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Expression of Fibroblast Growth Factor 5 (FGF5) and Its Influence on Survival of Breast Cancer Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The clinical outcome of patients with breast cancer (BC) remains poor.

Material/Methods: We analyzed BC microarray studies GSE37751, GSE7390, and GSE21653 to investigate the expression of FGF5 gene between BC patients and their normal counterparts and the relationship between FGF5 expression and age, tumor size, histopathological grading, estrogen receptors, clinical risk group according to St Gallen criteria, clinical risk group according to NPI criteria, clinical risk group according to Veridex signature, distant metastasis-free survival (DMFS), time to distant metastasis (TDM), disease-free survival (DFS), and overall survival (OS) of BC patients. Gene set enrichment analysis (GSEA) was used to investigate the exact mechanisms.

Results: FGF5 expression was significantly upregulated in BC patients relative to that in normal controls (P<0.0001). BC patients in the FGF5 low-expression group were correlated with better clinical characteristics, including tumor size, histopathological grading, estrogen receptors, clinical risk group according to St Gallen criteria, NPI criteria and Veridex signature, DMFS, TDM, and DFS compared with those in the FGF5 high-expression cohort. The result of GSEA indicated that FGF5 inhibits the proliferation of BC cells via ultraviolet response and TGF-β signaling. Quantitative PCR verified that FGF5 was overexpressed in patients with BC.

Conclusions: Our results suggest that FGF5 is an independent protective factor for BC patients.

MeSH Keywords: Breast Neoplasms • Genetic Association Studies • Prognosis • Receptor, Fibroblast Growth Factor, Type 5

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Background

Breast cancer (BC) is the most frequent form of malignancy found in women globally, with more than 1.7 million new cases per year [1]. Although it has been reported that BC is mostly diagnosed in women, it is known that 1 in 1100 men are diagnosed with it as well [2–4]. Significant advances have been made regarding management options during the past 3 decades, with about 87% of BC patients surviving their diagnosis for over 5 years compared with only 53% of those diagnosed in the early 1970s [5]. Treatment approaches for patients with BC are either a single method or a combination of surgery, chemotherapy, and/or radiotherapy. For patients with localized BC, surgery is recommended. About 6% of patients with localized BC will finally develop metastatic disease and 10–40% have systemic relapse [6]. Chemotherapy, radiotherapy, and immunotherapy are recommended for the treatment of BC patients with metastatic disease. Although great progresses (including the discovery of novel therapeutic targets and the understanding of mechanisms of resistance to treatment) have been made for the management of patients with metastatic BC, the disease remains incurable, which causes at least half a million deaths related to the disease per year [6–11]. Therefore, it is important to develop novel prognostic markers associated with clinical outcomes of BC patients and to develop targeted agents that disrupt specific biological processes critical to growth of cancer cells.

Fibroblast growth factor-5 (FGF-5) is a member of a group of 23 related fibroblast growth factor genes that are reported to participate in a variety of biological processes such as development, morphogenesis, tissue growth, and repair [12]. FGF5 was initially proved to be an oncogene, and subsequent studies demonstrated that FGF is involved in the pathological processes of several human cancers, including hepatocellular carcinoma, colorectal cancer, and prostate cancer [13–16]. In the present study, we explored the relationship between FGF5 expression and clinical features of patients with BC.

Material and Methods

Breast cancer microarray studies

We obtained 3 BC microarray studies – GSE37751 [17], GSE7390 [18,19], and GSE21653 [20,21] – from the Gene Expression Omnibus (GEO) database (*https://www.ncbi.nlm.nih.gov/geo/*) to conduct data analysis. GSE37751, annotated with Affymetrix Human Gene 1.0 ST Array and consisting of 61 samples of BC and 47 samples of normal breast tissue, was used to evaluate the mRNA level of FGF5 between normal breast tissues and BC samples. GSE7390, consisting of 198 samples of newly diagnosed BC patients with detailed clinical information and annotated with Affymetrix Human Genome U133A Array, was used to investigate the association between the clinical features of BC patients and the expression of FGF5. BC microarray GSE21653, consisting of 266 samples of BC and annotated with Affymetrix Human Genome U133 Plus 2.0 Array, was used to conduct gene set enrichment analysis (GSEA) [22,23].

