Identification of ATFs in Human Breast Cancer by Integrated Bioinformatic Analysis

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Abstract

Background: To obtain a thorough comprehension of the profile and prognosis of activating transcription factor (ATF) family members in breast cancer.

Method: We searched Oncomine, GEPIA, cBioPortal, Kaplan-Meier plotter, and CancerSEA databases to assess expression level, prognostic value, and functions of ATFs in breast cancer.

Results: In breast cancer, we found that the expression levels of genes like ATF1, ATF5, and ATF6, were higher than in normal tissues. While the expression levels of ATF3, ATF4, ATF7 were lower in the former than in the latter. Similarly, the ATFs protein expressions were consistent with this in the Human Protein Atlas database. High expressions of ATF2, ATF4, and ATF6-7 were associated with good relapse-free survival. Increased expressions of ATF4 and ATF7 had high overall survival. Conversely, the mRNA expression of ATF1 was negatively correlated with distant metastasis-free survival. Similarly, high expression of ATF2 had reduced post-progression survival.

Conclusions: ATF1 was a target of potential therapeutic interest for breast cancer, and ATF4 and ATF6-7 were potential prognostic factors in evaluating breast cancer.

Introduction

Breast cancer (BrCa) is the most commonly diagnosed cancer among women and the second leading cause of cancer death in women worldwide [1]. Many factors, including environmental, biological, lifestyle, and genetic factors, are currently studied to understand the causes of BrCa. BRCA1/2 genes mutations are the most common inherited mutations associated with BrCa [2]. Currently, the therapy of BrCa consists of surgery, radiation, chemotherapy, and hormone therapy [3]. According to different clinical subtypes of BrCa, specific treatments would be chosen. As the field of BrCa advances, the application of immunotherapy increases and becomes a potential future therapy in patients with BrCa. High heterogeneity is one of the characters of BrCa, and a challenge to targeted treatment for BrCa [4]. Therefore, using genomics to discover new molecular markers or targets to achieve precise therapies has become a recent research trend.

Activating transcription factor (ATF) family members are expressed in various tissues and tumor cell lines, playing significant roles in tumorigenesis and tumor progression [5]. As transcription factors, ATFs regulate the expression of downstream genes involved in growth, survival, and apoptosis. ATFs primarily diversify in size, protein sequence, and biological function [6–8]. ATFs contain seven members (ATF1-7) and belong to activating transcription factor/cAMP responsive element binding (ATF/CREB) protein family [9, 10]. All members share a typical basic-region leucine zipper (bZIP) element and bind target DNA with a consensus CRE (TGACGTCA) [11]. Based on previous studies, members of the ATF family were considered to participate in the progression, aggressiveness, and therapy resistance of BrCa [12]. At the same time, some molecules like ATF2, ATF3, ATF4 played an essential role in apoptosis [13–15]. However, the studies focused on the function of ATFs in BrCa were sporadic, and the systemic description

was scarce. Thus, the molecular events in cancer require a thorough investigation of the databases. In this study, we mined some databases, used bioinformatic analysis to determine the expression profiles and prognostic significance of ATFs, and obtained a comprehensive understanding of ATFs in BrCa.

Materials And Methods

Oncomine database analysis

Oncomine gene expression array datasets (<http://www.oncomine.org>; an online cancer microarray database) were used to display mRNA expression levels of the ATFs in different cancers. The mRNA expression analysis of each gene was acquired from tumor specimens and normal tissues. Cut-off of P -value and fold change were set at 0.01 and 1.5, respectively.

GEPIA database analysis

The GEPIA database (<http://gepia.cancer-pku.cn/>) is an online dataset based on the Cancer Genome Atlas (TCGA) (<https://www.cancer.gov/tcga>), which analyzed gene expression by comparing cancer specimens and paired normal tissues [16]. In the present study, the expression profiling of ATFs in BrCa and normal tissue and different pathological stages was demonstrated by GEPIA. Whether there were significantly different was defined with a cutoff $P < 0.01$.

Human protein atlas

Human Protein Atlas (<https://www.proteinatlas.org>) is a free database containing immunohistochemistry staining of more than 11,200 unique proteins in normal tissues and cancers [17]. It was based on staining intensity and fractional quantity of stained cells to define different expression levels of ATFs between BrCa and normal tissues.

