Identification of Crucial IncRNAs for Luminal A Breast Cancer through RNA Sequencing

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Background. The growing body of evidence indicates aberrant expression of long noncoding RNAs (lncRNAs) in breast cancer. Nevertheless, a few studies have focused on identifying key lncRNAs for patients with luminal A breast cancer. In our study, we tried to find key lncRNAs and mRNAs in luminal A breast cancer.

Methods. RNA sequencing was performed to identify differentially expressed mRNAs (DEmRNAs) and differentially expressed lncRNAs (DElncRNAs) in luminal A breast cancer. The protein-protein interaction (PPI), DElncRNA-DEmRNA coexpression, DElncRNA-nearby DEmRNA interaction networks, and functional annotation were performed to uncover the function of DEmRNAs. Online databases were used to validate the RNA sequencing result. The diagnostic value of candidate mRNAs was evaluated by receiver operating characteristic (ROC) curve analysis.

Results. A total number of 1451 DEmRNAs and 272 DElncRNAs were identified. Several hub proteins were identified in the PPI network, including TUBB3, HIST2H3C, MCM2, MYOC, NEK2, LIPE, FN1, FOXJ1, S100A7, and DLK1. In the DElncRNA-DEmRNA coexpression, some hub lncRNAs were identified, including AP001528.2, LINC00968, LINC02202, TRHDE-AS1, AC097534.1, MIR222HG, and AL662844.4. The mRNA expression result of TFF1, COL10A1, LEP, PLIN1, PGM5-AS1, and TRHDE-AD1 in the GSE98793 was consistent with the RNA sequencing result. The protein expression results of TUBB3, MCM2, MYOC, FN1, S100A7, and TFF1 were consistent with the mRNA expression result COL10A1, LEP, PLIN1, PGM5-AS1, and TRHDE-AD1 were capable of discriminating luminal A breast cancer and normal controls. Four lncRNA-nearby and coexpressed mRNA pairs of HOXC-AS3-HOXC10, AC020907.2-FXYD1, AC026461.1-MT1X, and AC132217.1-IGF2 were identified. AMPK (involved LIPE and LEP) and PPAR (involved PLIN1) were two significantly enriched pathways in luminal A breast cancer.

Conclusion. This study could be helpful in unraveling the pathogenesis and providing novel therapeutic strategies for luminal A breast cancer.

1. Introduction

Breast cancer is the cancer with the highest impact among women [1]. Breast cancer is recognized as a malignancy with high heterogeneity. Despite better advancement in prognosis and treatment, breast cancer remains associated with major morbidity and mortality. Breast cancer can be divided into 5 “intrinsic” subtypes, including luminal A, luminal B, HER2-enriched, basal-like, and normal-like [2–6]. However, a few studies have focused on identifying diagnostic biomarkers for patients within a subtype. Therefore, identifying reliable diagnostic markers for breast cancer that distinguish between the subtypes is needed.

RNA sequencing has been increasingly used in clinical studies to define changes in gene expression [7]. In fact, the gene expression profile of RNA sequencing is often used to integrate multiple molecular events and mechanisms associated with cancer progression [8]. Long noncoding RNAs (lncRNAs), defined as transcripts greater than 200 nucleotides and nonencoding proteins, are emerging as essential regulators of mRNA expression, including transcription regulation by affecting DNA methylation or transcription...
factor activity [9, 10]. In addition, lncRNAs can serve as ceRNAs and participate in the regulation of encoding miRNAs [11, 12]. Accumulating number of reports have indicated that lncRNAs are associated with the majority of biological processes and diseases, including breast cancer [13]. For example, the downregulated level of NKILA is associated with breast cancer metastasis [14]. DSCAM-AS1 is an underlying treatment target that may prolong survival of luminal breast cancer patients [13]. However, research on lncRNA diagnostic biomarkers in luminal A breast cancer is rare.