Data analysis

The 2 independent samples *t* test was used to assess the expression of FGF5 (the probe ID is 8096050 in GSE37751) in BC samples and normal breast tissues. BC samples in GSE7390 and GSE21653 were categorized into a FGF5 high-expression group and a FGF5 low-expression group, according to the median of FGF5 expression in these 2 gene expression profiles. Next, we conducted chi-square analysis to investigate the relationship between the FGF5 level and the clinical features of patients with BC (such as age, tumor size, histopathological grading, estrogen receptors, clinical risk group according to St Gallen criteria, clinical risk group according to NPI criteria, and clinical risk group according to Veridex signature). Log-rank test-based survival analysis was performed to clarify the association between FGF5 level and the distant metastasis-free survival (TMFS), time to distant metastasis (TDM), disease-free survival (DFS), and overall survival (OS) of BC patients. Any difference was considered to be statistically significant at P value less than 0.05 for the 2 independent-samples *t* test, chi-square test, and survival analysis. Ultimately, GSEA was conducted to investigate the relevant mechanisms involved in the regulation of FGF5 on BC cells. h.all.v5.2.symbols.gmt was treated as a reference gene set. Any difference at nominal p value <0.05 and false discovery rate <25% was defined as statistical significance.

RNA isolation and reverse transcription-PCR and quantitative PCR

Five samples of BC and 5 normal breast tissues were obtained from patients undergoing surgery at Jingzhou Central Hospital. The collection of breast tissue was approved by the Ethics Committee of Jingzhou Central Hospital and informed consent of the included participants was obtained. Total RNA of breast tissues was isolated by using TRIzol reagent according to the manufacturer's instructions (Ambion, Carlsbad, CA, USA), and then we reverse transcribed the total RNAs into cDNA. Finally, RT-PCR was conducted using SYBR Premix ExTaq (TaKaRa, Japan) on an ABI7500 real-time PCR instrument (ABI Company, Oyster Bay, NY, USA) following the manufacturer's protocol. Homo GAPDH was treated as an internal reference. Each assay was repeated 3 times. For the quantification of genes of interest, the comparative 2-ΔΔCT method was used to determine the expression changes of each target gene relative to GAPDH. Primers were as follows:

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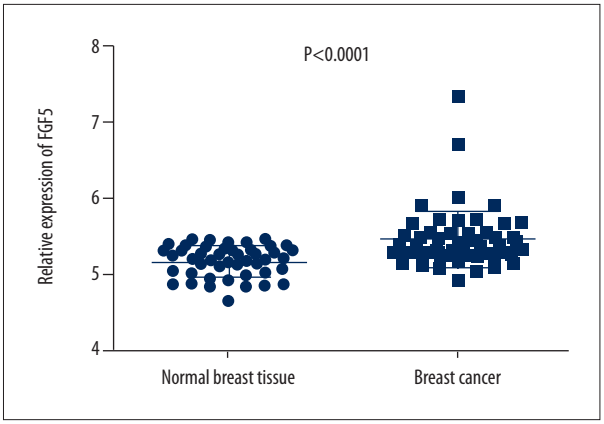

Figure 1. The expression of FGF5 in breast cancers and normal breast cancer tissues.

GAPDH: forward 5'-AATGTGTCCGTCGTGGATCTG-3', reverse 5'-CAACCTGGTCCTCAGTGTAGC-3';
FGF5: forward 5'-CCCGGATGGCAAAGTCAATGG-3', reverse 5'-TTCAGGGCAACATACCACTCCCG-3'.

Results

FGF5 was increased in BC cells

Firstly, we analyzed the expression of FGF5 in normal breast tissue and BC. As shown in Figure 1, the expression of FGF5 was significantly increased in BC samples (n=61) as compared to that in normal breast tissues (n=47) (5.466±0.361 *vs.* 5.193±0.201, P<0.0001).

The relationship of FGF5 expression and clinical characteristics of BC patients

Next, we investigated the relationship between FGF5 expression and the clinical characteristics of BC patients. As shown in Table 1, the ages of BC patients in the FGF5 high-expression group and the FGF5 low-expression group were similar (P=0.752). Clinical features, including tumor size, histopathological grading, estrogen receptors, clinical risk group according to St Gallen criteria, clinical risk group according to NPI criteria,

Table 1. The relationship between FGF5 expression and clinical features of patients with breast cancer.

