Original Article

Expression Patterns of Cofilin and Scinderin in Breast Cancer and their Association with Clinicopathological Features in Iranian Patients

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Abstract

Background: Cofilin-1 (CLF1) and scinderin (SCIN) are significant actin-binding proteins that are involved in the regulation of the actin polymerization dynamics. Overexpression of *CLF1* and *SCIN* has been associated with aggressive and tumorigenesis characteristics of various cancer types. The aim of the present study was to investigate the expression of *CFL1* and *SCIN* genes in breast cancer cells and their association with clinicopathological features. **Materials and Methods:** In this study, 65 breast cancer tissues were randomly selected, and quantitative real-time polymerase chain reaction was performed to measure the expression level of *CFL1* and *SCIN* genes in breast tumors. Then, the association of *CFL1* and *SCIN* expression level with clinicopathological features was assessed using Prism 5 software. **Results:** Overexpression of *CFL1* and *SCIN* was observed to be statistically significantly associated with tumor stage and lymph node involvement ($P < 0.05$). However, no association was found between the expression of the mentioned genes and tumor grade, tumor size, and patient age. **Conclusion:** The results of this study suggest that as *CFL1* and *SCIN* genes may play a role in the development of breast cancer; they have the potential to be examined as new biomarkers to predict the progression of the mentioned disease.

Keywords: *Breast cancer, cofilin, real-time polymerase chain reaction, scinderin*

Introduction

Breast cancer is one of the most common cancers in women worldwide.[1] According to the latest report in this regard, the incidence rate of breast cancer is approximately 12.5%; in other words, almost one in eight women is at risk of developing breast cancer during her lifetime.[2] The incidence rate of breast cancer is increasing in all societies. For instance, breast cancer in Asia has not only indicated a growing incidence rate but also has become the leading cancer among the Asian females.[2,3] Cancer is the third main cause of death in Iran after coronary heart disease and accidents. Among various types of cancer, breast cancer tends to extend rapidly among the Iranian females.[2]

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Several studies have demonstrated that remodeling of the actin cytoskeleton is essentially associated with tumor progression.[4] The actin cytoskeleton creates a complex system that performs a variety of cellular functions including adhesion, motility, exocytosis, endocytosis, and cell division.[5] A good piece of evidence had shown that remodeling of actin cytoskeleton plays a fundamental role in regulating the morphologic and phenotypic features of a malignant cell.[6] Cellular alterations that occur during the cancer progression have a significant influence on proteins that drive actin dynamics.[7]

In cells, the assembly, disassembly, and organization of actin filaments into functional networks are regulated by the proliferation of actin-binding proteins (ABPs).[8] ABPs play an essential function in remodeling actin filaments and are involved in the regulation of the actin polymerization dynamics. Over the years, determining the association between the expression of new cytoskeletal markers and the degree of malignancy of tumor cells has been at the forefront of recent studies.[9]

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ADF/cofilin family is one of the most important families of ABPs.[10] Cofilin-1 (CFL1) is a cytoskeletal protein and a nonmuscle isoform of the product of the *CFL1* gene. CFL1 is a small protein that can bind to both monomeric globular (G) and filamentous (F) actin. The mentioned protein is required for regulation of actin dynamics[11] and contributes to depolymerization of actin filaments. This process results in the formation of free barbed and pointed ends that are accessible for polymerization or depolymerization of actin filaments, which depends on the concentration of regional actin monomers.[12] CFL1 is the known substrate of LIM kinase 1 (LIMK1). The activity of CFL1 is regulated by its phosphorylation at serine 3 residue by LIMK1 or testis-specific kinase 1 and 2.[13,14] Phosphorylation mechanism inhibits actin-severing and depolymerization activities of CFL1, whereas dephosphorylation of this protein by Slingshot homolog leads to its activation.[14,15] CFL1 plays an essential role in different important cellular functions including cell motility, cytokinesis, and cell cycle progression.[13] It has been reported that CFL1 is associated with migration, metastasis, and aggressiveness in certain types of malignancies.[11] Endothelial growth factor stimulates cancer cells to utilize CFL1 to remodel the actin cytoskeleton network, which leads to cell migration and aggressiveness.[16] Recent studies also suggested that overexpression of *CFL1* is correlated with cancer progression and poor prognosis in patients with breast cancer.[17,18] Thus, regulation of *CFL1* expression and LIMK1/CFL1 pathway may provide potential therapeutic benefits for the prevention of breast cancer progression.[19-21]