Kaplan-Meier Plotter analysis

Kaplan-Meier Plotter (<http://kmplot.com/analysis/>) includes gene expression and associated survival data provided by TCGA, Gene Expression Omnibus (GEO) [18] and the Cancer Biomedical Informatics Grid [19]. In this study, Kaplan-Meier Plotter was used for evaluating the prognostic value of ATFs in BrCa. Overall survival (OS), post-progression survival (PPS), distant metastasis-free survival (DMFS), and relapse-free survival (RFS) were included in this analysis by splitting patients into two clusters according to high and low expression levels, based on the median. We also presented the hazard ratio (HR) with a 95% confidence interval (CI) and log-rank P value. Only the JetSet best probe set was used to assess gene expression. Patients' relative prognoses were denoted to the red and black line (high vs. low expression), respectively. Significance was assessed at the level of P value less than 0.05.

cBioPortal database analysis

The cBioPortal database (<http://www.cbioportal.org>) is a free database that offers visualization and analysis of multidimensional data of cancer genomics [20,21]. We explored genetic alterations of ATFs in the cBioPortal database based on 1084 BrCa samples in TCGA. The genomic alterations included mutation and putative copy number alterations (CNAs), which were identified by genomic identification of significant targets in cancer (GISTIC). Enrichment analysis was performed of co-expression genes associated with ATFs inspected by cBioPortal. Gene enrichment was conducted by GO enrichment analysis and KEGG pathway enrichment analysis and visualized by the R package ggplot2 (R version 3.6.3).

CancerSEA analysis

CancerSEA (<http://biocc.hrbmu.edu.cn/CancerSEA/>) is a web resource that helped to explore the cancer single-cell function. Human tumor single cell RNA-seq (scRNA-seq) data was integrated by three datasets, including the GEO database, ArrayExpress (<https://www.ebi.ac.uk/arrayexpress/>), and the Sequence Read Archive (<https://www.ncbi.nlm.nih.gov/sra>) [22]. In this study, CancerSEA was used to analyze ATFs. The correlation analysis of ATFs and 14 function states, including DNA repair, DNA damage, apoptosis, angiogenesis, differentiation, epithelial-mesenchymal transition (EMT), inflammation, cell cycle, hypoxia, invasion, stemness, metastasis, quiescence, and proliferation, were studied.

Results

ATFs transcript levels in BrCa patients

We compared the transcript levels of ATFs in tumors and normal tissues by using Oncomine databases (Fig. 1). As showed, most cancers had high expression of ATFs, especially ATF3, ATF5, ATF6. While in BrCa, only ATF5, ATF6, and ATF7 were upregulated in cancer tissues. In Curtis's dataset [23], ATF5 was significantly higher in medullary breast carcinoma than normal tissue (fold change=1.977) (Table 1). As reported by Richardson, high ATF5 expression was found in ductal breast carcinoma compared with normal tissues (fold change=1.760) [24]. Likewise, in Curtis's dataset, ATF6 was overexpressed in multiple types of BrCa, including tubular breast carcinoma with a fold change of 1.780, ductal breast carcinoma in situ with a fold change of 1.751, invasive ductal and invasive lobular breast carcinoma with a fold change of 1.731, breast carcinoma with a fold change of 1.630, medullary breast carcinoma with a fold change of 1.618, invasive ductal breast carcinoma with a fold change of 1.613, invasive lobular breast carcinoma with a fold change of 1.591, and invasive breast carcinoma with a fold change of 1.570, compared with normal breast tissues [23]. Furthermore, Ma et al indicated that ATF6 was overexpressed in invasive breast carcinoma in situ epithelia with fold change = 1.750, ductal breast carcinoma in situ epithelia with fold change = 1.986, versus normal tissues [25]. Similarly, Radvanyi et al showed that ATF6 had increased expression in invasive ductal breast carcinoma (fold change=4.518), invasive lobular breast carcinoma (fold change=4.377), and invasive mixed breast carcinoma (fold change= 6.122) [26]. In TCGA breast statistics, ATF6 had increased expression in multiple types of BrCa, including invasive lobular breast carcinoma (fold change = 1.593), invasive breast carcinoma (fold

change = 1.666), invasive ductal and lobular carcinoma (fold change = 1.974), mixed lobular and ductal breast carcinoma (fold change = 1.574), and invasive ductal breast carcinoma (fold change = 1.562) versus normal samples. Compared with normal tissue, ATF7 was overexpressed in invasive ductal and lobular carcinoma (fold change = 1.557). Ma et al stated that high expression of ATF7 could be seen in invasive breast carcinoma in situ epithelia (fold change = 1.616) and ductal breast carcinoma in situ epithelia (fold change = 1.918) versus normal tissues [25].

