



Construction of differentially expressed Her-2 related lncRNA-mRNA-miRNA ceRNA network in Her-2 positive breast cancer

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Background: Her-2 positive subtype breast cancer is characterized as Her-2 gene amplification with poor survival and increased invasiveness accounting for 20–30% of invasive infiltrated breast cancer. A lncRNA-miRNA-mRNA competing endogenous RNA (ceRNA) network is constructed to detect Her-2 specific RNAs in the development and progression of HER-2 positive breast cancer which may overcoming the anti-HER-2 therapy resistance of breast cancer cells.

Methods: One thousand one hundred and nine breast cancer samples obtained from The Cancer Genome Atlas (TCGA) database were classified into two cohorts including ER+/PR+ (n=461) and ER-/PR- breast cancer (n=152). Differently expressed mRNAs, lncRNAs and miRNAs were screened in ER+/PR+ and ER-/PR- breast cancer cohorts, respectively. lncRNA-miRNA interactions were preformed to predicted and verified by miRcode. miRNA-mRNA interactions were selected to predict targeted mRNAs of miRNAs by miRanda, Targetscan and miRTarBase.

Results: lncRNA-miRNA-mRNA ceRNA network was constructed by retained lncRNAs, miRNAs and mRNAs. Fifteen DEmiRNAs, 129 DELncRNAs and 269 DEmRNAs were retained in ER+/PR+ cohort after intersection with DEmiRNAs, DELncRNAs and DEmRNAs between breast cancer and normal tissues. Six hundred and ninety-three DEmRNAs, 25 DEmiRNAs and 364 DELncRNAs were retained in ER-/PR- cohort. ceRNA network in ER+/PR+ breast cancer cohort was constructed of the interactions of 4 DELncRNA-DEmiRNA pairs and 2 DEmiRNA-DEmRNA pairs included 4 DELncRNAs, 1 DEmiRNAs, and 2 DEmRNAs. ceRNA network in ER-/PR- breast cancer cohort was constructed of the interactions of 24 DELncRNA-DEmiRNA pairs and 1 DEmiRNA-DEmRNA pairs included 19 DELncRNAs, 4 DEmiRNAs, and 1 DEmRNA. MIR7-3HG- hsa-mir-204-NTRK2 axis was identified in both ER+/PR+ and ER-/PR- cohort in our study.

Conclusions: Based on the ceRNA hypothesis, a potential Her-2 related regulatory ceRNA networks are constructed which may provide novel insights into the mechanism underlying the biological processes of Her-2 positive breast cancer.

Keywords: Competing endogenous RNA; Her-2 positive breast cancer; long non-coding RNA; microRNA; triple negative breast cancer

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Introduction

Breast cancer as the most common malignant tumor is the primary cause of cancer-related death among women worldwide. Breast cancer is a multifaceted and heterogeneous disease with different molecular subtypes (1). Base on the 2013 St Gallen classification of intrinsic breast cancer subtypes, breast cancer is classified into luminal A, luminal B, Her-2 enrich and triple negative breast cancer, according to estrogen receptor (ER), progesterone receptor (PR) and Her-2 status (2). The epidermal growth factor receptor (Her/Neu) family are composed of Her-1, Her-2, Her-3, and HER-4 which involved in the regulation of proliferation, migration and differentiation (3,4). Her-2 enrich subtype breast cancer is characterized as Her-2 gene amplification with increased invasiveness and aggressiveness accounting for 20–30% of invasive infiltrate breast cancer (5,6). Despite systemic anti-Her-2 therapy including novel monoclonal antibodies (trastuzumab and pertuzumab), small molecule inhibitors (lapatinib), significantly improve the outcome of Her-2 positive breast cancer, treatment resistance and potential cardiotoxicity still remain unsolved issues (7-10).

MicroRNAs (miRNAs) are small non-coding RNAs participate in several biological processes and play an important part to regulate mRNA expression (11,12). lncRNAs are non-coding RNAs (ncRNAs) ranging from 200 nucleotides to 100 kb in length, regulating the activity of mRNAs by direct interact with one or more miRNA response elements (MREs) (13,14). Many researches reveal that lncRNAs may play an important part in post-transcriptional regulation and transcriptional regulation, and represent potential early diagnosis biomarkers and therapeutic targets (15,16).