Scinderin (SCIN) is a member of calcium-dependent gelsolin family of ABPs and can regulate the actin network by severing and capping of actin filaments. SCIN has been reported to regulate vesicle transport and exocytosis by organizing disassembly of actin filaments in response to intracellular calcium increase in secretory cells.[22] The available evidence has indicated that *SCIN* expression induces differentiation, maturation, and apoptosis in megakaryoblastic leukemia cells. However, overexpression of *SCIN* seems to be related to inhibition of the proliferation and tumorigenesis in these cells.[23]

A number of studies have confirmed that *SCIN* has an important role in the proliferation and tumorigenesis of different types of carcinoma cells such as prostate and lung cancer cells as well as tumor resistance in T-cell lysis-resistant tumor cells.[24-26]

In the present study, the expression level of *CFL1* and *SCIN* in patients with breast cancer was measured to determine the changes in *CFL1* and *SCIN* expression level in tumor and normal tissue samples. Moreover, any correlations between their expression levels and clinicopathological features were examined as well.

Materials and Methods

Sample collection

In the present case series study, 65 patients undergoing curative surgical resection with histologically confirmed breast cancer were enrolled. All tissue samples were collected from the Tumor Bank of Cancer Institute, Imam Khomeini Hospital, Tehran, Iran, from June 2013 to July 2014. Written informed consent was obtained from all the patients. Seven tissue samples from healthy individuals with no malignancies were obtained for normalization of tumor gene expression. Fresh tissue samples were immediately transferred to liquid nitrogen and then stored at −80°C.

Total RNA extraction and cDNA synthesis

Total RNA was isolated from 15-mg tumor and normal tissue samples using TriPure Isolation Reagent (Cat No. 11667165001, Roche Applied Science, Germany) following the manufacturer's instructions. The concentration and quality of the extracted RNA were measured using Nanodrop spectrophotometer ND-1000 UV-Vis (Thermo Fisher Scientific, USA). Only the RNAs with the absorbance ratio of A260/A280 within the range of 1.8–2.2 were used for cDNA synthesis. In addition, the quality of the RNAs was assessed by running the samples on 1.5% agarose gel electrophoresis. Complementary DNA (cDNA) was synthesized from approximately 1 μg of the total RNA using PrimeScript RT Reagent Kit (Cat No. RR037A, Takara Bio Inc., Japan) following the manufacturer's protocol. First, 1000-ng RNA of each sample was prepared. Briefly, each reaction contained 2 μl ×5 buffer, 0.5-μl Random Hexamers, 0.5-μl Oligo dT primer, and 0.5-μl reverse transcriptase enzyme. A total volume of 10 μl was prepared by adding Diethyl pyrocarbonate-treated water. The thermal cycling conditions were as follows: 37°C for 15 min followed by 85°C for 30 s.

Primer design and quantitative-real-time polymerase chain reaction

As Table 1 indicates, the forward and reverse primers were designed using Primer 3 program (http://primer3.ut.ee).

