Identification of differentially expressed lncRNAs and mRNAs in luminal-B breast cancer by RNA-sequencing

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Abstract

**Background:** Luminal B cancers show much worse outcomes compared to luminal A. This present study aims to screen key lncRNAs and mRNAs correlated with luminal-B breast cancer.

**Methods:** Luminal-B breast cancer tissue samples and adjacent tissue samples were obtained from 4 patients with luminal-B breast cancer. To obtain differentially expressed mRNAs (DEmRNAs) and lncRNAs (DElncRNAs) between luminal-B breast cancer tumor tissues and adjacent tissues, RNA-sequencing and bioinformatics analysis were performed. Functional annotation of DEmRNAs and protein-protein interaction networks (PPI) construction were performed. DEmRNAs transcribed within a 100 kb window up- or down-stream of DElncRNAs were searched, which were defined as cis nearby-targeted DEmRNAs of DElncRNAs. DElncRNA-DEmRNA co-expression networks were performed. The mRNA and IncRNA expression profiles were downloaded from The Cancer Genome Atlas (TCGA) database to validate the expression patterns of selected DEmRNAs and DElncRNAs.

**Results:** A total of 1178 DEmRNAs and 273 DElncRNAs between luminal-B breast cancer tumor tissues and adjacent tissues were obtained. Hematopoietic cell lineage, Cytokine-cytokine receptor interaction, Cell adhesion molecules (CAMs) and Primary immunodeficiency were significantly enriched KEGG pathways in luminal-B breast cancer. FN1, EGFR, JAK3, TUBB3 and PTPRC were five hub proteins of the PPI networks. A total of 99 DElncRNAs-nearby-targeted DEmRNA pairs and 1878 DElncRNA-DEmRNA co-expression pairs were obtained. Gene expression results validated in TCGA database were consistent with our RNA-sequencing results, generally.

**Conclusion:** This study determined key genes and lncRNAs involved in luminal-B breast cancer, which expected to present a new avenue for the diagnosis and treatment of luminal-B breast cancer.

**Keywords:** Luminal-B breast cancer, mRNA, Long non-coding RNA (lncRNA), RNA-sequencing

Background

Breast cancer is the leading cause of cancer-related death in women, both overall and in less developed countries (1). It is a heterogeneous disease with regard to molecular alterations, cellular composition, and clinical outcome, both between tumor subtypes and within a single tumor, which were commonly defined by gene expression profiling as four main subtypes including luminal A, luminal B, HER-2 enriched and basal-like, (2–4). Luminal B breast cancer is unique with regard to somatic point mutations, the profile of gene copy number alterations (CNAs), and DNA methylation (5). Expression profiles and gene sets, with prognostic, predictive functions, or both for patients with breast cancer, have been identified in multiple studies (6). Although both luminal-A and luminal-B breast cancers are ER-positive, luminal-B cancers showed worse outcomes as compared to luminal-A cancers (7, 8). Therefore, it is urgent to discover novel biomarkers with prognostic and predictive functions for luminal B breast cancer that can be therapeutically targeted.
With advances in high-throughput technology, it is discovered that human transcriptome mainly consists of non-coding RNAs (ncRNAs) with limited or no protein-coding capacity (9, 10). Long non-coding RNAs (lncRNAs), with over 200 nucleotides base long, attracts more attention and has been widely linked with various diseases, including cancers (11–14). The lncRNAs exert momentous roles in multiple cellular processes at transcriptional and post-transcriptional regulation level through transcriptional interference and histone modifications (15, 16). The higher expression of SPRY4-IT1 was reported to modulate apoptosis and invasion in melanoma (17). LncRNA UCA1a (CUDR) may promote proliferation and tumorigenesis in human bladder cancer (18).