	FGF5 expression		Chi-square	P value
	Low (n=99) (%)	High (n=99) (%)		
Age (year)				
≤50	70 (70.71)	72 (72.73)	0.1	0.752
>50	29 (29.30)	27 (27.27)		
Tumor size				
<1 ($T1_{ab}$)	14 (14.14)	4 (4.0)	63.413	<0.0001
1~2 (T_{1c})	45 (45.46)	48 (48.48)		
>2 (T_2)	40 (40.4)	47 (47.47)		
Histopathological grading				
Well differentiated	16 (16.16)	14 (14.14)	68.014	<0.0001
Intermediate	48 (48.48)	35 (35.35)		
Poorly differentiated	34 (34.34)	49 (49.49)		
Estrogen receptors				
Negative	24 (24.24)	40 (40.4)	5.91	0.015
Positive	75 (75.76)	59 (59.6)		
Clinical risk group according to St Gallen criteria				
Low risk	15 (15.15)	6 (6.06)	4.315	0.038
High risk	84 (84.85)	93 (93.94)		
Clinical risk group according to NPI criteria				
Low risk	27 (27.27)	18 (18.18)	4.514	0.034
High risk	71 (71.72)	81 (81.82)		
Clinical risk group according to Veridex signature				
Low risk	32 (32.32)	19 (19.19)	4.463	0.035
High risk	67 (67.68)	80 (80.81)		

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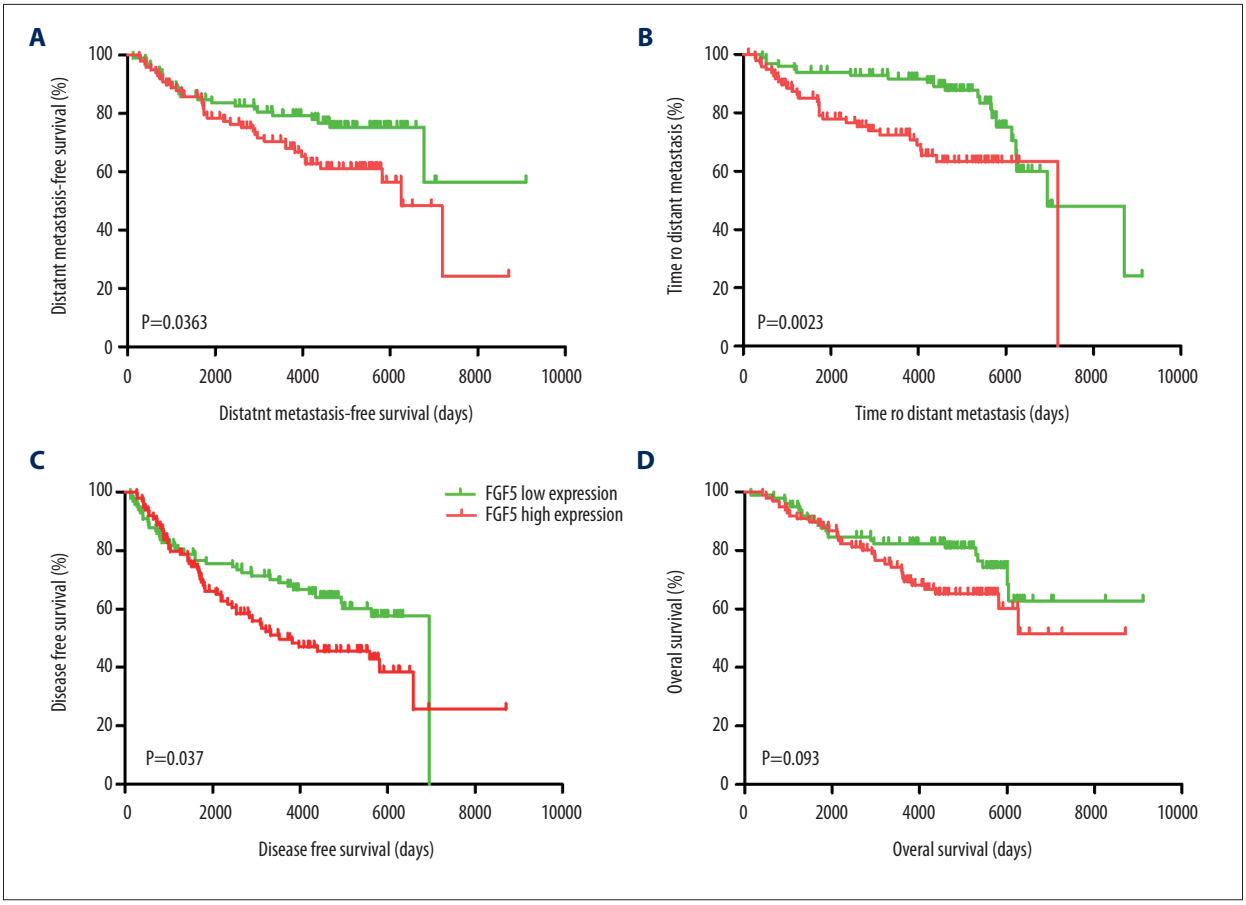