The relationship between ATFs Transcript Levels and pathology of BrCa

After searching the GEPIA dataset, we found that higher expression levels of ATF1, ATF5, and ATF6 were in BrCa. Conversely, lower expression levels of ATF3, ATF4, ATF7 were in BrCa versus normal tissues, although a statistically significant difference was observed on ATF3 only (Fig. 2). Also, the association between the tumor stages of BrCa and the expression of ATFs was analyzed. As showed in Fig. 3, there were no significantly difference of the mRNA expression levels of ATF1 ($P=0.0461$), ATF2 ($P=0.00719$), ATF3 ($P=0.0109$), ATF4 ($P=0.716$), ATF5 ($P=0.716$), ATF6 ($P=0.716$) and ATF7 ($P=0.00598$) in different stages of BrCa (stages I to IV).

The expression levels of ATFs proteins in BrCa and paracarcinoma tissues by immunohistochemical staining were retrieved via the Human Protein Atlas database. The results were shown in Fig. 4. It showed higher protein levels of ATF1, ATF5, and ATF6 were in BrCa tissues compared to normal tissue. In contrast, lower expression levels of ATF3, ATF4, ATF7 were in BrCa tissues, consistent with mRNA expression levels.

The prognostic value of ATFs expression in BrCa patients

Through the Kaplan-Meier plotter, we analyzed the correlation between the ATFs expression levels and the prognosis of BrCa patients. We estimated OS, RFS, PPS, and DMFS by Kaplan-Meier curves. As showed in Fig. 5, high expression of ATF2(HR, 1.31; 95% CI, 1.18 to 1.45), ATF4(HR, 1.13; 95% CI, 1.02-1.25), ATF6(HR,0.76; 95% CI,0.65 to 0.88), and ATF7(HR,0.76; 95% CI, 0.66 to 0.89) had high RFS. High expression of ATF7(HR,0.74; 95% CI, 0.56 to 0.96) and had ATF4(HR, 1.23; 95% CI, 1.01 to 1.48) high OS. In addition, high ATF1 expression (HR,0.79; 95% CI, 0.68 to 0.92) had worse DMFS. Likewise, high ATF2 expression (HR,1.35; 95% CI, 1.07-1.71; $P=0.012$) had reduced PPS. The other ATFs had no obvious prognostic significance on survival.

The changes of ATFs and predicted function and pathways of ATFs and neighbor genes

To analyze the alterations and correlations of ATFs, we downloaded the data using the cBioPortal for Cancer Genomics platform. There were 17% out of the samples in BrCa had altered ATFs (Fig. 6A). Genetic amplification was the most common change of ATFs, especially in ATF3(8%) and ATF6(10%). Correlations of ATFs with each other were calculated and showed in Fig. 6B. Both positive and negative correlations were visualized. ATF7 had the highest positive correlation with ATF1 and ATF2 with Pearson's coefficient of 0.45,0.45, respectively. Additionally, ATF7 had the strongest negative correlation

with ATF4 (Pearson's coefficient = -0.41). Meanwhile, the closest relation was demonstrated between ATF7 and other ATFs with a median Pearson's coefficient of 0.41.

Then, we applied the GO enrichment analysis and KEGG pathway analysis to predict the functions of ATFs and the genes mutated with ATFs (Fig. 7). GO enrichment analysis included cellular components, biological processes, and molecular function. Most of the genes frequently altered with ATFs were involved in ubiquitin-like protein transferase activity, regulatory RNA binding, ubiquitin-protein transferase activity, histone methyltransferase complex, transcriptionally active chromatin, nuclear speck, covalent chromatin modification, nucleosome disassembly, and histone modification. Second, we found that lysine degradation and transcriptional misregulation in cancer were associated with the functions of ATFs alterations by KEGG pathway analysis.

The functions of ATFs in single BrCa cell

By searching in CancerSEA, we found the primary relationship between ATFs and cell function was apoptosis (Fig. 8A). Chung et al showed that high ATFs mRNA levels positively correlated with quiescence (Spearman's coefficients, 0.39; $P < 0.01$) and apoptosis (Spearman's coefficients, 0.33; $P < 0.01$) (Fig. 8B) [27]. Jordan et al showed that ATFs were also positively associated with apoptosis (Spearman's coefficients, 0.41; $P < 0.01$) (Fig. 8C) [28]. In different cell groups, the ATFs were positively related to apoptosis (Spearman's coefficients, 0.49; $P < 0.01$) and DNA damage (Spearman's coefficients, 0.47; $P < 0.01$), while negatively related to stemness (Spearman's coefficients, -0.35; $P < 0.01$) and differentiation (Spearman's coefficients, -0.33; $P < 0.01$) (Fig. 8D) [27].