In this study, differentially expressed lncRNAs (DElncRNA) and mRNAs (DEmRNAs) in tumor tissues of patients with luminal-B breast cancer were identified by RNA-sequencing. Subsequently, protein-protein interaction (PPI) networks of DEmRNAs were conducted. Identification of cis nearby-targeted DEmRNAs of DElncRNAs and construction of DElncRNA-DEmRNA co-expression networks were performed. In this light, we expect this study could represent a new avenue to improve the understanding of the pathogenesis and be helpful for treatment of luminal B breast cancer.

### Methods

**Patients and samples**

Luminal-B breast cancer tissue samples and adjacent tissue samples were obtained from 4 patients with luminal-B breast cancer in People’s Hospital of Deyang City, which were free of treatment. The detailed characteristics of patients are displayed in Table 1. Written informed consent about the use of these samples was obtained from each patient. All procedures performed in this study was in accordance with the ethical standards of the ethics committee of People’s Hospital of Deyang City (2017–045) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

#### RNA isolation and sequencing

According to the manufacturer’s protocol, RNA was extracted with PAXgene blood RNA kit (PreAnalytiX...
Identification of DEmRNAs and DElncRNAs
In order to align the clean reads with the human reference genome, Ensemble GRCh38.p7 (ftp://ftp.ncbi.nlm.nih.gov/genomes/Homo_sapiens), HISAT2 version 2.1.0 (https://ccb.jhu.edu/software/hisat2/index.shtml) was applied. Expression of mRNAs and lncRNAs was normalized and outputted with StringTie version 1.3.3b (http://ccb.jhu.edu/software/stringtie/). Fragments per Kilobase of exon per million fragments mapped (FPKM) of lncRNAs and mRNAs were calculated with StringTie. With edgeR version 3.24 (http://www.bioconductor.org/packages/release/html/edgeR.html), both DEmRNAs and DElncRNAs were obtained with |log2FC| > 1 and p-value < 0.05. By using R package “pheatmap”, hierarchical clustering analysis of DElncRNAs and DEmRNAs were conducted.

Functional annotation of DEmRNAs
Functional annotation, including Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses was performed with Metascape (http://metascape.org/gp/index.html). A value of p < 0.05 was set as the cut-off for significance.

Protein-protein interaction (PPI) networks construction
Top 100 up- and down-regulated DEmRNAs were scanned with the BioGrid (http://www.uniprot.org/database/DB-0184). Then, PPI networks were visualized with Cytoscape software (version 3.5.0, http://www.cytoscape.org).

Cis nearby-targeted DEmRNAs of the DElncRNAs
DEmRNAs transcribed within a 100-kb window upstream or downstream of DElncRNAs were searched, which were defined as cis nearby-targeted DEmRNAs of DElncRNAs, to obtain the targeted DEmRNAs of DElncRNAs with cis-regulatory effects. The networks were visualized by Cytoscape software. Functional annotation of the cis nearby-targeted DEmRNAs of the DElncRNAs was performed with Metascape. A value of p < 0.05 was set as the cut-off for significance.

DElncRNA-DEmRNA co-expression networks
To further examine the potential roles of DElncRNAs and DEmRNAs in luminal-B breast cancer, the DElncRNA-DEmRNA co-expression networks were constructed. DElncRNA-DEmRNA pairs with an absolute value of PCC > 0.95 and p < 0.01 were defined as co-expressed DElncRNA-DEmRNA pairs. By using Cytoscape, the co-expressed DElncRNA-DEmRNA networks were visualized. Functional annotation of the DEmRNAs co-expressed with DElncRNAs was performed with Metascape. A value of p < 0.05 was set as the cut-off for significance.

Validation in the Cancer genome atlas (TCGA) database
The mRNA and lncRNA expression profiles of 171 patients with luminal B breast cancer and 59 normal tissues were downloaded from TCGA database to validate the expression patterns of selected DEmRNAs and DElncRNAs.