In order to detect the relative expression level of *SCIN* and *CFL1*, the quantitative-real-time polymerase chain reaction (q-RT PCR) was performed using Rotor-Gene TM 6000 machine (Corbett Life Science, Germany) with SYBR Premix Ex Taq II (Cat No. RR039A, Takara Bio Inc., Japan) following the manufacturer's protocol. Each q-RT PCR reaction was conducted in duplicate, and glyceraldehyde-3-phosphate dehydrogenase was chosen as a control to normalize the reactions. Each PCR reaction contained 1-μl cDNA, 5-μl SYBR Master Mix ×2, and 1-μl forward and reverse primers in a total volume of 10 μl. The PCR was performed as follows: predenaturation at 95°C for 10 min, 95°C for 1 min, 55°C for 30 s, and

Table 1: Sequences of gene primers for SYBR Green quantitative real-time polymerase chain reaction

Sequence	Tm	PCR product (bp)	Length	Primers
5' ATGCCCTCTATGATGCAACC 3'	53.6	153	20	COF forward
5' GCTTGATCCCTGTCAGCTTC 3'	53.5		20	COF reverse
5' GAA GGT GAA GGT CGG AGT CA 3'	53.6	109	20	GAPDH forward
5' AAT GAA GGG GTC ATT GAT GG 3'	53.3		20	GAPDH reverse
5' ACAGCCAAGAGGCTCCTACA 3'	53.6	179	20	SCIN forward
5' GCTACCTGGTTTGCCTTCAG 3'	53.7		20	SCIN reverse

GAPDH: Glyceraldehyde-3-phosphate dehydrogenase, SCIN: Scinderin, PCR: Polymerase chain reaction, COF: Cofilin, Tm: Primer melting temperature

72°C for 30 s. Melting curve analysis of each sample was utilized to determine the specificity of the PCR reaction.

Statistical analysis

The grade and stage of tumors were determined according to the WHO criteria and the tumor nodes metastasis staging system, respectively. Expression level of *CFL1* and *SCIN* was calculated using $2^{-\Delta\Delta CT}$. The association between the expression level of *CFL1* and *SCIN* and the clinical stage, grade, age, size, and lymph node involvement of tumors was examined using ANOVA and *t*-test. All data were analyzed by GraphPad Prism 5.0 software (GraphPad Software Inc., San Diego, CA, USA).

Results

Average expression level of cofilin-1 and scinderin in the tissue samples

In this study, the expression level of *CFL1* and *SCIN* was measured using $2^{-\Delta\Delta Ct}$ in tumor and normal tissue samples. Out of 65 tumor samples, 52 tumor tissue samples (80%) as compared with normal tissue samples had an elevated expression level of *CFL1*. Similarly, upregulation of *SCIN* was observed in 50 (76.9%) out of 65 tumor tissues as compared with normal samples. The clinicopathological features of the patients are indicated in Table 2.

Correlation between cofilin-1 and scinderin expression level and tumor stage in patients with breast cancer

The results of comparing the expression levels of *CFL1* and *SCIN* in Stage III with those in Stage I and II showed a significant correlation between the elevated expression levels of both *CFL1* and *SCIN* in Stage III as compared to those in Stage I/II (*CFL1*, $P = 0.02$; *SCIN*, $P = 0.002$). Therefore, upregulation of these genes may be associated with tumor stage [Figures 1 and 2].

Correlation between cofilin-1 and scinderin expression level and tumor grade in patients with breast cancer

The patients were categorized into Grade I, II, and III groups. Then, the expression level of *CFL1* and *SCIN* in these subgroups was compared [Figures 1 and 2]. Data analysis showed that there was no statistically significant correlation between the expression level of these genes and tumor grades (*CFL1*, $P = 0.83$; *SCIN*, $P = 0.99$).

Table 2: Clinical characteristics of 65 patients with breast cancer

Variable		*n*
Lymph node status	N0	29
	N	36
TNM staging	I	2
	II	38
	III	26
Histological grading	1	9
	2	30
	3	26
Tumor size	T1	7
	T2	41
	T3	17
Age (years)	<50	37
	≥50	28

TNM: Tumor node metastasis

Correlation between cofilin-1 and scinderin expression level and lymph node involvement in patients with breast cancer

In this study, 36 (55.38%) and 29 (44.61%) patients had positive and negative lymph node involvement, respectively. According to the results, a statistically significant correlation was observed between the overexpression of *CFL1* and *SCIN* and lymph node-positive samples (*CFL1*, $P = 0.01$; *SCIN*, $P < 0.0001$) [Figures 1 and 2].