Figure 2. The relationship between the expression of FGF5 and the clinical prognosis of patients with breast cancer. (**A**) Distant metastasis-free survival; (**B**) time to distant metastasis; (**C**) disease-free survival; (**D**) overall survival.

and clinical risk group according to Veridex signature favored BC patients in the FGF5 low-expression group over BC patients in the FGF5 high-expression group (P<0.0001, P<0.0001, P=0.015, P=0.038, P=0.034, and P=0.035, respectively). These results suggest that FGF5 promotes the growth of BC cells.

Higher expression of FGF5 was associated with worse clinical outcomes of BC patients

To clarify the impact of FGF5 expression on the survival of patients with BC, log-rank test-based survival analysis of BC patients in the FGF5 high-expression group and BC patients in the FGF5 low-expression group was performed using BC microarray GSE7390. As shown in Figure 2, BC patients in the FGF5 low-expression group had better DMFS (HR=0.5865, 95% CI: 0.3559–09666, P=0.0363, Figure 2A), TDM (HR=0.4068, 95% CI: 0.2284–0.7246, P=0.0023, Figure 2B), and DFS (HR=0.6439, 95% CI: 0.4257–0.9739, Figure 2C) and OS (HR=0.6375, 95% CI: 0.3770–1.078, P=0.093) compared with those in the FGF5 low-expression group, suggesting that BC patients in the FGF5 high-expression group had longer overall survival than those in the FGF5 low-expression group.

Gene set enrichment analysis (GSEA) of BC samples

To investigate certain mechanisms involved in the influence of FGF5 on the growth of BC cells, BC samples of another independent BC gene expression profile GSE21653 were categorized into a FGF5 high-expression group and a FGF5 low-expression group according to the median of FGF5 mRNA levels, and then GSEA was performed. As shown in Figure 3, BC samples in the FGF5 high-expression group were correlated with gene sets associated with ultraviolet response (Figure 3A) and TGF-β signaling (Figure 3B).

FGF5 was upregulated in patients with BC

To confirm the above results, we used RT-PCR to investigate whether FGF5 was upregulated in BC patients. As shown in Figure 4, FGF5 was upregulated in 5 BC patients relative to that in normal breast tissue (0.7925±0.097 *vs.* 0.321±0.052, P<0.0001). The result of RT-PCT suggested that FGF5 was increased in BC patients compared with that in normal BC patients.