### Table 3 Top 10 up- and down-regulated DElncRNAs between luminal-B breast cancer tumor tissues compared with adjacent tissues

| ID            | Symbol | log. FC | p-value | Regulation |
|--------------|--------|---------|---------|------------|
| ENSG00000235123 | DSCAM-AS1 | 6.99539501 | 2.71E-06 | up         |
| ENSG00000273445 | AC1336442 | 7.01588171 | 3.65E-06 | up         |
| ENSG00000261039 | LIN02544 | 7.125889953 | 1.29E-05 | up         |
| ENSG00000225783 | MIAT | 2.369853869 | 3.75E-05 | up         |
| ENSG00000229490 | AL3900661 | 2.33212245 | 7.65E-05 | up         |
| ENSG00000270120 | AC0077283 | 5.314205083 | 8.62E-05 | up         |
| ENSG00000279930 | AL0328192 | 5.526214467 | 2.85E-03 | down       |
| ENSG00000247774 | PCED1B-AS1 | 1.82134551 | 1.78E-04 | up         |
| ENSG00000261218 | AC0995241 | 4.377268771 | 2.60E-04 | up         |
| ENSG00000234261 | AL1387201 | 4.488627977 | 2.87E-04 | up         |
| ENSG00000253434 | LINC02237 | -6.553462635 | 1.53E-04 | down       |
| ENSG00000250961 | AC0254702 | -5.149166872 | 1.76E-04 | down       |
| ENSG00000236333 | TRHDE-AS1 | -8.62423419 | 4.38E-04 | down       |
| ENSG00000261441 | AC1204682 | -4.394333958 | 7.43E-04 | down       |
| ENSG00000261888 | AC1448311 | -3.00198307 | 1.98E-03 | down       |
| ENSG00000251600 | AC0073636 | -2.997221226 | 2.05E-03 | down       |
| ENSG00000260947 | AL3564892 | -3.611436753 | 2.33E-03 | down       |
| ENSG00000235033 | AL5909991 | -2.980398474 | 2.69E-03 | down       |
| ENSG00000230333 | AC0041601 | -3.679435378 | 2.71E-03 | down       |
| ENSG00000272701 | MESTITT | -3.52881654 | 2.85E-03 | down       |

DElncRNAs, differentially expressed IncRNAs. FC, fold change.
Results
DEmRNAs and DElncRNAs between luminal-B breast cancer tumor tissues and adjacent tissues
A total of 1178 DEmRNAs (666 up-regulated and 512 down-regulated DEmRNAs) and 273 DElncRNAs (181 up-regulated and 92 down-regulated DElncRNAs) were obtained. The top 10 up- and down-regulated DEmRNAs and DElncRNAs were exhibited in Table 2 and Table 3, respectively. Hierarchical clustering analysis of top 100 10 up- and down-regulated DEmRNAs and DElncRNAs was showed in Fig. 1a and Fig. 1b, respectively. Furthermore, the distribution of DElncRNAs and
DEmRNAs on all chromosomes was showed in Fig. 1c. The raw-data have been uploaded to Gene Expression Omnibus (GEO) (GSE139274, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE139274).

**Functional annotation**

Lymphocyte activation ($p = 1.14E-50$), cytokine-mediated signaling pathway ($p = 5.74E-44$) and cytokine production ($p = 8.78E-38$) were significantly enriched GO terms in luminal-B breast cancer (Fig. 2a). Hematopoietic cell lineage ($p = 7.75E-21$), Cytokine-cytokine receptor interaction ($p = 8.19E-21$), Cell adhesion molecules (CAMs) ($p = 3.61E-18$) and Primary immunodeficiency ($p = 1.17E-14$) were significantly enriched KEGG pathways in luminal-B breast cancer (Fig. 2b).

**Protein-protein interaction (PPI) networks**

The PPI networks included 281 nodes and 263 edges. FN1 (degree = 28), EGFR (degree = 14), JAK3 (degree = 11), TUBB3 (degree = 11) and PTPRC (degree = 10) were five hub proteins of the PPI networks (Fig. 3).