In 2014, Yang *et al.* present that upregulated FOXO1 and E-cadherin expression level in breast cancer cells inhibited EMT (epithelial–mesenchymal transition) and metastasis progress in breast cancer while miR-9 inactivating (17,18). The noncoding RNA CXCR4 sponging of miR-146a which may result the upregulated of expression level of TNF receptor-associated factor 6 (TRAF6) and epidermal growth factor receptor (EGFR), stimulate tumor cell proliferation, invasion and migration in breast carcinoma and other various cancer types (19-22).

Nonetheless, the molecular pathogenesis mechanism of ceRNA in Her-2 enrich subtype breast cancer have not been further investigated and discovered. It is important to explore interaction of miRNA and ceRNA which stable and

differentially expressed in different breast cancer molecular subtypes, which may act as new molecular biomarkers

Methods

RNA expression data and clinical feature associations

RNA expression data sets and detailed clinical data of 1,109 invasive infiltrating ductal breast carcinoma tissues and 113 adjacent tissues were collected from TCGA database. The corresponding information met the inclusion criteria as follows: (I) histologic diagnosis were invasive infiltrating ductal breast cancer; (II) clinical data (TNM stage, age, gender, overall survival and ER, PR and Her-2 receptor) were complete. As result, 1,109 breast cancer samples were classified into two cohorts including ER+/PR+ cohort (n=461) and ER-/PR- cohort (n=152). Moreover, ER+/PR+ cohort were divided into ER+/PR+/Her-2+ group (n=98) and ER+/PR+/Her-2- group (n=39); and ER-/PR- cohort were divided into ER-/PR-/Her-2+ group (n=39) and ER-/PR-/Her-2- group (n=113).

Screening for DemRNAs, DemiRNAs, and DelncRNAs

Differently expressed mRNAs, lncRNAs and miRNAs between 1,109 breast cancer samples and 113 normal samples were analysis by a Bioconductor package, edgeR based on R language with the threshold of $|\log_2FC| > 1.5$ and P value < 0.05 . In ER+/PR+ breast cancer cohort, differently expressed mRNAs, lncRNAs and miRNAs between ER+/PR+/Her-2+ breast cancer (n=98) and ER+/PR+/Her-2- breast cancer (n=363) were screened with the same threshold of $|\log_2FC| > 1.5$, false discovery rate (FDR) $< 5\%$, and P value < 0.05 . In ER-/PR- breast cancer cohort, differently expressed mRNAs, lncRNAs and miRNAs between ER-/PR-/Her-2+ breast cancer (n=39) and ER-/PR-/Her-2- breast cancer (n=113) were screened with the same threshold. lncRNA-miRNA interactions were preformed to predicted and verified by miRcode. miRNA-mRNA interactions were selected to predict targeted mRNAs of miRNAs by miRanda, TargetsScan and miRTarBase.

Construction of lncRNA-miRNA-mRNA ceRNA network

To be more accurate, DEMRNAs, DEMiRNAs and DELncRNAs (breast cancer *vs.* normal tissue) were intersected with DEMRNAs, DEMiRNAs and DELncRNAs

