Int J Clin Exp Med 2016;9(6):11612-11618
www.ijcem.com /ISSN:1940-5901/IJCEM0023040

Original Article

High level of STAT4 expression is associated with the deterioration of breast cancer

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Received December 31, 2015; Accepted March 22, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: *Purpose:* Dysregulation of signal transducers and activators of transcription 4 (STAT4) has been reported in several classes of malignancies. However, its expression and clinicopathological contribution in breast cancer remains unclarified. The purpose of the current study was to explore the clinicopathological significance of STAT4 and its role on the deterioration in breast cancer. *Methods:* A total of 81 samples from breast cancer patients and 40 cases of adjacent non-cancerous breast tissues were recruited, and the expression of STAT4 was detected with immunohistochemistry. Additionally, the association between STAT4 and clinical parameters was analyzed. *Results:* The expression level of STAT4 in breast cancer was significantly higher than that in non-cancerous breast tissues ($P<0.001$). Moreover, a notable correlation was found between STAT4 expression and the tumor size ($r=0.504$, $P<0.001$). There were also positive associations of STAT4 with lymph nodes with cancer spreading ($r=0.419$, $P<0.001$), and with clinical TNM stage of breast cancer ($r=0.541$, $P<0.001$). *Conclusions:* Up-regulation of STAT4 in breast cancer could indicate the deterioration of breast cancer. STAT4 should be taken into consideration in the development of novel diagnostic and therapeutic program for breast cancer.

Keywords: STAT4, breast cancer, immunohistochemistry, deterioration, TNM

Introduction

Breast cancer is one of the most common diseases in women. Incidence and mortality due to breast cancer has been growing for last 50 years [1, 2]. There were estimated 227,000 new cases of breast cancer diagnosed in women in the United States and estimated 39,500 breast cancer deaths in 2012 [3, 4]. As World Health Organization (WHO) 2012 reported, breast cancer is the prominent cause of death in women, accounting 23% of all cancer deaths. In Asian countries, one in every three females faces the possibility of breast cancer in their lifetime [5, 6]. Breast cancer is a heterogeneous disease, not only in its features and clinical course, but also in its molecular profile [7]. Current approaches for assessing disease prognosis, using clinicopathological elements such as age, tumor size, tumor grade, and extent of nodal involvement in their evaluation, are inadequate in value for estimating the risk of the prognosis of breast cancer. Thus, there is a disquieting requirement for the identification of best diagnosing and predicting marker for breast cancer.

The Janus Kinase-Signal Transducers and Activators of Transcription (JAK-STAT) pathways have been reported to play essential roles in the immune, neuronal, hematopoietic and hepatic systems. STAT family members can be divided into two groups according to their specific functions. One is made up of STAT1, STAT3, and STAT5, activated in diverse tissues by means of a sequence of ligands and involved in IFN signaling, development of the mammary gland, response to growth hormone, and embryogenesis. The other group includes STAT2, STAT4, and STAT6, which are activated by a few cytokines and play a distinctive role in the development of T-cells and in IFN-gamma signaling [8]. Among the STAT family members, STAT4 is a vital transcription factor that is critical for the differentiation of Th1 cells in promoting cellular immune reaction [9]. Furthermore, the role of STAT4 has also been investigated in a small number of malignancies, that is, abnor-

Table 1. Relationship between STAT4 and Ki-67 expression and clinicopathological features