Discussion

As members of the ATF/CREB protein family, activated ATFs bind to CREs and promote CRE-mediated multiple genes transcription, which is involved in cell growth, inflammation, proliferation, apoptosis, and DNA damage response [29-31]. Despite some studies had confirmed the expression and function of ATFs in BrCa, a thorough, comprehensive analysis of ATFs has not been performed. As far as we know, this was the first bioinformatics of the ATF family, which dug out the mRNA expression, prognostic values, and single cell function. We hope that the results of this study could be beneficial for clinical research.

ATF1 was confirmed to regulate downstream target genes functioned as growth and survival [32-34], and involved in tumorigenesis in some cancers, including colorectal cancer [35], prostate cancer [36], and clear cell sarcoma [37]. However, there is limited information about ATF1 and BrCa. Houvras Y et al reported that ATF1 could interact with BRCA1 leading to the maintenance of genome integrity after DNA damage [38]. In the study of Jones DT and his colleges, high expression of ATF1 in invasive ductal carcinoma (IDC) could induce VEGF-stimulated angiogenesis in vitro.³⁹ In the current study, higher ATF1 expression was in BrCa compared to normal tissues by searching the Oncomine and GEPIA. This finding was consistent with the protein expression of ATF1 obtained from the Human Protein Atlas. High ATF1 expression had worse DMFS in BrCa patients analyzed by the Kaplan-Meier plotter.

ATF2 regulated many genes involved in the various cellular signal pathway [39]. A series of studies had focused on ATF2 and BrCa. In murine mammary cancer, ATF2 was critical to induce FOXP3 exerted an effect and FOXP3-mediated apoptosis [40], and ATF2 gene knockout mice were more likely to develop BrCa [41]. It was also reported that lower ATF2 mRNA level was in human BrCa compared to normal tissues [41]. Thus, it can be seen that ATF2 tended to have a tumor-suppressive function in BrCa. Nevertheless, some studies concluded opposite results. It was reported that ATF2 could increase the expression of matrix metalloproteinase 13 (MMP13), which had an essential role in bone metastasis of BrCa [42,43]. Moreover, ATF2 could promote proliferation by inducing the transcriptional activation of cyclin A [44]. In tumor development and metastasis progress, the complex consisted of ATF2 and c-Fos, and c-Jun also participated by regulating the induction of cyclooxygenase-2(COX2) [45]. Increased protein expression of ATF2 measured by immunohistochemistry (IHC) was associated with prolonged survival [46]. In our report, the mRNA and protein level of ATF2 had no significant difference in BrCa versus normal tissues. In comparison, high ATF2 expression was associated with good RFS but poor PPS. Our findings were consistent with the previous result that whether ATF2 played cancer-suppressive or cancer-promoting function depended on cancer stage progression [47,48].

ATF3 played a dual role, either repressing or activating in transcription depended on binding molecules [49-52]. As an adaptive-response gene, in quiescent cells, the expression of ATF3 was low while under stressful conditions including ischemia, hypoxia, and injury, it would increase [53,54]. It was also reported as an oncogene or suppressor in different tumor models [55]. The location of the ATF3 gene is in the 1q amplicon of the chromosome, which is the most prone to the amplified region in BrCa and the second-largest amplified area in solid tumors [56]. In this study, we also found genetic amplification in 8% of ATF3. Through the upregulation of the TGF β pathway or WNT/ β -catenin pathway, ATF3 is a proto-oncogene in BrCa [57,58]. Cao et al concluded that high expression of ATF3 would lead to poor OS in breast cancer [59]. Some studies pointed out that through promoting cell cycle progression and preventing apoptosis, the overexpression of ATF3 could participate in resistance to radiotherapy [60], however, several studies showed differences. Hasim et al noted that high expression of ATF3 could improve OS in response to chemotherapy [61]. The previous study has pointed that ATF3 could bind to and stabilize p53 to promote apoptosis [62]. Our finding showed significantly lower mRNA and protein levels of ATF3 in BrCa compared to normal tissues, and we speculate that ATF3 could suppress BrCa. However, there was no prognostic significance on survival.

