Basic Medical Research

Expression of DUSP1, LINC02202, and LINC01554 as a biomarker panel in the diagnosis and prognosis of breast cancer

Seyedeh Mahdieh Khoshnazar[1], Mandana Kazemi[2], Parnian Jahanbani[2], Mohammad Reza Moghare Abed[3], Shamim Afshoon[4]

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Authors' affiliations:
[1]Gastroenterology and Hepatology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran, [2]Department of Biology, Faculty of Basic Sciences, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran, [3]Department of Cell and Molecular Biology and Microbiology, Faculty of Biological Science and Technology, University of Isfahan, Isfahan, Iran, [4]Department of Biotechnology, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

Corresponding author:
Mandana Kazemi
Department of Biology, Faculty of Basic Sciences, Shahrekord Branch, Islamic Azad University, Rahmatieh Street, Shahrekord, Chaharmahal and Bakhtiari, Iran
Tel/Fax: +98-3136638600/ +98-3136614423
E-mail: mandanakazemi1374@gmail.com

ABSTRACT

BACKGROUND Breast cancer is a major global health challenge, with diverse and complex gene expression profiles. Long noncoding RNAs (lncRNAs) have emerged as key regulators of various cancers, including breast cancer. This study aimed to investigate the expression and prognostic value of dual specificity phosphatase 1 (DUSP1), LINC02202, and LINC01554 in breast cancer tissues and explore their association with clinical parameters.

METHODS DUSP1, LINC02202, and LINC01554 expression in healthy and breast tumor tissues were compared using *in vitro* and *in silico* conditions. *In silico* conditions examined their association with patient survival and disease prognosis through Kaplan–Meier and receiver operating characteristic curves. *In vitro* conditions examined the association between their expression and clinical parameters, such as tumor size, disease stage, and disease prognosis.

RESULTS Our study found that DUSP1, LINC02202, and LINC01554 were significantly downregulated in breast tumor tissues compared to healthy tissues, as shown by both *in vitro* and *in silico* analyses. Their expression levels are also significantly associated with the prognosis of breast cancer. Notably, only LINC02202 expression was significantly correlated with reduced patient survival and tumor size.

CONCLUSIONS This study provides novel insights into the expression and function of DUSP1 mRNA, LINC02202, and LINC01554 lncRNAs in breast cancer and identifies potential biomarkers and therapeutic targets for this disease.

KEYWORDS biomarkers, breast cancer, dual specificity phosphatase 1, gene expression

Breast cancer results from abnormal growth of breast cells. While cell proliferation in benign tumors halts at a certain stage, while growth in malignant tumors continues uncontrollably and can metastasize throughout the body if untreated.[1] Women with early-stage breast cancer commonly receive systemic adjuvant therapies, such as chemotherapy, endocrine therapy, anti-HER2 therapies, or a combination of these, based on the tumor's characteristics and the patient's overall condition.[2] Tools such as Adjuvant! Online[3] and PREDICT Plus[4] can assist in treatment selection but often overlook individual biological differences.[5] Gene expression studies have identified at least four molecularly distinct types of breast cancer,[6] leading to the development of genomic tests for improved treatment predictions.[7] The use of genetic markers in these studies is crucial, and researchers are actively seeking additional markers to enhance the prognosis and treatment of breast cancer.[8,9]

Dual specificity phosphatase 1 (DUSP1) was first discovered in cultured murine cells. This protein consists of a non-catalytic N-terminal domain and a C-terminal catalytic domain exhibiting ATPase activity.[10] DUSP1 plays a crucial role in deactivating various mitogen-activated protein kinase (MAPK) isoforms,[11] including extracellular signal-regulated kinases (ERKs), c-Jun-NH2-terminal kinase (JNK), and p38 MAPKs, that contribute to cell proliferation and apoptosis.[12] DUSP1 achieves this by dephosphorylating these MAPKs, thereby regulating cell proliferation, differentiation, stress responses, inflammation, and apoptosis through the MAPK pathway.[12] DUSP1 expression levels have been altered in different human tumors, including lung, ovary, and prostate cancers. Studies indicate a higher risk of triple-negative breast cancer associated with DUSP1 promoter methylation in peripheral blood leukocytes. Additionally, the progesterone receptor suppresses breast cancer cell proliferation by promoting DUSP1 expression.[13]