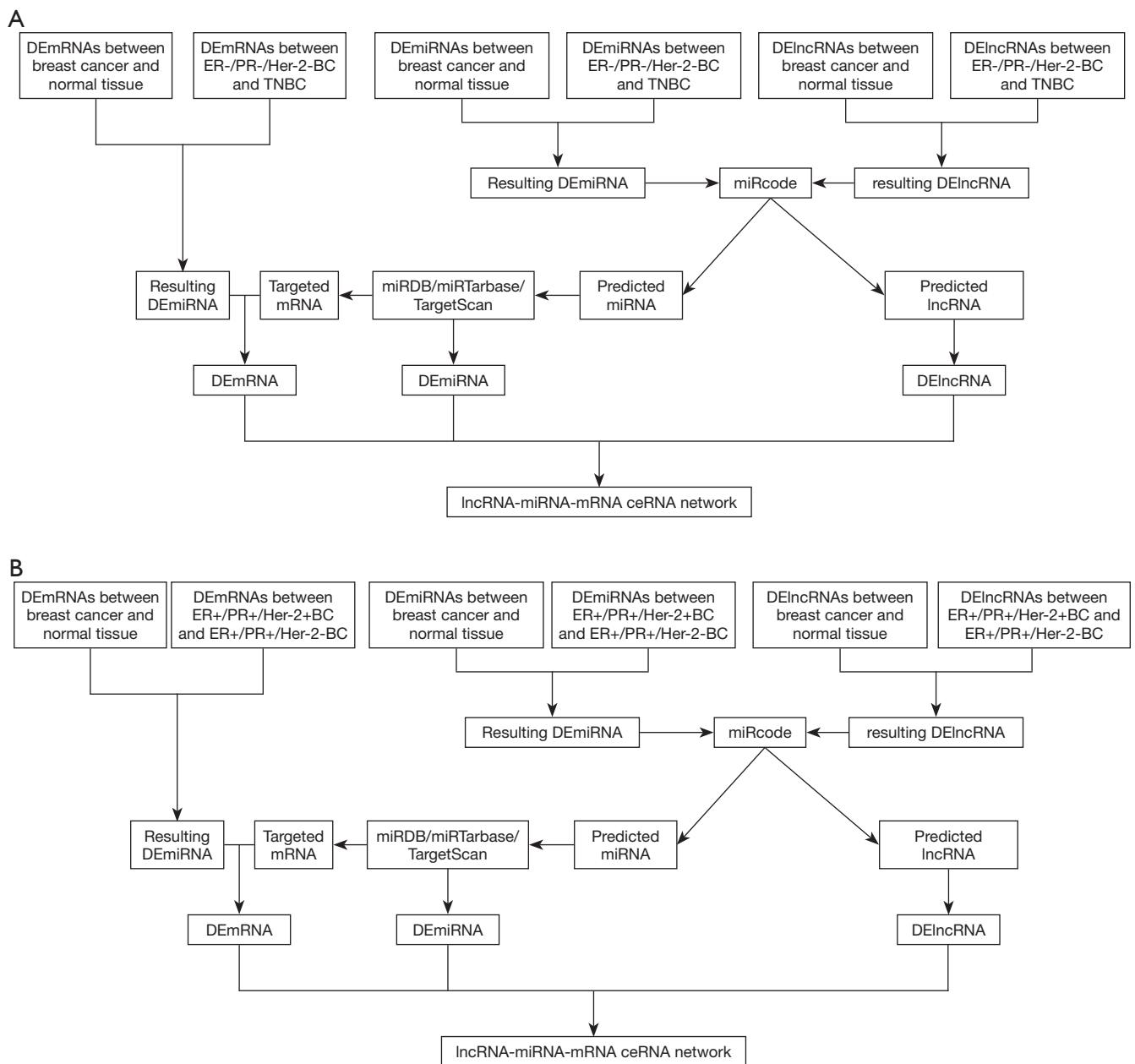


Figure 1 The flow charts of competing endogenous RNA (ceRNA) network construction by bioinformatic analysis. (A) The flow chart of ceRNA network construction in Estrogen Receptor (ER)+/Progesterone Receptor (PR)+ breast cancer cohort; (B) the flow chart of ceRNA network construction in ER-/PR- breast cancer cohort.

in ER+/PR+ and ER-/PR- cohort, respectively. The resulting mRNAs were also intersected with targeted mRNAs predicted by miRNAs selected by lncRNA-miRNA interactions in miRcode. ceRNA network was integrated of interaction among retained lncRNA, miRNA and mRNA.

The construction of the network was visualized using the Cytoscape 3.4.0 software.

The flow chart in ER+/PR+ and ER-/PR- breast cancer cohort for the construction of ceRNA networks are illustrated (Figure 1A,B).

Table 1 Clinical features of 613 patients in TCGA

Clinical feature	ER+/PR+ cohort		ER-/PR- cohort	
	Her-2-	Her-2+	Her-2-	Her-2+
Age (years)				
>60	207	45	82	21
≤60	156	53	31	16
Stage				
I	72	11	19	2
II	201	56	70	23
III	80	29	16	10
IV	3	1	2	1
Not available	8	1	3	1
Margin				
Positive	28	4	3	6
Negative	309	81	100	31
Not available	27	13	10	0
Pathological T				
T1	109	18	26	6
T2	192	63	71	26
T3	51	12	12	2
T4	10	5	4	3
Tx	2	0	0	0
Pathological N				
N0	173	40	73	10
N1	122	37	24	14
N2	39	13	12	5
N3	24	8	4	6
Nx	6	0	0	2
Pathological M				
M0	313	78	96	36
M1	3	1	2	1
Mx	48	19	15	0

Results

At last, a total of 461 ER+/PR+ cohort including 98 Her-2-positive and 363 Her-2-negative breast cancers and a

total of 152 ER-/PR- cohort were enrolled in our research (Table 1).