ATF4 played a significant role in regulating genes involved in cell stress and induced by PKR-like ER kinase (PERK), an endoplasmic reticulum (ER) sensor. It would overcome hypoxic and ischemic stress during tumor progression, proliferate, and metastasis by upregulating ATF4 to promote cancer survival [63]. Based on the above reason, ATF4 was proposed as a promoting factor for the pathogenesis and development of BrCa. Some studies also revealed that ATF4 could regulate the expression of specific genes to promote BrCa metastasis [64,65]. Higher expression of ATF4 was found in BrCa than normal tissue and associated with lymph node metastases [66,67]. Meanwhile, high expression of ATF4 mRNA tended to poor prognosis in BrCa [67,68]. Other studies reported opposite results. Zong et al found that loss of ATF4 could enhance survival, and over-expressing ATF4 could promote radiation-induced

apoptosis in MCF7 cells [69]. The current study also found lower mRNA and protein levels of ATF4 in BrCa, compared to normal tissues. Moreover, high ATF4 would lead to long RFS in BrCa patients.

ATF5 was widely present in many tissues and permanently restricted to epithelial cells. In the breast, it was expressed mainly by the luminal ductal epithelium [70]. Under stress, ATF5 could promote the survival of cancer cells and play a critical role in multiple cellular activities, which included apoptosis, survival, growth, and autophagy by regulating specific genes [71,72]. ATF5 was considered as an anti-apoptotic factor, and if loss of function would cause apoptosis [73]. It was also found that ATF5 knockdown could inhibit aggressiveness and growth while triggering massive apoptosis of BrCa [70,74]. ATF5 upregulated growth response factor 1 (Egr-1) and BCL-2 to promote the cell survival of BrCa [75,76]. There is a significant difference in ATF5 between neoplasms and normal tissues, especially in adenocarcinomas. Monaco et al reported that high expression of ATF5 also existed in BrCa [77]. Similarly, we found higher mRNA and protein levels of ATF5 in BrCa than normal tissues in our study. Though ATF5 was critical in BrCa carcinogenesis, which indicated ATF5 might be a target for BrCa therapy, it was not detrimental to survival in current studies as far as we know.

ATF6 is currently the most studied family member because it is one of the three prominent endoplasmic reticulum stress sensors. ER stress plays an essential role during the various stages of cancer progression. Its activation is associated with highly aggressive cancers [78,79]. In BrCa, researchers reported that ER stress had an essential impact on oncogenic, cancer-promoting, and resistance to therapy [80]. The ER stress triggered unfolded protein response (UPR) to restore metabolic and protein processing functions. Once UPR occurred, ATF6 moved to the Golgi apparatus and been sheared into an active fragment and transported into the nucleus subsequently to regulate target genes expression [81]. Based on the above discussion, ATF6 increased in many cancers, including colorectal cancer, hepatocellular cancer, and BrCa. Sicari et al concluded that ATF6 was essential for viability and invasion phenotypes in triple-negative breast cancer (TNBC) cells [82]. In our study, these results were similar to ours. ATF6 was higher expressed in BrCa than normal tissues. Interestingly, patients with high ATF6 performed better RFS rates. We speculated that ATF6 might also perform a different role in cancer progression as ATF2 played.

ATF7 has the most similar structure among the ATF family with ATF2 [83,84]. The distribution of ATF7 in tissues was also vided as ATF2 [84,85]. Likewise, ATF7 participated in cell activity by forming complex c with c-Jun, Fra2, or c-Fos [84,86]. ATF7 was highly expressed in hepatocellular carcinoma, promoting cell proliferation and suppressing apoptosis by binding with heat shock protein A member 1B (HSPA1B) [87]. There was a negative association between ATF7 expression and pathological stage in colorectal cancer while the positive correlation with OS and PFS [88]. Studies of ATF7 in BrCa were scarce. We found that lower expression of ATF7 was in BrCa than in normal tissues in this study. Similarly, high expression predicted better OS and RFS.

Conclusion

We systematically analyzed the association between expression and prognosis of the ATFs in BrCa in this study. The results showed that high expression of ATF1 might be necessary to BrCa progression and associated with poor survival. ATF2 played either suppressive or promoting function depended on cancer stage progression. Expression of ATF4, ATF6, and ATF7 had a significant positive correlation with survival. As mentioned above, we speculated that ATF1 was a target of potential therapeutic interest for BrCa, and ATF4 and ATF6-7 were potential prognostic factors in evaluating BrCa. However, these results were concluded based on bioinformatics. Further validation of this hypothesis by experimental verification is required.