Long noncoding RNAs (lncRNAs) are RNA molecules of at least 200 nucleotides in length that lack protein-coding potential. These poorly conserved molecules regulate gene expression through mechanisms that not well understood.[14] Altered lncRNA expression in breast cancer is a significant factor in metastasis and mortality.[15] For instance, LINC02202 is recognized as a crucial lncRNA in adipocyte differentiation, influencing adipogenesis by acting as competing endogenous RNAs or co-expressing with target genes. This dysregulated expression has also been observed in cervical cancers, with bioinformatics studies indicating reduced LINC02202 levels in breast cancer cells.[16] Similarly, LINC01554 has been shown to suppress hepatocellular carcinoma (HCC) tumorigenesis by decreasing PKM2 gene expression and inhibiting the Akt/mammalian target of the rapamycin signaling pathway.[17]

This study aimed to identify appropriate biomarkers for breast cancer diagnosis and treatment. Analysis of The Cancer Genome Atlas (TCGA) data showed a positive correlation between two lncRNAs, LINC02202 and LINC01554, and the DUSP1 gene. Subsequent investigations under *in silico* and *in vitro* conditions confirmed their association with breast cancer, indicating reduced expression of DUSP1 and the two lncRNAs in breast cancer tissues. This decrease was likely attributed to physical interaction, confirming the potential of LINC02202 and LINC01554 as molecular markers for breast cancer.

METHODS

In silico conditions

The study was approved by the Ethics Committee of the Shahrekord Branch, Islamic Azad University (IR.IAU.SHK.REC.1403.029). RNA-Seq data for breast tumors were obtained from TCGA (https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga). Raw data were uploaded using the TCGAbiolinks package in STAR-Counts format, comprising 1,109 cancer and 113 normal samples. Clinical information for all samples was retrieved. Data analysis was conducted in R version 4.0.1. The LIMMA package facilitated data normalization, excluding genes with minimal or zero expression. Subsequently, data underwent logarithmic transformation via the edgeR package, yielding an expression matrix for further analyses.

Clinical data were utilized to evaluate the effects of gene expression on patient survival. Candidate genes' expression in the matrix was standardized (z-score) logarithmically, followed by conducting a Cox regression test with the clinical data from each sample. Subsequently, the log-rank test was utilized to detect significant correlations between gene expression and patient survival. Additionally, Kaplan–Meier plots were generated. Samples were classified into high- (z-score >0) and low- (z-score <0) expression groups.

In vitro conditions

A power calculation with a significance level of 0.05 and a power of 80% indicated that at least 25 paired samples would be necessary to detect significant variations in gene expression.[18] After obtaining patient consent, 28 breast cancer tissue samples and 28 healthy tissue samples adjacent to the tumor were obtained from the same individuals at Al-Zahra Hospital in Isfahan, Iran. Following pathological confirmation, the samples were frozen in liquid nitrogen and preserved at –70°C until analysis. This study was conducted in compliance with the Declaration of Helsinki of the World Medical Association for research involving human participants.