Clinicopathological features		N (total)	n (STAT4 positive, %)	Z	*P*
Tissue	Non-cancerous	40	9 (22.5%)	4.426	<0.001
	Breast cancer	81	53 (65.4%)		
Age	<50	38	26 (68.42%)	-0.528	0.597
	≥50	43	27 (62.79%)		
Histological grade*	Carcinoma *in situ*	2	0 (0.00%)	4.168	0.244
	I	5	3 (60.00%)		
	II	55	38 (69.09%)		
	III	19	12 (63.16%)		
Tumor size*	Tis	2	0 (0.00%)	21.417	<0.001
	T1	15	4 (26.67%)		
	T2	44	30 (68.18%)		
	T3	16	15 (93.75%)		
	T4	4	4 (100%)		
Lymph node metastasis*	N0	38	17 (44.74%)	14.604	0.002
	N1	18	14 (77.78%)		
	N2	17	14 (82.35%)		
	N3	8	8 (100%)		
TNM*	0	2	0 (0.00%)	26.197	0.000
	I	10	1 (10.00%)		
	II	37	23 (62.16%)		
	III	32	29 (90.63%)		
Molecular subgroup*	Luminal A	23	15 (65.22%)	0.805	0.669
	Her2	36	22 (61.11%)		
	TN	22	16 (72.73%)		
ER and PR	Negative	58	38 (65.52%)	-0.025	0.980
	Positive	23	8 (34.78%)		
HER2	Negative	45	31 (68.89%)	-0.727	0.467
	Positive	36	22 (61.11%)		
Ki-67 grade	Low	5	4 (80.00%)	0.500	0.479
	High	76	49 (64.47%)		
P53 grade	Low	42	30 (71.43%)	1.387	0.239
	High	39	23 (58.97%)		
P16 grade	Low	28	15 (53.57%)	1.014	0.314
	High	53	38 (71.70%)		
E-cadherin	Low	24	18 (75.00%)	1.380	0.240
	High	57	35 (61.40%)		
Vimentin	Negative	56	41 (73.21%)	4.858	0.028
	Positive	25	12 (48.00%)		

*Kruskal-Wallis H test was performed. The following pairwise comparisons were performed with chi-square test: Tumor size: T1 vs T2: Z=-2.786, P=0.005; T1 vs T3: Z=-3.77, P<0.001; T1 vs T4: Z=-2.569, P=0.010; T2 vs T3: Z=-2.006, P=0.045. Lymph node metastasis: N0 vs N1: Z=-2.302, P=0.021; N0 vs N2: Z=-2.576, P=0.010; N0 vs N3: Z=-2.821, P=0.005. TNM stages: stage I vs stage II: Z=-2.896, P=0.004; stage I vs stage III: Z=-4.867, P<0.001; stage II vs stage III: Z=-2.716, P=0.007.

mal expression of STAT4 was found in different neoplasia, including colorectal cancer [10, 11], gastric cancer [12], cutaneous T-cell lymphoma [13-15] and hepatocellular carcinoma (HCC) [9, 16, 17]. However, there is a lacuna in the possible function of STAT4 in breast cancer. Thus, in the current study, we detected the STAT4 protein expression in the clinical samples of 81 cases of breast cancer and investigated its clinical significance.

Methods

Tissue samples

A total of 81 cases of FFPE breast cancer and 40 of their corresponding non-cancerous adjacent breast tissues were enrolled in the current study. The age of the breast cancer patients ranged from 30 to 76 years, with a mean age of 50.69 years. All samples were from female patients. Clinicopathological information was provided from medical records and the main parameters were listed in **Table 1**. All cases were initial tumorectomies without treatment and randomly selected in the First Affiliated Hospital of Guangxi Medical University, China, between January 2012 and December 2013. The study protocol was approved by the Ethical Committee of the First Affiliated Hospital of Guangxi Medical University. Written informed consent was obtained from the patients and clinicians for the usage of the samples for research. All samples were reviewed and diagnosed by two independent pathologists.