In view of this, we performed RNA sequencing to identify DEmRNAs and DElncRNAs in luminal A breast cancer. The protein-protein interaction (PPI), DElncRNA-DEmRNA coexpression, DElncRNA-nearby DEmRNA interaction networks, and functional annotation were performed to uncover the function of DEmRNAs. We also performed the validation experiment and receiver operating characteristic (ROC) curve analysis. Our study identified potential key DEmRNAs and DElncRNAs in luminal A breast cancer and may provide a novel field in understanding the pathological mechanism of the disease.

2. Materials and Methods

2.1. Patients. Four patients with luminal A breast cancer were included in our study. Tumor samples and 4 paired adjacent normal tissue samples were selected from 4 patients with luminal A breast cancer. Clinical characteristics of patients are shown in Table 1. All the participants submitted the signed informed consent. The protocol was approved by the Medical Ethics Committee of Deyang People’s Hospital (2017-041).

2.2. RNA Sequencing. Total RNA was isolated from samples using the TRIzol reagent. The RNA quality was checked using a NanoDrop ND-2000 spectrophotometer. RNA integrity was detected using agarose gel electrophoresis. Total RNA was further purified using the Ribo-Zero Magnetic kit. The Illumina HiSeq X Ten platform was used to conduct sequencing of lncRNA and mRNA. lncRNA and mRNA levels were evaluated as the sum of fragments per kilobase of the exon model per million reads mapped (FPKM). Expression levels of lncRNA and mRNA were compared using edgeR. mRNAs and lncRNAs with a p value <0.05 and |log2 fold change (FC)| >1 were, respectively, considered significant DEmRNAs and DElncRNAs. The heatmap of DEmRNAs and DElncRNAs in the luminal A breast cancer was obtained by using the heatmap package in R language. In the clustering method, clustering_method parameter was set to “complete.” The method for calculating the class-clustering distance was “Euclidean.”

2.3. Functional Enrichment. David 6.8 was used to perform the Gene Ontology (GO) classification and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. p value <0.05 was considered to indicate statistically significant differences.

| Case   | Age (years) | Gender | TNM stage | ER | PR | HER-2 | KI-67 (%) |
|--------|-------------|--------|-----------|----|----|-------|-----------|
| 1      | 54          | Female | T2N0M0    | A  | A  | Positive | 5         |
| 2      | 64          | Female | T1N1M0    | Positive | A  | Positive | 10        |
| 3      | 69          | Female | T1N0M0    | Positive | Positive | Negative | 10        |
| 4      | 48          | Female | T2N0M0    | Positive | Positive | Negative | 10        |

Table 1: Patient characteristics.

2.4. PPI Network. Top 50 upregulated or downregulated DEmRNAs in the luminal A breast cancer were used to perform the PPI network by using BioGRID and Cytoscape 3.5.1. Node and edge was used to respectively represent the protein and interaction between two proteins.

2.5. DEmRNA-DElncRNA Interaction Network. To identify nearby DEmRNAs of DElncRNAs with cis-regulatory effects, DEmRNAs (transcribed within a 100 kb window up-or down-stream of DElncRNAs) were searched. The DEmRNAs coexpressed with DElncRNAs were also identified. The pairwise Pearson correlation coefficients between DEmRNAs and DElncRNAs were calculated. p value <0.01 and the Pearson correlation coefficient |r| <0.96 were considered as significant mRNA-lncRNA coexpression pairs. The DEmRNA-DElncRNA interaction network feature was presented by Cytoscape 3.5.1.

2.6. Expression Validation of Identified DEmRNAs and DElncRNAs. First, the mRNA expression level of selected DEmRNAs and DElncRNAs was validated in the published Gene Expression Omnibus (GEO) dataset (GSE65194), which was published on Jan 23, 2015, and examined tissue samples consisting of 29 patients with luminal A breast cancer and 11 normal controls. Second, an online immunohistochemical study of selected DEmRNAs was conducted using “The Human Protein Atlas” database.