RNA was extracted using the TRIzol kit (Sigma-Aldrich, Germany). Approximately 50–100 mg of tissue

Table 1. Specifications of primers used for real-time PCR

Gene	Primer	5'-sequence-3'	Product size (bp)
DUSP1	Forward	ATCCTGCCCTTTCTGTACCTG	173
	Reverse	CTGATGTCTGCCTTGTGGTTG	
LINC02202	Forward	CTGTGAGATGGTTTTCTTGGGT	186
	Reverse	AATGGTGATGGTGTTAGGGTG	
LINC01554	Forward	ATTGTTGTCACTCTTAGCTCC	168
	Reverse	GCATTTCTTACCCCAGTCGTC	

bp=base pair; PCR=polymerase chain reaction

was homogenized in 1 ml of YTzol solution (Invitrogen, USA) following the manufacturer's instructions. RNA quality and quantity were evaluated using agarose gel electrophoresis and spectrophotometry, respectively. Complementary DNA (cDNA) was synthesized using the Takara cDNA synthesis kit (BioFact, South Korea) according to the manufacturer's protocol. Primers for DUSP1, LINC02202, and LINC01554 were designed using Oligo 7 software version 7.6 (OLIGO, USA) and synthesized by Bioneer (Bioneer Global Center, South Korea), with the sequences listed in Table 1. Real-time polymerase chain reaction was conducted using the Mic device (Bio Molecular Systems, Australia) and SYBR Green Master Mix (Takara Bio Inc., Japan). Denaturation was performed for 40 cycles at a temperature range of 60–95°C, with each cycle involving 30 sec of incubation at 95, 60, and 72°C. Glyceraldehyde 3-phosphate dehydrogenase served as a reference gene for absolute evaluation. The mean cycle threshold of each sample was calculated at the end of each reaction. The difference between target and reference genes was determined as ΔCt. Fold change in expression was calculated using the formula $2^{-\Delta\Delta Ct}$. Gene expression analysis was performed using the GraphPad Prism software version 8.0 (GraphPad Software, Inc., USA).

Statistical analysis

Data were analyzed using GraphPad Prism software version 8.0 (GraphPad Software, Inc.). An independent *t*-test compared gene expression between patients with breast cancer and healthy individuals. One-way analysis of variance compared gene expression at different stages, and an independent *t*-test was used to compare gene expression based on tumor size. A *p*-value of <0.05 was considered statistically significant.

RESULTS

In silico conditions

According to TCGA data from breast cancer and co-lncRNA databases, the linear regression method indicated a relationship between lncRNAs and DUSP1. LINC02202 and LINC01554 were chosen based on their positive correlation coefficients (0.569 and 0.055, with p = 0.0068 and 0.035, respectively). Nevertheless, their expression in breast cancer has not been investigated before (Figure 1).

The levels of DUSP1, LINC02202, and LINC01554 were compared in tumor and healthy tissues using TCGA data. Figure 2 illustrates a significant decrease in the expression of all three genes in tumor tissue compared to normal tissue (p<0.0001).

Kaplan–Meier curves were utilized to investigate the relationship between gene expression and patient survival rates. The findings indicated a notable correlation between modified LINC02202 expression and diminished patient survival, suggesting that alterations in this gene expression could result in reduced survival (p = 0.0021). Conversely, no significant correlation was detected between patient survival rate and variations in DUSP1 (p = 0.721) or LINC01554 (p = 0.4406) expression (Figure 3).

Receiver operating characteristic (ROC) curve analysis demonstrated a significant correlation between low expression of DUSP1, LINC02202, and LINC01554 and cancer prognosis (p<0.0001). The 95% confidence interval (CI) values for DUSP1, LINC02202, and LINC01554 were 0.87–0.92, 0.96–0.98, and 0.84–0.88, respectively (Figure 3).

In vitro conditions

Gene expression analysis in tumor tissues and adjacent healthy tissues revealed a notable reduction in the expression levels of DUSP1 (p = 0.0008), LINC02202 (p = 0.0045), and LINC01554 (p = 0.0033) in tumor tissues compared to healthy tissues (Figure 4).

The ROC curve results aligned with those of the *in silico* analysis, demonstrating a notable correlation between DUSP1, LINC02202, and LINC01554 expression and cancer prognosis (p<0.001). The 95% CI values for DUSP1, LINC02202, and LINC01554 were estimated as 0.70–0.94, 0.57–5.84, and 0.65–0.90, respectively.