Immunohistochemistry

The fixed tissue samples were embedded in paraffin. Sections were deparaffinized in xylene and hydrated through a graded series of ethanol and then rehydrated and subjected to antigen retrieval by microwaving. Endogenous peroxidase activity was quenched with 3% hydrogen peroxide for 10 min at room temperature. Antigen retrieval of the sections was achieved in a multifunctional microwave histoprocessor at 100°C by microwave heating of the samples on slides in 0.01 mol/L of pH 6.0 citrate buffer for 20 min. Biomarker expression was immunohistochemically detected by primary antibodies of mouse monoclonal antibody STAT4 (PL68, sc-101160, Santa Cruz Biotec.CO., CA, USA, 1:300 dilution), rabbit monoclonal antibody Ki-67, P53, P16, E-cadherin, Vimentin (Beijing Zhongshan Jinqiao Biotec.CO., China) for 60 min at room temperature followed by 30 min staining with biotinylated secondary anti-mouse/rabbit antibody (Cat. No. D-3004, Shanghai Long Island Biotec. CO., LTD, China). Finally, positive staining was visualized with diaminobenzidine and cell nuclei were counterstained with haematoxylin. The positive signals of STAT4, E-cadherin and Vimentin locate in the cytoplasm. Negative (-), weakly positive (+), moderately positive (++), and strongly positive (+++) were determined according to the immunodetection of stain intensity and amounts of positive cells by two pathologists (HC and GC), who discussed each case until they reached a consensus. All of (+), (++), and (+++) were considered as positive expression [18]. The positive signal of Ki-67, P53 and P16 is distributed in the nuclei. The proliferation index (PI) of Ki-67 was calculated with the formula (number of positive cells/total number of the cells ×100%) by counting at least 10 representative visions of high magnification (40×40). P53 and P16 were scored with the same strategy as Ki-67.

Statistical analysis

SPSS20.0 was used for statistical analysis. Chi-square test and Kruskal-Wallis H test were performed to analyze the difference of STAT4 expression between distinct clinicopathological groups. Bivariate correlations between two independent variables were analyzed by calculating the Spearman's correlation coefficients. Moreover, ROC curve was performed to analyze the predictive value of STAT4 to distinguish cancer from non-cancer. Statistical significance was determined at a $P<0.05$ level.

Results

STAT4 protein was found to be expressed in 53 out of 81 cases breast cancer tissues (65.4%) and the positive rate was significantly higher than that in the non-cancerous breast tissue (22.5%, 9/40, $P<0.001$, **Table 1**; **Figure 1**). In addition, ROC curve was performed to explore the diagnostic value of STAT4 for breast cancer. The area under curve (AUC) of STAT4 was 0.715 (95% CI: 0.618-0.812, $P<0.001$). In terms of the tumor size of breast cancer, the STAT4 expression was 0%, 26.67%, 68.18%, 93.75%, and 100%, for Tis, T1, T2, T3 and T4, respectively. Spearman's correlation test showed a positive association between STAT4 expression and tumor size ($r=0.504$, $P<0.001$, **Figure 2**). Similar trend was also observed between STAT4 expression and lymph node metastasis. The positive rate of STAT4 expression was 44.74%, 77.78%, 82.35%, 100%, with the increasing numbers of lymph nodes with cancer spreading ($r=0.419$, $P<0.001$, **Figure 2**). Furthermore, STAT4 expression was closely related to the clinical TNM stage of breast cancer ($r=0.541$, $P<0.001$, **Figure 2**). With the deterioration of