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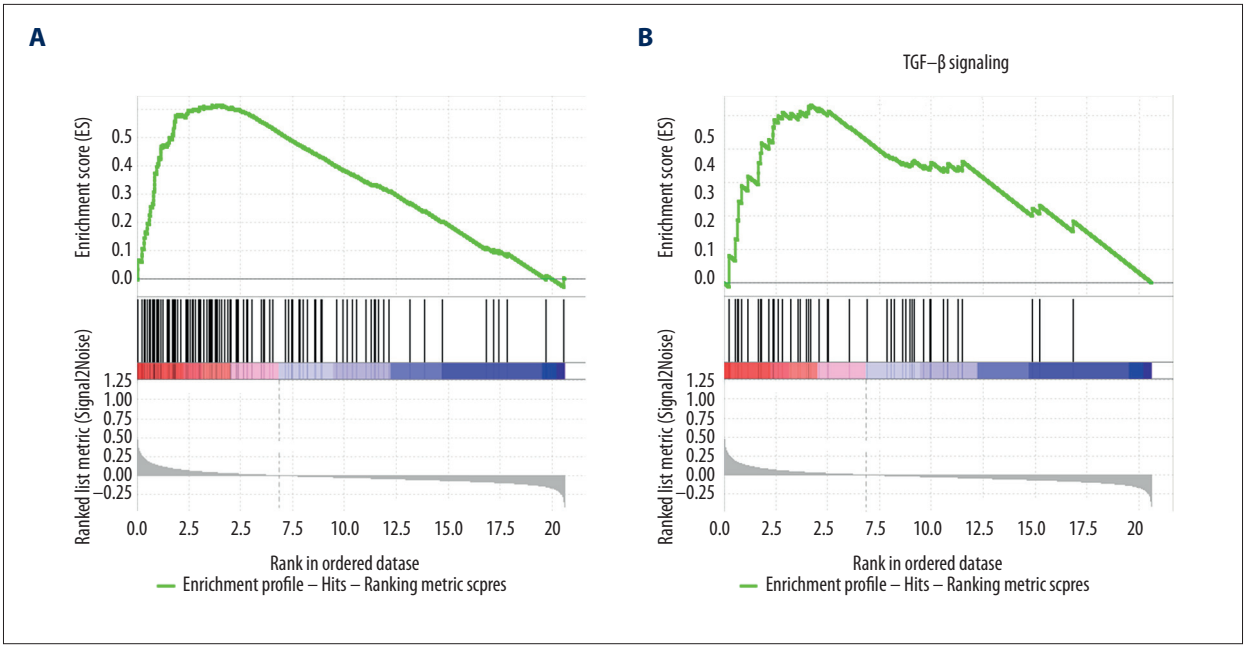

Figure 3. Gene sets enriched in breast cancer patients in the FGF5 high-expression group. (**A**) ultraviolet response, (**B**) TGF-β signaling.

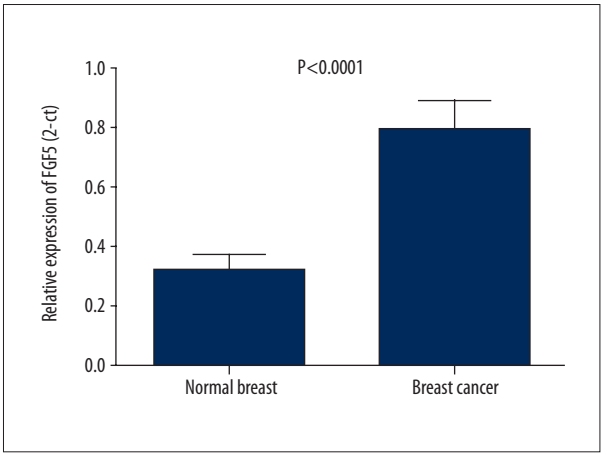

Figure 4. FGF5 was upregulated in patients with BC.

Discussion

As stated above, BC is one of the most common cancers worldwide, contributing to 29% of all new cancers diagnosed in women in 2016 [1]. Current management approaches of BC, such as surgery, chemotherapy, radiotherapy, and hormone therapy, are not targeted. The major concern regarding the above management is the treatment-related adverse effects, including anemia, nausea, vomiting, loss of appetite, fatigue, and immune suppression, as well as the impairment of cognitive function, which severely limits the treatment of BC and significantly reduces QOL (quality of life) of BC patients. Furthermore, although the efficacy of treatment for patients with early stages of BC is evident, many patients will inevitably develop disease relapse and metastasis, and the median OS of patients with metastatic BC is about 2–3 years [24,25]. Thus, novel diagnosis and treatment strategies for BC patients are needed.

Herein, our results showed that FGF5 was upregulated in BC cells, and patients in the FGF5 low-expression group had better clinical characteristics (including tumor size, histopathological grading, estrogen receptors, clinical risk group according to St Gallen criteria, clinical risk group according to NPI criteria, and clinical risk group according to Veridex signature). Patients in the FGF5 low expression group were associated with better DMFS, TDM, DFS, and OS.