Correlation between cofilin-1 and scinderin expression level and tumor size in patients with breast cancer

The patients were divided into three groups of T1, T2, and T3 according to tumor size. Tumor size classification was as follows: T1 ≤2 cm, T2 >2 cm and ≤5 cm, and T3 >5 cm. The expression levels of *CFL1* and *SCIN* in three groups are shown in Figures 1 and 2. There was no significant correlation between tumor size and the expression level of the examined genes.

Correlation between cofilin-1 and scinderin expression level and age in patients with breast cancer

The patients were divided in two groups as follows: Group I: <50 years and Group II: ≥50 years. A significant correlation was observed between the expression level of *SCIN* and the age range of <50 years; however, there was

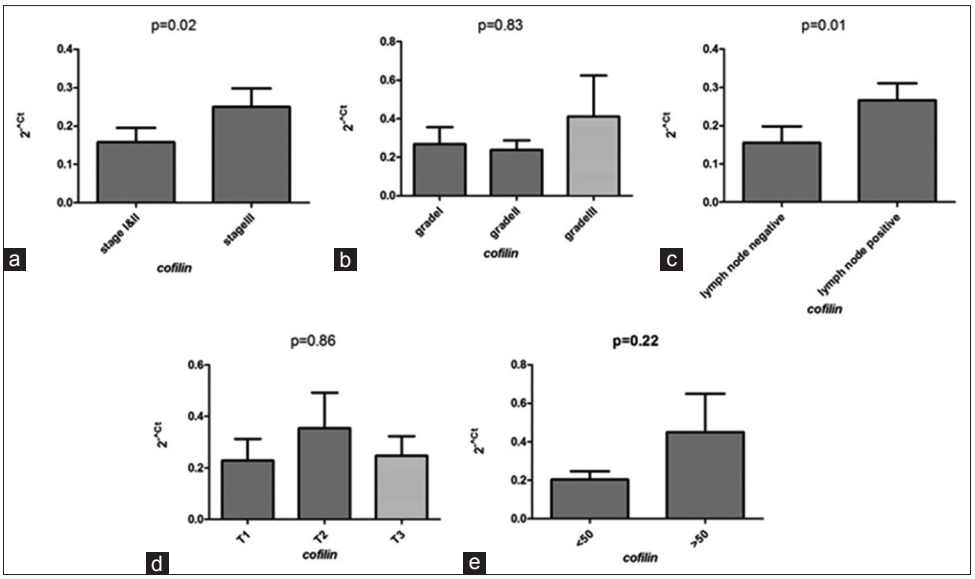

Figure 1: (a) The correlation between the expression level of *CFL1* and the stage of breast cancer tissues. (b) The correlation between the expression level of *CFL1* and the grade of breast cancer tissues. (c) The correlation between the expression level of *CFL1* and the lymph node involvement of breast cancer tissues. (d) The correlation between the expression level of *CFL1* and the tumor size of breast cancer tissues. (e) The correlation between the expression level of CFL1 and the age of patients with breast cancer