2.7. Diagnostic Analysis. To evaluate the diagnostic value of DEmRNAs and DElncRNAs in luminal A breast cancer, the “pROC” package was used to generate ROC. When the area under the ROC curve (AUC) value was greater than 0.8, the DEmRNAs/DElncRNAs were able to distinguish between case and normal controls with good specificity and sensitivity.

3. Results

3.1. DEmRNAs and DElncRNAs. Based on the RNA-seq data, we found 1451 DEmRNAs and 272 DElncRNAs in the luminal A breast cancer. Among which, 651 mRNAs and 151 lncRNAs were upregulated and 800 mRNAs and 121 lncRNAs were downregulated. Top 20 mRNAs and lncRNAs
are, respectively, listed in Tables 2 and 3. A heatmap of the top 100 mRNAs and all lncRNAs between the luminal A breast cancer and normal tissue is, respectively, shown in Figures 1(a) and 1(b). Circos plots represent the distribution of DElncRNAs and DEMRNAs on chromosomes (Figure 1(c)).

### 3.2. Functional Enrichment

GO enrichment analysis showed that these DEMRNAs were significantly enriched in the nucleosome assembly ($p$ value $= 1.39E-15$), chromatin silencing at rDNA ($p$ value $= 3.27E-10$), nucleosome ($p$ value $= 1.84E-29$), proteinaceous extracellular matrix ($p$ value $= 2.50E-17$), protein heterodimerization activity ($p$ value $= 4.29E-15$), and heparin binding ($p$ value $= 5.95E-08$). Top 15 GO terms of DEMRNAs in luminal A breast cancer are shown in Figures 2(a)–2(c). KEGG pathway enrichment analysis showed that cell cycle ($p$ value $= 5.85E-08$), viral carcinogenesis ($p$ value $= 6.93E-06$), ECM-receptor interaction ($p$ value $= 5.00E-05$), PI3K-Akt signaling pathway ($p$ value $= 0.001557342$), and pathways in cancer
(p value = 0.011811389) were five significantly enriched pathways in luminal A breast cancer. Top 15 significantly enriched KEGG pathways of DEmRNAs in luminal A breast cancer are shown in Figure 2(d).

3.3. PPI Network. The PPI network consisted of 150 nodes and 136 edges (Figure 3). TUBB3 (upregulation, degree = 13), HIST2H3C (upregulation, degree = 11), MCM2 (upregulation, degree = 10), MYOC (downregulation, degree = 7), NEK2 (upregulation, degree = 6), LIPE (downregulation, degree = 5), FN1 (upregulation, degree = 5), FOXJ1 (upregulation, degree = 5), S100A7 (upregulation, degree = 5), and DLK1 (upregulation, degree = 5) were considered as the hub proteins.

3.4. DElncRNA-Nearby DEmRNA Interaction Network. In total, 37 DElncRNAs-nearby target DEmRNA pairs were identified which consisted of 34 DElncRNAs and 37 DEmRNAs (Figure 4). IncRNAs and nearby mRNAs in the DElncRNA-nearby DEmRNA pairs are displayed in Table 4.
Figure 2: Top 15 significantly enriched GO terms and KEGG pathways in luminal A breast cancer. (a) Biological process, (b) cellular component, (c) molecular function, and (d) KEGG pathways.
Figure 3: Luminal A breast cancer-specific PPI network. Ellipse and line are used to represent the node and edge, respectively. Red and green represent upward and downward adjustments, respectively. The black border indicates the top 10 upregulated and downregulated proteins.