FGF5 is associated with several malignances and the role of FGF5 in different tumors is controversial. Fang et al. demonstrated that the expression of FGF5 is required for the proliferation of hepatocellular carcinoma, and enforced expression of miR-188-5p suppresses the expression of FGF5 [14]. Meng et al. demonstrated that genetic variants of several SNPs (including FGF1 SNP rs7727832, SNP rs3806929, FGF7 SNP rs9920722, FGF23 SNP rs12812339, and FGF5 SNP rs3733336) in the FGF-FGFR axis are significantly associated with a favorable treatment response and clinical outcome in patients with ovarian cancer [16]. Casimiro et al. demonstrated that FGF5, accompanied by other genes, including MMP-1, FGF5, and CTGF, is upregulated in tumor cells of human bone metastases relative to a human normal epithelial cell line [26]. Metzner demonstrated that the expression of FGF2, FGF5, and FGF18 are increased in cutaneous melanoma cell lines, and the inhibition of FGF signaling is associated with reduced melanoma cell proliferation, and colony formation, as well as anchorage-independent growth and increased apoptosis [27].

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Tumor size of BC indicates the TNM staging and the outcome of BC patients. Our results suggest that the tumor sizes of BC patients in the FGF5 low-expression group were smaller compared with those in the FGF5 high-expression group, suggesting that FGF5 is associated with the TNM staging of BC patients. Previous studies demonstrated that patients with triple-negative BC were more likely to progress to visceral and central nervous system metastases and had earlier recurrence and worse survival rates relative to their estrogen receptor-positive counterparts [28,29]. The present results indicate that fewer BC patients in the FGF5 low-expression group were estrogen receptors-positive compared with those in the FGF5 high-expression group, indicating that the expression of FGF5 is associated with the expression of estrogen receptors in patients with BC.

Histological tumor grade is associated with the degree of differentiation of tumor tissue. In BC, it is associated with the semi-quantitative evaluation of morphological characteristics. Rakha et al. found a significant correlation between histological grade and pattern of survival. Akin to high-grade lymphoma, high-grade BCs tend to recur and metastasize early following diagnosis [30]. The Nottingham prognostic index (NPI), introduced by Haybittle et al. in the 1980s, is widely accepted for the prediction and classification of clinical prognosis of patients with BC. Doctors estimate the value of NPI according to lymph-node stage, tumor size, and pathological grade [31]. Furthermore, St Gallen criteria and Veridex signature are also widely used in the classification and treatment of patients with BC [32,33]. Results of the present study suggest that patients in the FGF5 high-expression group had better clinicopathological features (including histopathological grading, clinical risk group according to St Gallen criteria, clinical risk group according to NPI criteria, and clinical risk group according to Veridex signature) relative to those in the FGF5 low-expression group, indicating that higher expression of FGF5 predicts better prognosis of patients with BC.

BC patients in the FGF5 low-expression group were associated with favorable DMFS, TDM, and DFS compared with those in the FGF5 high-expression group. Even though the difference did not reach statistical significance, the OS of patients in the FGF5 low-expression group tended to be better than that in the FGF5 high-expression group (HR=0.6375, 95% CI: 0.3770–1.078, P=0.093). These results indicate that BC patients in the FGF5 low-expression group had better survival compared with those in the FGF5 high-expression group.

The results of GSEA suggest that FGF5 regulates the growth of BC cells through ultraviolet response and TGF-β signaling. Kim et al. demonstrated that deleted breast cancer 1 (DBC1) deficiency resulted in apoptosis of breast cancer cells through impaired responses to ultraviolet-induced DNA damage [34]. Some previous studies demonstrated that TGF-β suppresses primary tumor growth while promoting metastasis through EMT of the responding breast carcinoma cells, and plays a role in mediation of stromal-epithelial interface during oncogenesis of breast cancer [35]. Fuchshofer et al. suggested that FGF5, accompanied by several other genes, including CAPZA1, CDC42BPB, EFEMP1, FSTL3, HBEGF, LTBP1, LTBP2, MATN2, NRP1, SERPINE1, SH3MD1, SMTN, SMAD7, TFPI2, TNFAIP6, and VEGF, was regulated by TGF β in human trabecular meshwork cells [35]. Together, these results suggest that FGF5 affects the growth of breast cancer cells through the TGF-β associated pathway.

The above conclusions were validated by quantitative PCR, showing that the expression of FGF5 was overexpressed in BC cells compared to normal breast tissues. Thus, FGF5 is associated with poor clinical outcome of patients with BC.

Conclusions

Our results prove that FGF5 is increased in BC cells, and higher expression of FGF5 is associated with better prognosis of BC patients. Thus, FGF5 might be independent biomarker for patients with BC.

Conflicts of interest

None.

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