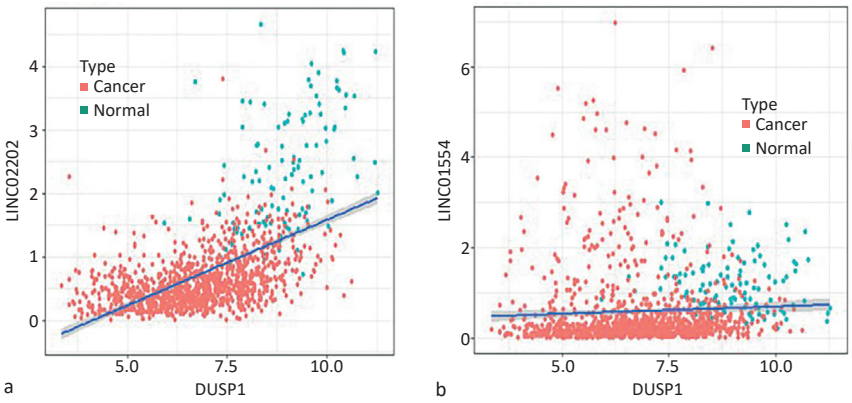

Figure 1. Positive correlation with Pearson coefficient between dual specificity phosphatase 1 (DUSP1) gene and LINC02202 (a) and LINC01554 (b)

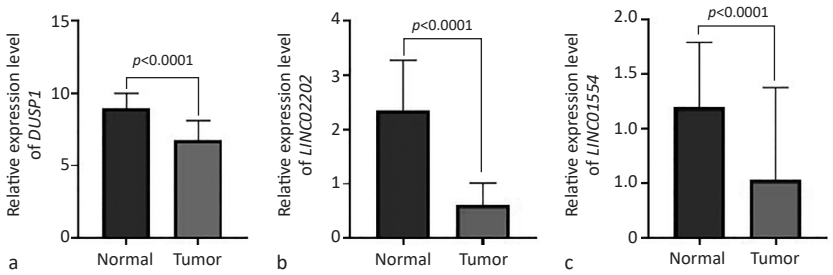

Figure 2. Expression of studied genes in healthy and breast tumor tissues using data obtained from TCGA. (a) DUSP1; (b) LINC02202; (c) LINC01554. DUSP1=dual specificity phosphatase DUSP1; TCGA=The Cancer Genome Atlas

