	22		
Molecular typing										
Luminal A		15	10	5	5.414	0.144	7	8	1.847	0.764
Luminal B		56	26	30			27	29		
Her-2 over expression		17	11	6			8	9		
Triple negative		24	17	7			11	13		
Histological grading										
I		21	7	14	6.021	0.049*	12	9	8.459	0.015*
II		55	34	21			29	31		
III		36	23	13			12	24		
Clinical grading										
I + II		67	34	33	2.786	0.095	37	30	4.177	0.041*
III + IV		45	30	15			16	29		

Note: *, $P < 0.05$. ER, Estrogen receptor; PR, Progesterone receptor; Her-2, Human epidermal growth factor receptor 2.

Table 4. Relationship between the expressions of Thrsp and TRβ1 in human breast cancer tissues

Group	No. of cases	TRβ1 (+)	TRβ1 (-)	χ^2	*P*
Thrsp (+)	64	41	23	16.789	< 0.001*
Thrsp (-)	48	12	36		

Note: *, $P < 0.05$.

A study shows that patients with low TH level tend to have breast cancer, and high TH level may exert protective effects [21]. We speculate that low TH level or TR mutations interrupt the normal interactions between TH and TR, leading to the activation of a series of other signaling pathways that finally result in breast cancer. It is suggested that mutated TRβ1 gene competitively inhibits the binding of unmutated TRβ1 gene with PI3K, thereby mediating the sustained activation of AKT-mTOR-p70S6K and ILK-MMP2 pathways that both play important roles in the proliferation, invasion and metastasis of cancer cells. It is also reported that abnormal mTOR signaling pathway is closely related with the occurrence and development

of malignant tumors such as endometrial cancer, prostate cancer, lung cancer and breast cancer [22, 23].

Thrsp has been demonstrated to play important roles in regulating fatty acid synthase gene transcription [24, 25]. The present study shows that Thrsp expression level in breast cancer tissues is higher than that in tumor-adjacent tissues. Overexpression of Thrsp is related with the amplification of THRSP gene. CCND1 gene is a downstream candidate cancer gene, and its overexpression is involved in the occurrence and development of breast cancer [26]. We hypothesize that CCND1 gene may be functionally related with THRSP gene, resulting in the co-expression of both genes that mediates the occurrence of lipid breast cancer. The present study also shows that the expression of Thrsp and TRβ1 in breast cancer is positively correlated with each other. It is widely accepted that TR gene mutations activates MAPK, PI3K and Wnt pathways and mediates downstream CCND1 gene, finally leading to promoted tumor cell apoptosis and reduced tumor cell proliferation. In summary, the present study demonstrates that TRβ1 and Thrsp are not independent prognostic factors for breast cancer. TH/TRβ1/Thrsp may be involved in energy and substance metabolisms in breast cancer cells, and affect their mitotic process.

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Disclosure of conflict of interest

None.

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