Figure 4: DElncRNA-nearby DEmRNA interaction network in luminal A breast cancer. Ellipse and rhombus represent DEmRNA and DElncRNA, respectively. Red and green colors represent upregulation and downregulation, respectively. The black border indicates the top 10 upregulated and downregulated IncRNAs.
3.5. DElncRNA-DEmRNA Coexpression Network. In total, 1678 DElncRNA-DEmRNA coexpression pairs including 105 DElncRNAs and 786 DEmRNAs were identified. Among which, 1131 lncRNA-mRNA pairs were positively coexpressed (Supplementary Tables 1) and 547 lncRNA-mRNA pairs were negatively coexpressed (Supplementary Table 2). The positively coexpressed DElncRNA-DEmRNA network is shown in Figure 5. Some hub lncRNAs were identified, including AP001528.2 (downregulation, degree = 80), LINC00968 (downregulation, degree = 71), LINCO2202 (downregulation, degree = 65), TRHDE-AS1 (downregulation, degree = 56), and LINCO1140 (downregulation, degree = 54). The negatively coexpressed DElncRNA-DEmRNA network is shown in Figure 6. Besides being based on the relevant literature, some lncRNAs were identified according to the degree, including AL354707.1 (upregulation, degree = 54), AC097534.1 (downregulation, degree = 33), MIR222HG (downregulation, degree = 28), and AL662844.4 (downregulation, degree = 27). It is noted that a total of 4 lncRNA-mRNA pairs were identified between the DElncRNA-nearby DEmRNA interaction network and the DElncRNA-DEmRNA coexpression network, including HOXC-AS3-HOXC10, AC020907.2-FXYD1, AC026461.1-MT1X, and AC132217.1-IGF2.

3.6. Functional Enrichment of DEmRNAs Coexpressed with DElncRNAs. Nucleosome assembly \((p = 1.06E^{-07})\), G1/S transition of mitotic cell cycle \((p = 1.08E^{-06})\), nucleosome \((p = 3.63E^{-15})\), protein heterodimerization activity \((p = 1.85E^{-09})\), and heparin binding \((p = 1.04E^{-05})\) were most significantly enriched GO terms. Top 15 GO terms in luminal A breast cancer are shown in Figures 7(a)–7(c). In addition, we found that AMPK (involved LIPE and LEP) \((p = 0.00340464)\) and PPAR (involved PLIN1) \((p = 0.01873201)\) were two significantly enriched pathways in luminal A breast cancer. Top 15 most significantly enriched pathways are shown in Tables 4.
3.7. Expression Validation of Selected DEmRNAs and DElncRNAs. The mRNA expression patterns of four DEmRNAs (upregulated TFF1 and COL10A1 and downregulated LEP and PLIN1) and two downregulated IncRNAs (PGM5-AS1 and TRHDE-AD1) were verified in the GSE65194 dataset. As shown in Figure 8, mRNA expression of TFF1 and COL10A1 was increased and LEP, PLIN1, PGM5-AS1, and TRHDE-AD1 were decreased, which was consistent with our RNA sequencing result. In addition, an online immunohistochemical study of selected DEmRNAs (TUBB3, MCM2, MYOC, FN1, S100A7, and TFF1) was conducted using The Human Protein Atlas database (Figure 9). The result showed that the protein expression of TUBB3, MCM2, FN1, S100A7, and TFF1 was increased, and the protein expression of MYOC was downregulated in luminal A breast cancer, which was consistent with the result of RNA expression.

3.8. ROC Curve Analyses. By using GSE65194, we performed ROC curve analysis to access the diagnostic value of four DEmRNAs (TFF1, COL10A1, LEP, and PLIN1) and two DElncRNAs (PGM5-AS1 and TRHDE-AD1) in luminal A breast cancer. The results indicated that except for TFF1 (AUC = 0.774), COL10A1 (AUC = 1.000), LEP (AUC = 0.984), PLIN1 (AUC = 0.966), PGM5-AS1 (AUC = 0.969), and TRHDE-AD1 (AUC = 1.000) were capable of discriminating luminal A breast cancer and normal controls (Figure 10).

4. Discussion

Although some evidence has demonstrated aberrant expression of IncRNA in breast cancer [15], a few studies have systematically examined the function of IncRNA in luminal A breast cancer. In this study, 1451 DElncRNAs and 272 DEmRNAs were identified in luminal A breast cancer. Then, we constructed a luminal A breast cancer-specific PPI, DElncRNA-DEmRNA coexpression, and DElncRNA-nearby DEmRNA interaction networks. In addition, functional analysis of DEmRNAs was performed. We also performed the validation experiment and ROC curve analysis.