**Cis-nearby-targeted DEmRNAs of DElncRNAs**

A total of 99 DElncRNAs-nearby-targeted DEmRNA pairs, involving in 78 DElncRNAs and 86 DEmRNAs, were detected (Fig. 4). Top two DElncRNAs with most
nearby DEmRNAs were AL121985.1 and AL031316.1, which owned 5 and 4 nearby DEmRNAs, respectively. Regulation of cell adhesion \( (p = 1.84 \times 10^{-13}) \), regulation of cell-cell adhesion \( (p = 7.86 \times 10^{-12}) \), cytokine binding \( (p = 3.41 \times 10^{-07}) \), T cell selection \( (p = 7.75 \times 10^{-07}) \) and negative regulation of secretion \( (p = 1.38 \times 10^{-06}) \) were significantly enriched GO terms (Fig. 6a). Cell adhesion molecules (CAMs) \( (p = 1.72 \times 10^{-04}) \), Cytokine-cytokine receptor interaction \( (p = 2.81 \times 10^{-03}) \), Primary immunodeficiency \( (p = 7.71 \times 10^{-03}) \), AMPK signaling pathway \( (p = 9.30 \times 10^{-03}) \) and Wnt signaling pathway \( (p = 1.46 \times 10^{-02}) \) were significantly enriched KEGG pathways (Fig. 6b).

**DElncRNA-DEmRNA co-expression networks**

A total of 1878 DElncRNA-DEmRNA co-expression pairs including 225 DElncRNAs and 737 DEmRNAs were obtained with an absolute value of PCC > 0.95 and \( p < 0.01 \) (Fig. 5).

Lymphocyte activation \( (p = 7.08 \times 10^{-50}) \), cytokine-mediated signaling pathway \( (p = 9.35 \times 10^{-28}) \), cytokine production \( (p = 1.68 \times 10^{-27}) \), leukocyte migration \( (p = 3.20 \times 10^{-22}) \) and alpha-beta T cell activation \( (p = 4.89 \times 10^{-20}) \) were significantly enriched GO terms (Fig. 6c). Cytokine-cytokine receptor interaction \( (p = 2.18 \times 10^{-18}) \), Hematopoietic cell lineage \( (p = 9.66 \times 10^{-16}) \), Primary immunodeficiency \( (p = 2.85 \times 10^{-15}) \), Th1 and Th2 cell differentiation \( (p = 3.38 \times 10^{-13}) \) and Cell adhesion molecules (CAMs) \( (p = 1.66 \times 10^{-12}) \) were significantly enriched KEGG pathways (Fig. 6d).

**Validation in TCGA database**

With mRNA and lncRNA expression profiles downloaded from TCGA database, the expression patterns of four DEmRNAs, including S100A7, CCL5, MIAT and WT1-AS, were verified. As shown in Fig. 7, compared to normal controls, MIAT was down-regulated in luminal B breast cancer tumor tissues which were inconsistent with our results, while S100A7, CCL5 and WT1-AS were up-regulated in luminal B breast cancer tumor tissues which were consistent with our results.

**Discussion**

Breast cancer, as the most common non-cutaneous type of cancer, is the leading cause of cancer-related mortality among female globally (19). As luminal-B cancers showed poorer prognosis as compared to luminal-A cancers, we performed this study and identified abundant
DElncRNAs and DEmRNAs between luminal-B breast cancer tumor tissues and adjacent tissues.