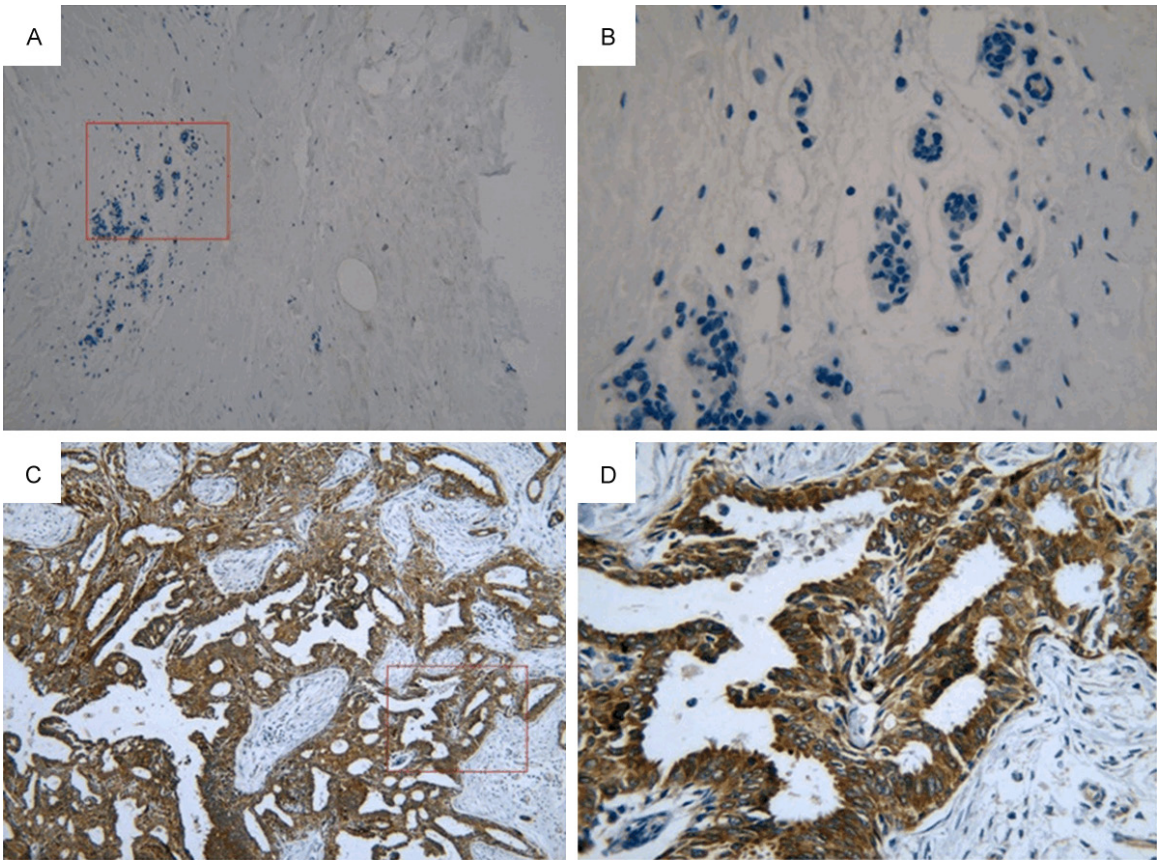

Figure 1. STAT4 expression in breast cancer and non-cancerous breast tissues. Negative STAT4 expression in non-cancerous breast tissue (A: ×100; B: ×400, visualized by the red boxed area from A); Positive STAT4 expression in breast cancer tissue (C: ×100; D: ×400, enlarged from the area within the red box in C, immunohistochemistry).

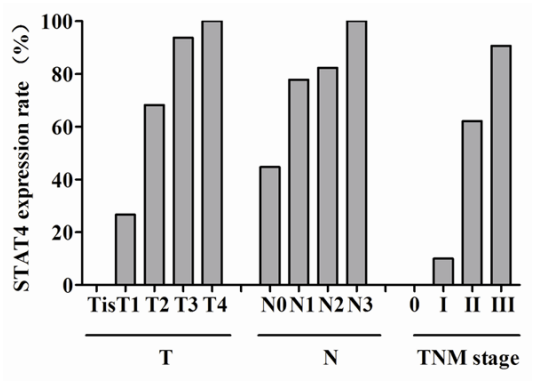

Figure 2. Different STAT4 expression rate in diverse subtypes of breast cancer. T: the size of tumor, N: lymph node with cancer spreading.

breast cancer, the positive rate of STAT4 expression rose with 0%, 10%, 62.16% and 90.63% for stage 0, stage I, stage II and stage III, respectively. However, no relative relationship was observed between STAT4 expression and other parameters, such as age, histology, molecular subtype, the status of ER, PR or HER2 (all $P>0.05$, **Table 1**).

To further understand the potential mechanism of STAT4 in breast cancer, we investigated the relationship between the expression of STAT4 and some other biomarkers, which are representative of the status of cell proliferation, invasion and metastasis. The STAT4 expression rate in the Vimentin positive group was 48% (12/25), markedly lower than that in the Vimentin negative group (73.21%, 41/56, $P=0.028$). STAT4 expression was negatively related to Vimentin expression ($r=-0.286$, $P=0.01$). No significant relationship was found between STAT4 expression and other markers, such as Ki-67, P53, P16 or E-cadherin (**Table 1**).