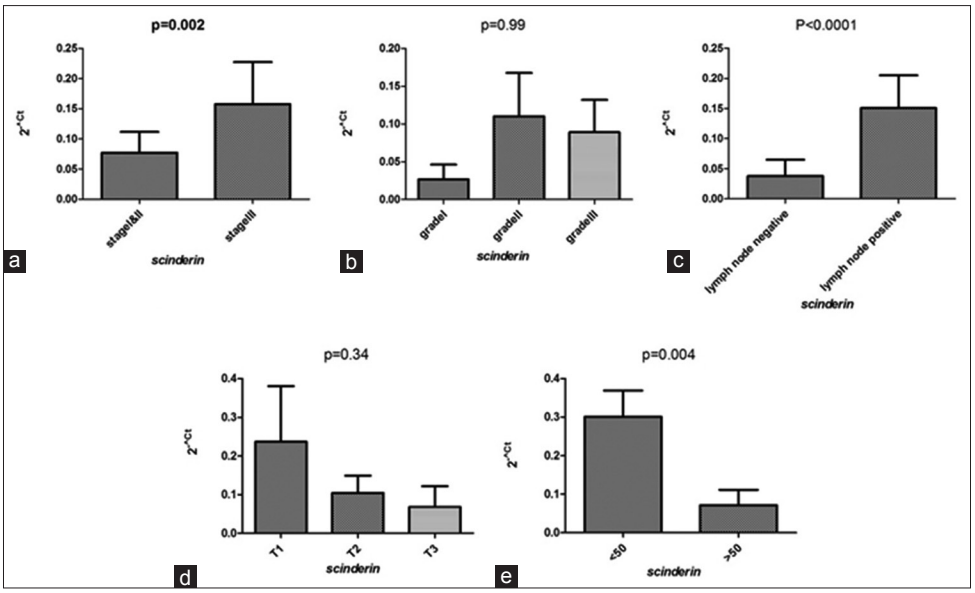

Figure 2: (a) The correlation between the expression level of *SCIN* and the stage of breast cancer tissues. (b) The correlation between the expression level of *SCIN* and the grade of breast cancer tissues. (c) The correlation between the expression level of *SCIN* and the lymph node involvement of breast cancer tissues. (d) The correlation between the expression level of *SCIN* and the tumor size of breast cancer tissues. (e) The correlation between the expression level of *SCIN* and the age of patients with breast cancer

no significant correlation between the expression level of *CFL1* and patient age.

Discussion

Breast cancer is one of the most common malignancies and still one of the most important health problems in the world considering its increasing incidence rate.[27] Uncontrollable growth and dissemination of tumor cells to distant organs are two major characteristics of malignant breast tumor cells. Adjuvant radiotherapy and chemotherapy are commonly used to target the aforementioned phenotypes of cancer cells. However, resistance to adjuvant radio-chemotherapy has made researchers to study novel therapeutic targets to prevent the growth and metastasis of cancer cells.[28]

The actin cytoskeleton dynamics play a crucial role in mediating the motility and metastatic characteristics of cancer cells. ABPs including CFL1 and SCIN are crucial components of cell-motility machinery. Therefore, aberrant expression of ABPs could possibly participate in cell invasion

and distant dissemination of cancer cells.[13,28,29] In an effort to figure out the relative expression level of *CFL1* and *SCIN* and its correlation with clinicopathological features of tumor tissues, the present study used q-RT PCR. The results of the study indicated not only a high expression level of *CFL1* and *SCIN* in breast tumor tissues, but also its significant association with tumor stage and lymph node involvement. The mentioned findings may reveal the significant roles of these genes in the development of breast cancer.

CFL1 is an actin cytoskeleton protein that severs actin filaments in plasma membrane and plays an essential role in regulating actin dynamics during cell migration. In the current study, 80% of tumor samples had indicated a high expression level of *CFL1*. Similar to the findings of the present study, overexpression of *CFL1* has been reported in various types of cancer cells including, human glioblastoma, oral squamous cell carcinoma, lung adenocarcinoma, renal and ovarian cancer, and C6 glioblastoma cell line.[11,27-31] Excessive expression of *CFL1* has also been associated with an increase in cell motility and invasion. In 2007, Yamaguchi and Condeelis reported that overexpression of *CFL1* up to 2–4 folds at protein level increased cell motility.[30] A study conducted by Tsai *et al*. revealed that overexpression of *CFL1* was associated with distant metastasis in breast cancer. The mentioned study also indicated that excessive overexpression of *CFL1* up to 15 folds in H1299 cells stopped cell invasiveness, growth, and cycle progression.[28] A number of recent studies have indicated that silencing of *LIMK1* remarkably impedes breast cancer progression. For example, Li *et al*. demonstrated that Mir-519d-3p regulated the LIMK1/CFL1 pathway in breast cancer by decreasing not only the expression level of *LIMK1* but also the phosphorylation and expression level of *CFL1*. In addition, the mentioned study indicated that miR-200b-3p and miR-429-5p could also suppress breast cancer migration and metastasis by targeting the LIMK1/CFL1 pathway.[20] In addition, Lu *et al*. concluded that Curcolonol, a furan-type sesquiterpene, had suppressive effects on breast cancer cell motility by reducing phosphorylation of *CFL1*, which might be correlated to the inhibition of LIMK1 activity.[32] Moreover, the findings with respect to the upregulation of *CFL1* in stage III in our research are in good agreement with those of Zhang and Tong's study that reported a positive correlation between excessive expression of *CFL1* and the cancer stage in esophageal squamous cell carcinoma.[29] The role and activities of CFL1 in the motility of malignant tumor cells indicate that this protein acts in a dose-dependent manner. Moreover, some regulatory processes including its phosphorylation and dephosphorylation processes could possibly affect its role in cancer progression.[15,31-34] In this study, a significant association was observed between the overexpression of *CFL1* and lymph node involvement. In addition, the overexpression of *CFL1* was observed in stage III as compared to Stage I/II. The mentioned results indicate that this factor might have a critical role in the progression of breast cancer.