S100A7 is a member of the S100 protein family, which have been associated with preinvasive ductal carcinoma in situ (DCIS) (20). During breast tumorigenesis and/or progression, several S100 s, including S100A2, S100A4 and S100A7, exhibit altered expression levels based on molecular analysis of breast tumors (21). Cancemi et al. suggested that S100A7 was involved in critical phases of the breast cancer growth and progression (22). Mayama et al. proposed that S100A7 was linked to an aggressive phenotype of ER-positive breast carcinoma, and was potent marker for distant metastasis of ER-positive breast cancer patients (23). In current study, S100A7 was the most significant up-regulated DEmRNAs in luminal B breast cancer tumor tissues, which may indicated that S100A7 exert momentous roles in luminal B breast cancer.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a highly conserved lncRNA, and its over-expression in multiple cancerous tissues has been linked to the proliferation and metastasis of tumor cells. It was first identified as being up-regulated in lung tumors, and a prognostic marker for metastasis and patient survival in non-small cell lung cancer (NSCLC), specifically in early stages of lung adenocarcinoma (24). Subsequently, MALAT1 was shown to be up-regulated in a broad spectrum of tumor types, such as endometrial stromal sarcoma and hepatocellular carcinomas (25, 26). Additional, it has been found that MALAT1 gene mutations frequently occurred in luminal-type breast tumors (27). Besides, MALAT1 was one of the top 10 up-regulated DElncRNAs in this study, and co-expressed with S100A7, which emphasized the critical role the MALAT1 in luminal B breast cancer and suggested that MALAT1 may involve in luminal B breast cancer by regulating S100A7.

Chemokines, small-molecular-weight cytokines involved in the physiological control of immune cell migration, were reported to perform a crucial function in breast cancer tumorigenesis and progression (19). Recent years, the chemokine C-C motif ligand 5 (CCL5), also known as RANTES, is a member of the CC subfamily, has been associated with aggressive breast cancer (28). Svensson et al. identified CCL2 and CCL5 as two therapeutic targets for estrogen-dependent breast cancer.
Previous study suggested that endothelial cells (ECs) enhance endothelial-mesenchymal transition (EMT)-induced triple-negative breast cancer (TNBC) cell metastasis through PAI-1 and CCL5 signaling (30). Zhang et al. found that CCL5-mediated Th2 polarization of CD4+ T cells promotes metastasis in luminal breast cancer (31). In our analysis, CCL5 was significant up-regulated in luminal B breast cancer tumor tissues, cancer (29).
which indicated the key role of CCL5 in luminal B breast cancer.

LncRNA myocardial infarction-associated transcript (MIAT) is primarily expressed in heart and fetal brain tissue (32). Dysregulated MIAT was first reported to correlated with myocardial infarction and involved in cardiac hypertrophy and diabetic cardiomyopathy (32–35). Recent studies suggested that MIAT promoted gastric cancer growth and metastasis by regulation of miR-141/DDX5 pathway, promoted proliferation and

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**Fig. 6** Significantly enriched GO terms and KEGG pathways of DElncRNA-nearby DEmRNAs (a–b) and DEmRNAs co-expressed with DElncRNAs (c–d). The x-axis represented -lg p-value and the y-axis shows GO terms or KEGG pathways.

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**Fig. 7** Validation in TCGA database. The x-axis shows luminal-B breast cancer tumor tissues and adjacent tissues, and the y-axis shows expression levels, respectively. A) S100A7; B) CCL5; C) MIAT; D) WT1-AS.
metastasis of non-small cell lung cancer via MMP9 activation, promoted hepatocellular carcinoma cells proliferation and invasion through sponging miR-214 (36–38). Luan et al. proposed that overexpression of MIAT was related to the TNM stage and lymphnode metastasis of breast cancer (39). MIAT was found to be overexpressed in both ER-positive breast cancer tissues and ER-positive breast cancer cell line MCF-7, and play a pivotal role in ER-positive breast cancer cell growth (40). Almnaese-M et al. suggested that MIAT performs a critical function in breast tumorigenesis (41). MIAT was detected to be one of the top 10 up-regulated DElncRNAs, and co-expressed with CCL5. All these findings suggest that MIAT may involve in luminal B breast cancer by regulating the expression level of CCL5.