Discussion

Breast cancer is a complex and heterogeneous disease. Due to the heterogeneity, the mecha-

nism of breast tumorigenesis remains still not completely understood [19, 20]. STAT4, locating on chromosome 2q32, is a member of the STAT superfamily of transcription factors. Dysregulation of STAT4 has been reported in several cancers. In colorectal cancer [10, 11] and gastric cancer [12], over-expression of STAT4 protein was detected. In contrast, under-expression of STAT4 protein was found in cutaneous T-cell lymphoma [13-15] and HCC [9, 16, 17]. In the present study, we found STAT4 protein expression in 22.5% samples of non-cancerous breast tissues using immunohistochemistry, which is consistent with the previous report [21], showing that STAT4 was expressed in mammary tissue. However, we primarily discovered that significantly higher STAT4 expression was noted in breast cancer tissues (65.4%) than that in non-cancerous breast, which is similar as the fact that the high expression of STAT4 was observed in colorectal cancer [10, 11] and gastric cancer [12]. Furthermore, the potential mechanism of STAT4 has been studied in these two classes of cancers. Cheng et al. [10] reported that silencing of STAT4 gene could suppress cell proliferation and invasion of colorectal cancer cells. Zhou et al [12] found that STAT4 could function as a target gene of miR-141 in gastric cancer, which was down-regulated. Over-expression of STAT4 *in vitro* could mimic miR-141 action in the growth and invasion of gastric cancer. To date, no available study has been performed to explore the mechanism of STAT4 on breast cancer. Future work is urgently needed to figure out the role of STAT4 in breast cancer. However, the immunostaining result in current study indicates that STAT4 might play an essential role in the carcinogenesis of breast cancer and could also be a potential tool for the diagnosis of breast cancer.

We are also interested in the relationship between STAT4 protein and the progression of breast cancer. In the current study, we found that the positive ratio of STAT4 expression was rising with the deterioration of breast cancer. Higher STAT4 expression was observed in the groups of larger tumor, more lymph nodes with cancer spreading and more advanced clinical stage, which suggests that STAT4 might play a vital role in the development of breast cancer. Cheng et al [10] reported an analogous phenomenon in colorectal cancer and STAT4 expression was related with the Duke's staging and depth of invasion in colorectal cancer patients. However, the molecular mechanism involved has not yet been clarified.

Signaling by estrogen receptor (ER), progesterone receptor (PR), and/or human EGF-like receptor 2 (HER2) is a key driver in the progress of a great majority of breast cancers [22-24]. Molecular characterization of primary cancers has identified major subtypes that relate with ER/PR/HER2 status, and also subgroup divisions that indicate other molecular and cellular characteristics of the tumors [25, 26]. However, several challenges remain to improve breast cancer controlling and patient survival, for which the integration of novel markers into current practice should be advantageous [27, 28]. In the current study, we have compared the STAT4 expression to the status of ER, PR, HER2 in breast cancer. However, no significant correlation has been found between STAT4 and ER/PR/HER2 status so far. The relationship of STAT4 with ER/PR/HER2 status needs further investigation with larger patient size and functional experiments.

Finally, we compared STAT4 expression to some biomarkers representing the cell proliferation, migration and epithelial-mesenchymal transition (EMT) in breast cancer [29-33]. No significant relationship was found between STAT4 and Ki-67, P53, P16 or E-cadherin. However, reverse correlation was observed between STAT4 and Vimentin, which is important in the transformation of a normal cell to an invasive tumor cell [34]. Vimentin is an intermediate filament expressed in tissues of normal mesenchymal origin. It is known to express aberrantly in epithelial cancers of prostate, gastrointestinal tract, breast, central nervous system, lung, and malignant melanomas [35]. In recent years, Vimentin has been recognized as a marker for EMT. However, more researches would be crucial to evaluate the link between STAT4 and EMT, between STAT4 and Vimentin in breast cancer.

In conclusion, the current finding reveals that high-level STAT4 expression might be a novel molecular alteration involved in the carcinogenesis and progression of breast cancer. STAT4 might serve as a valuable biomarker to monitor the clinical course of patients with breast cancer. Chemotherapy-induced STAT4 deficiency was reported to be due to the reduced levels of

STAT4 mRNA and the protein stability [14]. Hence, STAT4 should be taken into consideration in the development of novel diagnostic and molecular therapeutic program for breast cancer, although more consolidated studies are still required.

Acknowledgements

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure of conflict of interest

None.

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