SCIN, another ABP, has been recently grasped the attention of many researchers due to its significant role in tumorigenesis. Increasing evidence suggests that changes in the expression level of *SCIN* play a role in cell invasion and metastasis. Overexpression of *SCIN* has been reported in different types of cancer. Several studies have indicated that the high expression level of *SCIN* is in association with lymph node metastasis and invasion. Moreover, knocking down of *SCIN* expression inhibits migration in metastatic cancer cell lines. In 2014, Chen *et al*. investigated the biological function of *SCIN* in human gastric cancer cell line SGC-7901 and revealed that silencing of *SCIN* expression stopped cell proliferation and caused impairment in cell migration *in vitro*.[35] Another study conducted in 2014 showed that suppression of *SCIN* expression in human prostate cancer cell line (PC3) prevented cell proliferation and led to the expression of carcinogenic phenotype.[24] Liu *et al*. reported that *SCIN* was excessively expressed in gastric cancer cells and was in association with lymph node involvement. The mentioned finding was in agreement with that of the present study. Moreover, the mentioned study indicated that inhibition of *SCIN* expression promoted cells to lose their invasive and migratory characteristics.[36] Furthermore, another research performed in 2015 investigated the role of *SCIN* expression in lung cancer and indicated that knocking down of *SCIN* expression led to inhibition of cell proliferation and induced cell apoptosis.[25] Jian *et al*. demonstrated that *SCIN* knockdown in MDA-MB-231 and T-47D cell lines using lentivirus-mediated small interfering RNA technology considerably inhibited cell proliferation and promoted apoptosis.[37] In addition, Tanic *et al*. concluded that SCIN plays an essential role in the generation of cell membrane extensions and degradation of collagen in MCF7 cells that may in turn result in the formation and metastasis of invasive structures.[38] However, in 2001, Zunino *et al.* reported that megakaryoblastoma leukemia cells were unable to express *SCIN,* while exogenous expression of *SCIN* in these cells led to the inhibition of cell proliferation and tumorigenic characteristics.[23] In the present study, 76.9% of breast tumor tissue samples as compared to normal tissue samples showed excessive expression of *SCIN*, which was positively in association with lymph node involvement and tumor stage. To the best of the authors' knowledge, it is for the first time that overexpression of *SCIN* has been found to be associated with lymph node involvement and tumor stage in breast cancer.

Conclusion

The present study revealed the high expression level of *CFL1* and *SCIN* in breast tumor tissue samples that was significantly in association with tumor stage and lymph node involvement. The obtained results suggest that

CFL1 and *SCIN* may have a role in the development of breast cancer and have the potential to be studied as new biomarkers to predict the progression of breast cancer. Besides, the expression of the mentioned genes at the protein level requires further examinations. Furthermore, it is of great value to address the coordination of proteins in cell-motility machinery to shed more light on the invasive characteristics of cancer cells.

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Conflicts of interest

There are no conflicts of interest.

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