The Wilms tumor 1 (WT1) was first cloned in 1990 as a suppressor in Wilms’ tumor, which was located at chromosome 11p13 (42). WT1 gene mutations are linked with a subset of Wilms’s tumors, the most common pediatric renal cancer (43). Substantial evidence has linked WT1 with the pathogenesis of breast cancer. WT1 is linked to the progression of breast cancer, including migration, invasion and angiogenesis. Knockdown of WT1 was demonstrated to lead to mitochondrial damage and then inhibit malignant cell growth (44). Highly expressed WT1 was linked to poor prognosis of patients with breast cancer (45). Over expression of WT1 was detected in TNBC (46). In agreement with previous studies, the expression of WT1 was observed significant up-regulated in luminal B breast cancer tumor tissues in present study.

Wilms tumor 1 Antisense RNA (WT1-AS) is located upstream of the WT1 gene, and these two genes are bidirectionally transcribed from the same promoter region. Down-regulation of WT1-AS was related to a poorer prognosis in ovarian clear cell adenocarcinoma (47). Lv et al. suggested that WT1-AS promoted cell apoptosis in hepatocellular carcinoma (HCC) and may function as a tumor suppressor in HCC (48). It is reported that WT1-AS was significantly down-regulated in gastric cancers and may correlates with tumor progression (49). In addition, WT1-AS was detected to be under-expressed in cervical carcinoma and suppress cervical cancer cell growth and aggressiveness (50, 51). In the current study, we found that WT1-AS was a DElncRNA and WT1 was a nearby-targeted DEmRNA of WT1-AS, which reminded us to explore the role of WT1-AS-WT1 in luminal B breast cancer.

Conclusion
In conclusion, a total of 1178 DEmRNAs and 273 DElncRNAs between luminal-B breast cancer tumor tissues and adjacent tissues were obtained. We discussed and emphasized the importance role of three DElncRNA-DEmRNA pairs, including MALAT1-S100A7, MIAT-CCL5 and WT1-AS-WT1, involved in luminal B breast cancer, which expected to provide new insight into understanding the mechanism underlying pathogenesis of luminal B breast cancer. The small sample size was a limitation of our study. Although the validation results in TCGA database indicated that our RNA-sequencing results were generally reliable, larger cohorts of patients and further experimental validation studies are needed to conduct to verify this conclusion.

Abbreviations
CAMs: Cell adhesion molecules; CCL5: Chemokine C-C motif ligand 5; CNAs: Copy number alterations; DCIS: Ductal carcinoma in situ; DElncRNA: Differentially expressed lncRNA; DEmRNA: Differentially expressed mRNA; ECs: Endothelial cells; EMT: Endothelial-mesenchymal transition; FPKM: Per million fragments mapped; GO: Gene Ontology; HCC: Hepatocellular carcinoma; KEGG: Kyoto Encyclopedia of Genes and Genomes; IncRNAs: Long non-coding RNAs; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; MIAT: Myocardial infarction-associated transcript; ncRNAs: Non-coding RNAs; NSCLC: Non-small cell lung cancer; PCC: Pearson’s correlation coefficient; PPI: Protein-protein interaction network; RIN: RNA integrity number; TNBC: Triple-negative breast cancer; WT1: Wilms’ tumor 1; WT1-AS: Wilms tumor 1 Antisense RNA

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Authors’ contributions
CY and NZ2 made substantial contributions to conception and design. CY, XJ and YY performed the experiment. JE, NZ1 and XL collected and analyzed the data. WW and YL interpreted the data. All authors were involved in drafting and revising the manuscript and gave final approval of the manuscript.

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Availability of data and materials
The raw-data have been uploaded to Gene Expression Omnibus (GEO) (GSE139274, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE139274 ) and is publicly available until October 2020 due to data confidentiality.

Ethics approval and consent to participate
Written informed consent about the use of these samples was obtained from each patient. This study was approved by the ethical committee of People’s Hospital of Deyang City (2017–045).

Consent for publication
Not applicable.

Competing interests
The authors declared that they have no competing interests.

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