Declarations

Acknowledgments

Not applicable.

Authors' contributions

CG, QP, and ST were responsible for the design of the study, collection of databases, and drafted the manuscript. WG and HW performed the statistical analysis and analyzed the data. HG and GZ revised the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Qilu Hospital and conformed with the Declaration of Helsinki. As the datasets were collected from published literature, informed consent was obtained from patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Comparison of ATFs transcript levels between breast cancer and normal tissues from Oncomine database.

Type of Breast Cancer versus Normal Breast		Fold	P Value	t Test	Source and/or
	Tissue	Change			Reference
ATF1	NA	NA	NA	NA	NA
ATF2	NA	NA	NA	NA	NA
ATF3	NA	NA	NA	NA	NA
ATF4	NA	NA	NA	NA	NA
ATF5	medullary breast carcinoma	1.977	1.87E-09	7.862	Curtis Breast
	ductal breast carcinoma	1.760	8.34E-05	4.148	Richardson Breast
ATF6	tubular breast carcinoma	1.780	2.05E-27	14.887	Curtis Breast
	ductal breast carcinoma in situ	1.751	1.79E-04	5.398	Curtis Breast
	invasive ductal and invasive lobular breast carcinoma	1.731	3.39E-33	15.609	Curtis Breast
	breast carcinoma	1.630	1.33E-05	0.067	Curtis Breast
	medullary breast carcinoma	1.618	6.72E-08	6.59	Curtis Breast
	invasive ductal breast carcinoma	1.613	3.71E-66	24.661	Curtis Breast
	invasive lobular breast carcinoma	1.591	2.16E-38	15.291	Curtis Breast
	invasive breast carcinoma	1.570	2.53E-09	8.657	Curtis Breast
	invasive breast carcinoma in situ epithelia	1.750	2.00E-03	3.554	Ma breast
	ductal breast carcinoma in situ epithelia	1.986	3.28E-06	6.319	Ma breast
	invasive ductal breast carcinoma	4.518	0.002	4.058	Radvanyi Breast

	invasive lobular breast carcinoma	4.377	0.002	3.833	Radvanyi Breast
	invasive mixed breast carcinoma	6.122	8.60E-04	5.011	Radvanyi Breast
	invasive lobular breast carcinoma	1.593	6.04E-11	8.04	TCGA Breast
	invasive breast carcinoma	1.666	2.56E-21	11.362	TCGA Breast
	invasive ductal and lobular carcinoma	1.974	4.21E-11	21.159	TCGA Breast
	mixed lobular and ductal breast carcinoma	1.574	1.00E-03	4.771	TCGA Breast
	invasive ductal breast carcinoma	1.562	2.24E-29	14.442	TCGA Breast
ATF7	invasive ductal and lobular carcinoma	1.557	2.63E-06	6.539	TCGA Breast
	invasive breast carcinoma in situ epithelia	1.616	3.00E-03	3.326	Ma breast
	ductal breast carcinoma in situ epithelia	1.918	2.07E-04	4.637	Ma breast

Figures

Figure 1

ATFs transcript levels in different tumor types (Oncomine).

Figure 2

Comparison of ATFs transcript levels in BrCa and normal tissues (GEPIA). A, scatter diagram; B, box plot.

Figure 3

The relationship between the mRNA levels of ATFs and the stage of BrCa (GEPIA).

Figure 4

The expression levels of ATFs proteins in BrCa and normal tissues by immunohistochemical staining (The Human Protein Atlas).

Figure 5

The correlation between the ATFs expression levels and the prognosis of BrCa patients (Kaplan-Meier Plotter).

Figure 6

Mutation type of ATF gene in BrCa (cBioPortal). (A) Summary of alternations of ATFs in BrCa. (B) Correlations of ATFs with other family members; Pearson's coefficients were presented.

Figure 7

The functions of ATFs and genes mutated with ATFs (GO enrichment and KEGG pathway analysis).

Figure 8

Functional analysis of ATFs in BrCa (CancerSEA). (A) Correlated functions of ATFs in BrCa patients; blue bubble represents negatively correlated, red bubble represents positively correlated, bubble size represents the average correlation strength. Detailed functional correlations in BrCa chip (B, C) and in different cell groups(D). *** $P \leq 0.001$, ** $P \leq 0.01$, and * $P \leq 0.05$.