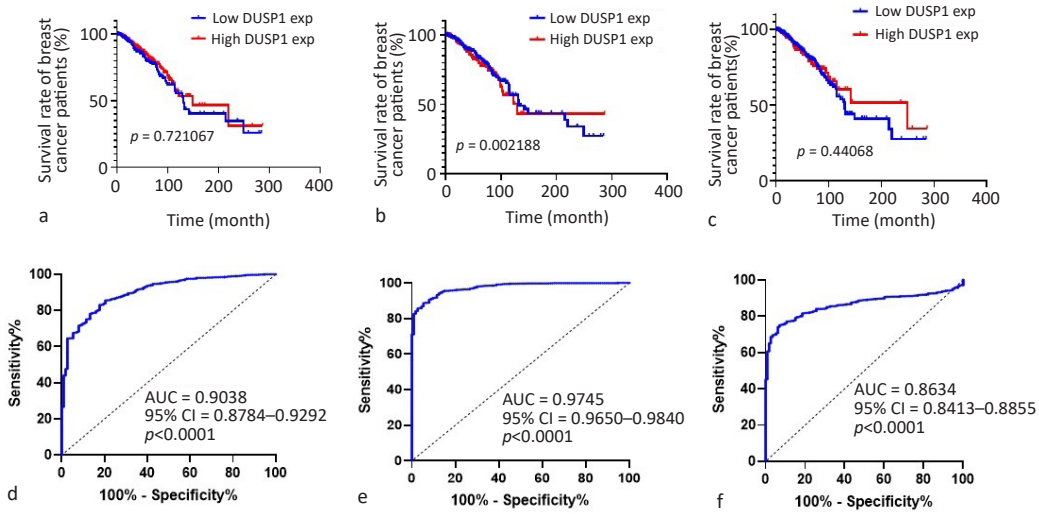

Figure 3. Kaplan–Meier curve to examine the association of gene expression with survival rate of breast cancer patients using data from TCGA (a–c: DUSP1, LINC02202, and LINC01554). ROC curve to investigate the possibility of predicting breast cancer through the expression level of the studied genes using data obtained from TCGA (d–f: DUSP1, LINC02202, and LINC01554). AUC=area under the curve; CI=confidence interval; DUSP1=dual specificity phosphatase 1; ROC=receiver operating characteristic; TCGA=The Cancer Genome Atlas

A significant difference in LINC02202 expression existed between tumors larger and smaller than 5 cm (p = 0.0115), suggesting a correlation between gene expression and tumor size. Nevertheless, no significant correlation was observed between the expression levels of DUSP1 (p = 0.4828) or LINC01554 (p = 0.6898) and tumor size (Figure 5).

Figure 5 illustrates the variations in the levels of DUSP1, LINC02202, and LINC01554 expression across various breast cancer stages. However, statistical analysis revealed non-significant disparities (p = 0.5857, 0.4546, and 0.3286, respectively), indicating no correlation between the expression levels of DUSP1, LINC02202, and LINC01554 and breast cancer.

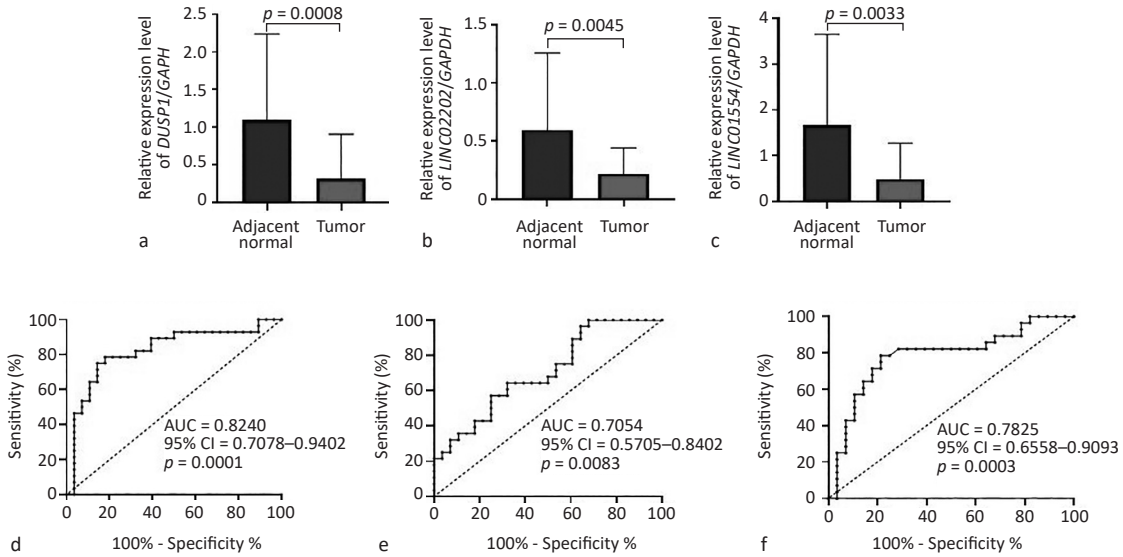

Figure 4. Comparison of expression levels of genes studied in breast tumor tissues and surrounding healthy tissue (a–c: DUSP1, LINC02202, and LINC01554). ROC curve to investigate the possibility of predicting breast cancer through the expression level of the studied genes using real-time PCR data (d–f: DUSP1, LINC02202, and LINC01554). AUC=area under the curve; CI=confidence interval; DUSP1=dual specificity phosphatase 1; GAPDH=glyceraldehyde 3-phosphate dehydrogenase; PCR=polymerase chain reaction; ROC=receiver operating characteristic