COL10A1, a collagen-type X alpha 1 chain, is elevated in multiple cancers including the lung, stomach, breast, colon, pancreas, and bladder [16]. Herein, COL10A1 was also upregulated in our RNA sequencing and GSE65194 dataset. In addition, we identified COL10A1 as potential diagnostic biomarkers of luminal A breast cancer. CLEC3A, a C-type lectin domain family 3 member A, has been reported in human breast cancer [17]. It is reported that CLEC3A expression is markedly higher in breast invasive ductal cancer tissues, and elevated CLEC3A expression may be correlated with breast invasive ductal cancer metastatic potential [18]. In this study, CLEC3A, as top 10 DEmRNAs, was also upregulated in our RNA sequencing. Our results are further
Figure 6: Negatively coexpressed DElncRNA-DEmRNA network. Ellipse and rhombus represent DEmRNA and DElncRNA, respectively. Red and green colors represent upregulation and downregulation, respectively. The black border indicates the top 10 upregulated and downregulated DElncRNAs and DEmRNAs.

Figure 7: Continued.
supported by the fact that CLEC3A is a promising treatment target for breast cancer.

TFF1, trefoil factor 1, is cloned from the breast cancer cell line MCF-7. Smid et al. reported that TFF1 could play an important role in tumor metastasis by binding to cysteine-rich enteroprotein 1 in metastatic breast cancer [19]. Markičević et al. revealed that TFF1 expression levels were significantly higher in breast tissue samples in premenopausal patients [20]. Ishibashi et al. reported that serum TFF1 was significantly higher in women with breast cancer [21]. Elnagdy et al. reported TFF expression levels were markedly higher in blood in breast cancer patients with metastatic disease [22]. In our study, TFF1, as top 10 DEmRNA, was also upregulated in our RNA sequencing results, GSE65194 dataset, and The Human Protein Atlas database. We speculated that serum TFF1 could be a diagnostic biomarker of breast cancer.

DSCAM-AS1, down syndrome cell adhesion molecule antisense lncRNA, is a member of the immunoglobulin superfamily of cell adhesion molecules [23]. Previous studies have indicated that DSCAM-AS1 is involved in the progression of cancer cells [24, 25]. Yashar et al. reported that DSCAM-AS1 could interact with hnRNPL to mediate tumor progression [24]. DSCAM-AS1 enhances non-small cell lung cancer cell migration by elevating BCL11A, and DSCAM-AS1 may be a potential therapeutic target for non-small cell lung cancer [26]. Overexpression of DSCAM-AS1 promotes the cell proliferation of the luminal breast cancer cell line [25]. DSCAM-AS1 is upregulation in invasive ductal carcinoma of the breast and has potential as the diagnostic biomarker [27]. It is suggested that DSCAM-AS1 can be acted as a competing endogenous RNA of miR-137 and regulate EPS8 to accelerate cell reproduction in tamoxifen-resistant breast cancer [28]. Of note, DSCAM-AS1 promotes

Figure 7: Top 15 significantly enriched GO terms and KEGG pathways of DEmRNAs coexpressed with DElncRNAs in luminal A breast cancer. (a) Biological process, (b) cellular component, (c) molecular function, and (d) KEGG pathways.
cell growth and impairs apoptosis of breast cancer cells via reducing miR-204-5p and enhancing RRM2 expression [29]. In the present study, DSCAM-AS1 was top 10 DElncRNA and was upregulated in our RNA sequencing results. However, the mechanism of DSCAM-AS1 in luminal A breast cancer progression largely remains unknown. Further study of DSCAM-AS1-regulated networks is needed.