DEmRNAs, DEmiRNAs and DELncRNAs in ER+/PR+ breast cancer cohort

Two hundred and sixty-nine DEmRNAs including 176 downregulated and 93 upregulated DEmRNAs were identified (98 Her-2-positive *vs.* 363 Her-2-negative breast cancers) in ER+/PR+ cohort after intersection with 3,201 DEmRNAs (breast cancer *vs.* normal tissues). Fifteen DEmiRNAs including 6 downregulated and 9 upregulated were identified (98 Her-2-positive *vs.* 363 Her-2-negative breast cancers) in ER+/PR+ cohort after intersection with 143 DEmiRNAs (breast cancer *vs.* normal tissues). One hundred and twenty-nine DELncRNAs including 71 downregulated and 58 upregulated (98 Her-2-positive *vs.* 363 Her-2-negative breast cancers) were identified in ER+/PR+ cohort after intersection with 1,772 DELncRNAs (breast cancer *vs.* normal tissues).

DEmRNAs, DEmiRNAs and DELncRNAs in ER-/PR- breast cancer cohort

After intersected with DEmRNAs, DEmiRNAs and DELncRNAs (breast cancer *vs.* normal tissues). Six hundred and ninety-three DEmRNAs including 431 downregulated and 262 upregulated DEmRNAs were retained for future analysis. Twenty-five DEmiRNAs (17 downregulated and 8 upregulated) and 364 DELncRNAs (223 downregulated and 141 upregulated) were retained for future analysis, respectively.

Prediction of DELncRNA-DEmiRNA and DEmiRNA-DEmRNA interactions

Four DELncRNA-DEmiRNA pairs were retained base on online software including 4 DELncRNAs and 1 DEmiRNA. target mRNA of DEmiRNA were marked by Targetscan, miRanda and miRTarBase prediction software and simultaneously intersected with 269 DEmRNAs in ER+/PR+ cohort online. Finally, 2 target genes were obtained.

In ER-/PR- cohort, 25 DELncRNA-DEmiRNA pairs were retained and target genes of 4 DEmiRNAs was also predicted. In result one target gene was selected for future analysis in ER-/PR- breast cancer cohort.

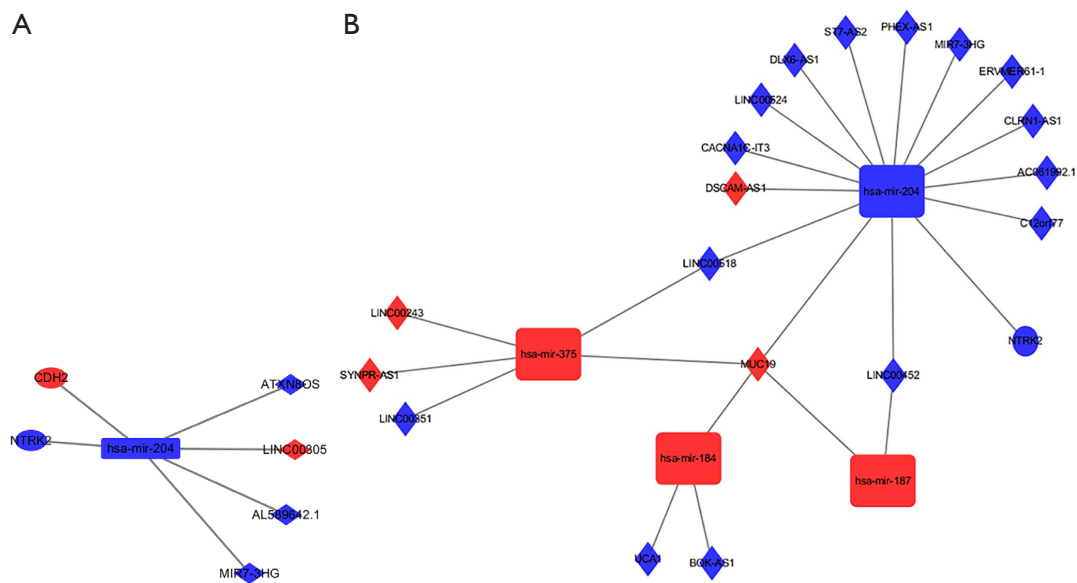


Figure 2 ceRNA network in ER+/PR+ and ER-/PR- cohort. (A) ceRNA network in ER+/PR+ cohort; (B) ceRNA network in ER-/PR- cohort.