DISCUSSION

The cancer transcriptome is more intricate than previously understood. Initial research on detecting biomarkers in breast cancer has primarily focused on protein-coding genes such as Ki-67, ER, PR, and HER2.[19] However, lncRNAs are more abundant than protein-coding genes and offer a valuable source of biomarkers. Recently, there has been a growing interest in the roles and functions of lncRNAs in cancer. This study illustrated that two lncRNAs, LINC02202 and LINC01554, might contribute to breast cancer development by interacting with DUSP1 and modifying its expression. The findings also indicated that the expression levels of all three factors could serve as prognostic markers for breast cancer.

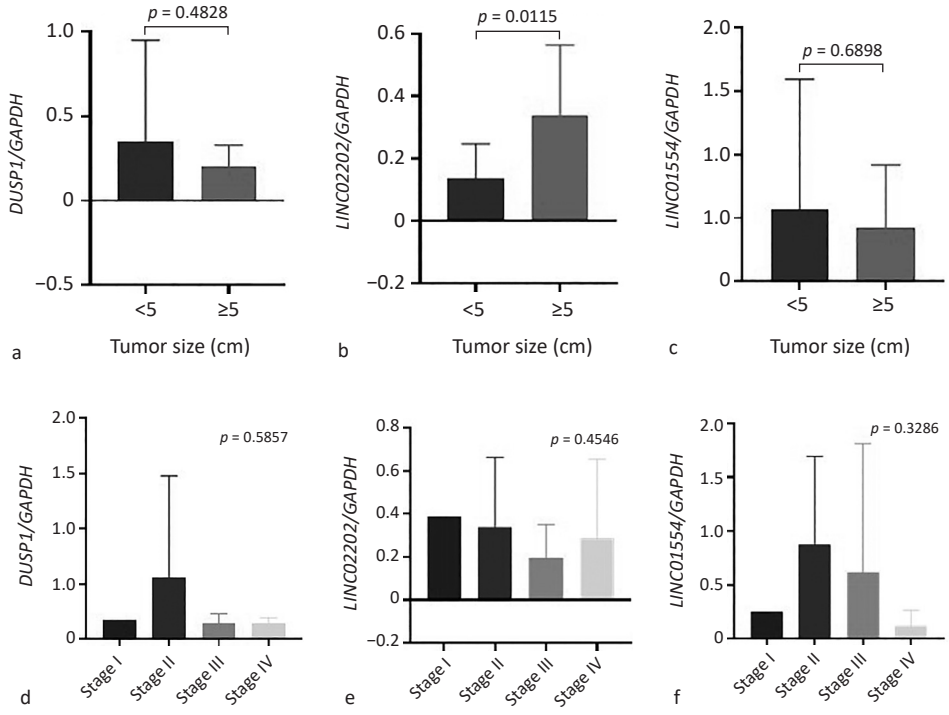

Figure 5. Comparing the expression of genes studied in: tumors smaller and larger than 5 cm in size (a–c: DUSP1, LINC02202, and LINC01554) and breast tumors at different stages (d–f: DUSP1, LINC02202, and LINC01554). DUSP1=dual specificity phosphatase 1; GAPDH=glyceraldehyde 3-phosphate dehydrogenase