GPD1, glycerol-3-phosphate dehydrogenase 1, is considered a key element that connects carbohydrate and lipid metabolism. Its expression level is significantly downregulated in human breast cancer patients, and overexpression of GPD1 markedly suppresses cell proliferation, migration, and invasion of breast cancer cells [30]. PLIN1, perilipin-1, has been considered as a candidate gene that contributes to the polygenic disease phenotype of human obesity [31]. PLIN1 is markedly declined in human breast cancer, and overexpression of PLIN1 in human breast cancer cells dramatically suppresses cell proliferation, invasion, and in vivo tumorigenesis [32]. In our study, PLIN1 was downregulated in our RNA sequencing and GSE65194

![Figure 8: Expression validation of selected DEGs in GSE65194.](image)

![Figure 9: Protein expression validation of selected DEGs in The Human Protein Atlas database.](image)
dataset and was capable of discriminating luminal A breast cancer and normal controls. Based on the DElncRNA-DEmRNA interaction network, GPD1 and PLIN1 were coexpressed with AC245452.1. Therefore, the study suggested that AC245452.1 may be involved in the occurrence of luminal A breast cancer by regulating the GPD1 and PLIN1. Interestingly, a total of 4 lncRNA-mRNA pairs were identified between the DElncRNA-nearby DEmRNA interaction network and the DElncRNA-DEmRNA coexpression network, including HOXC-AS3-HOXC10, AC020907.2-FXYD1, AC026461.1-MT1X, and AC132217.1-IGF2. The significantly upregulated expression level of HOXC-AS3 is found in tissues of breast cancer, and the expression of HOXC-AS3 is well associated with the prognosis of breast cancer [33]. AC020907.2 is positively related to overall survival in glioma [34]. Correlation analysis between AC026461.1 and has-miR-330-5p has been found in ovarian cancer [35]. HOXC10 is implicated in luminal breast cancer [36]. It is found that FXYD1 is downregulated in breast tumors [37]. MT1X is upregulated in young breast cancer patients [38]. High IGF2 gene expression in cancer-associated fibroblasts from luminal breast carcinomas is significantly related to a shortened relapse-free survival [39]. This suggested that HOXC10, FXYD1, MT1X, and IGF2 may play an important role in the development of luminal A breast cancer under the regulation of HOXC-AS3, AC020907.2, AC026461.1, and AC132217.1.

In addition, based on functional enrichment of DEmRNAs coexpressed with DElncRNAs, we found that AMPK (involved LIPE and LEP) and PPAR (involved PLIN1) were two significantly enriched pathways in luminal A breast cancer. It is found that targeting AMPK regulatory processes at points can provide additional approaches to prevent breast cancer neoplasia, growth, and metastasis [40]. Apostoli et al. found that the downregulation of PPARγ expression led to a probreast tumorigenic environment [41].

5. Conclusions

We identified 1451 DEmRNAs and 272 DElncRNAs in luminal A breast cancer. The expression validation of TFF1, COL10A1, and LEP and PLIN1, PGM5.AS1, and TRHDE-AD1 in the GSE98793 dataset was consistent with the RNA sequencing result. COL10A1, LEP, PLIN1, PGM5-AS1, and TRHDE-AD1 were capable of discriminating luminal A breast cancer and normal controls. In addition, lncRNA-mRNA pairs of HOXC-AS3-HOXC10, AC020907.2-FXYD1, AC026461.1-MT1X, and AC132217.1-IGF2 may be involved in the process of luminal A breast cancer. Our results may be helpful in improving the understanding of the mechanisms associated with the pathogenesis and progression of luminal A breast cancer. However, there are a few limitations in our study. First, the sample size in the RNA sequencing was small and a larger number of luminal A breast cancer samples are further needed. Second, biological functions of identified DEmRNAs and DElncRNAs in luminal A breast cancer were not studied. Therefore, some experiments are needed to investigate the biological function of these molecules in luminal A breast cancer in future work.

Data Availability

All data are available in the article.
Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Supplementary Materials

Supplementary Table 1. Positively coexpressed IncRNA-mRNA network. Supplementary Table 2. Negatively coexpressed IncRNA-mRNA network. (Supplementary Materials)

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