Construction of mRNA-miRNA-lncRNA ceRNA network in ER+/PR+ and ER-/PR- cohort

ceRNA network in ER+/PR+ breast cancer cohort was constructed of 4 DElncRNA-DEmiRNA pairs and 2 DEmiRNA-DEmRNA pairs, including 4 DElncRNAs, 1 DEmiRNAs, and 2 DEMRNAs. ceRNA network in ER-/PR- breast cancer cohort was constructed of 24 DElncRNA-DEmiRNA pairs and 1 DEmiRNA-DEmRNA pairs, including 19 DElncRNAs, 4 DEmiRNAs, and 1 DEMRNA. The ceRNA networks were visualized by Cytoscape software (Figure 2A,B).

Discussion

ncRNAs work as miRNA sponges in result to regulate miRNA activity and function. Additionally, many studies reveal that ncRNAs binding to miRNAs regulate many biological processes participated in proliferation and invasion of tumor cells (16,23). Previous studies reveal that Her-2 inhibition blockade PI3K-Akt-mTOR signal pathways, while PARP inhibitors showing anti-tumor activity in BRCA-related triple negative breast cancer (24).

The expression of Her-2 protein is regulated by several miRNAs, such as miR-34a, miR-31, miR15a, miR16, miR-363 and miR-21, which may modulate to increased multidrug resistance (25-28). In our study, ceRNA network

is constructed to detect key RNAs in the progression and development of Her-2 enrich breast cancer downloaded from TCGA database. We divide breast cancer samples into different molecular subgroups according to gene expression-based classifications. MIR7-3HG- hsa-mir-204-NTRK2 axis is identified in both ER+/PR+ and ER-/PR- cohort in our study.

In previous studies reveal that downregulation of miR-204 accelerate breast cancer cell growth proliferation, and migration. Using real-time qPCR (RT-qPCR), Shen *et al.* show that compare to normal breast epithelial HBL-100 cell s, the expression level of miR-204 is decreased in MCF-7 cells (29). Our analysis show that miR-204-5p is significantly downregulated in ER+/PR+/Her-2+ and ER+/PR+/Her-2- breast cancer cohort, which is also downregulated in ER-/PR-/Her-2+ and ER-/PR-/Her-2- breast cancer cohort. Neurotrophic tyrosine receptor kinase type 2 (NTRK2) as a novel target of miR-200cis aberrantly expressed in carcinoma cells (30). Common polymorphisms in NTRK2 influence the severity of symptoms and symptom burden in patients undergoing treatment for breast cancer (31). MIR7-3HG acts as a tumor suppressor, which promotes the expression of the tumor suppressor AMBRA1 (32). It is reported that modulating the expression of MIR7-3HG in lung cancer cells lead to a less proliferative state (33). However, in some studies MIR7-3HG overexpression is associated with poor prognosis in

lung carcinoma (33). Gao *et al.* detect LINC00466-Has-mir-204-NTRK2 axis in invasive breast cancer which may associated with the prognosis of invasive breast cancer (34). Our result is consistent with previous studies which also present new therapeutic target for Her-2 positive breast cancer. In previous study, ZEB1 and CDH2 act as epithelial-to-mesenchymal transition (EMT) activators in breast cancer cells may inhibit the sensitivity of breast cancer cells to chemotherapy and enhance breast cancer cell progression and metastasis (35). We identify that CDH2 was upregulated ER+/PR+/Her-2+ subtype compared to ER+/PR+/Her-2- subtype, which may promote breast cancer cell EMT.

However, there are still some limitations in our study. Limited number of breast cancer patients are included in this study, and still need to be verified and confirmed in future studies. Other factors including races, stages, histological types and application of chemotherapy and endocrine therapy need to be accounted in. Predictive biomarkers to identify patients who will benefit from anti-Her-2 targeted therapy need to be verified in further analysis.

Conclusions

In conclusion, Her-2 related differently expressed lncRNAs, miRNAs and mRNAs are identified. According to ceRNA hypothesis, a potential Her-2 related regulatory ceRNA network may responsible for interpreting the mechanism underlying the biological processes of Her-2 positive breast cancer.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.03.34>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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