Previous research has shown that the lncRNA HOX transcript antisense RNA (HOTAIR) enhances breast cancer metastasis by altering chromatin structure. The expression level of this gene serves as a prognostic indicator for metastasis and survival. HOTAIR expression increases in early breast tumor stages and metastasis, establishing it as a robust prognostic marker for metastasis and mortality.[19] Several studies have investigated the relationship between lncRNAs and cancer-related genes. Liu et al[15] identified multiple breast cancer-associated lncRNAs. Chen et al[20] reported that the lncRNA cancer susceptibility candidate 9 induces gefitinib resistance in lung cancer cells by epigenetically suppressing DUSP1. Peng et al[21] demonstrated that the lncRNA Lnc-FAM84B-4 acts as an oncogene, inhibiting DUSP1 expression in colorectal cancer through interaction with heterogeneous nuclear ribonucleoprotein K. In a study by Pan et al,[22] LINC01111 suppressed pancreatic cancer cell invasion by modulating DUSP1 expression via microRNA 3924. Moreover, growth arrest-specific 5 lncRNAs can suppress the inflammatory response and apoptosis of alveolar epithelial cells by targeting miR-429/DUSP1. Therefore, the role of DUSP1 in various cancers may differ based on the influence of lncRNAs.

This study revealed a decrease in the expression of LINC02202 and LINC01554 in breast cancer cells, leading to the downregulation of DUSP1 owing to the close physical proximity of these two lncRNAs to the gene. Sun et al[16] confirmed the reduced expression of LINC02202 in breast cancer through an *in silico* analysis. Additionally, a bioinformatics investigation on HCC demonstrated that LINC01554 could influence the expression of several crucial genes, indicating its potential as a viable target for HCC.[23] The study also validated the tumor suppressor function of LINC01554 by demonstrating its role in decreasing cancer-induced expression.

The role of DUSP1 varies in different cancers, playing a crucial part in carcinogenesis through the inhibition of JNK-induced apoptosis.[8] DUSP1's involvement in the progression of carcinogenesis has been documented in prostate, colon, bladder, stomach, breast, and lung cancers.[24] However, in HCC, this protein acts as a suppressor of carcinogenesis by associating with resistance to hepatocarcinogenesis. It also inhibits carcinogenesis in head and neck squamous cell carcinoma by reducing interleukin-1 beta levels in the tumor microenvironment. DUSP1 also promotes tumor progression by targeting the ERKs and P53 pathways.[25] Its role has been explored in various cancer treatment modalities, including chemotherapy, radiation, immunotherapy, and biotherapy. Studies have indicated that DUSP1 enhances resistance to chemotherapy and radiotherapy in different cancers by decreasing JNK-dependent apoptosis.[24] It mitigates the cytotoxic effects of tumor necrosis factor-alpha produced by CD8+ T cells. Sheng et al[26] identified an association between DUSP1 and HER2 in breast cancer, demonstrating that DUSP1 serves as a critical downstream target of HER2. It is translocated to the mitochondria to prevent apoptosis by limiting the accumulation of active JNK forms.

The findings of this study indicated that reduced expression of LINC02202 and LINC01554 in breast tumor cells may lead to the downregulation of DUSP1, potentially through physical interaction. Therefore, these lncRNAs might serve as molecular markers for breast cancer detection. Moreover, considering the impact of lncRNAs on gene expression in cancer, they hold promise as therapeutic targets for breast cancer. The approach employed in this study is applicable for uncovering additional connections between lncRNAs and protein-coding genes across different cancer types.

A limitation of this study is that the sample size for the *in vitro* analysis was relatively small (28 patients), which may limit the generalizability of the findings. The lack of functional validation and reliance on single-source data may affect the study's generalizability and statistical power. The absence of comparisons with other biomarkers limits the broader clinical context of this study. Finally, we examined the associations between gene expression and factors such as patient survival, tumor size, and disease stage. However, we did not consider other clinical variables, such as treatment type, which could influence outcomes and provide a more comprehensive understanding of the impact of gene expression on prognosis. The DUSP1 genes, LINC02202, and LINC01554 are important indicators of the molecular processes involved in breast cancer formation. The main findings of this study can help reduce the lack of understanding of the illness process and create new opportunities for research on developing treatments to alleviate breast cancer. Our study provides vital insights into the functions of these mRNA and lncRNAs in breast cancer. However, further research and functional investigations are required to

elucidate their specific mechanisms and assess their potential as therapeutic targets or biomarkers.

Conflict of Interest
The authors affirm no conflict of interest in this study.

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