Reconstruction and analysis of the aberrant lncRNA-miRNA-mRNA network based on competitive endogenous RNA in CESC

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Abstract
A growing body of studies has demonstrated that long non-coding RNA (lncRNA) are regarded as the primary section of the ceRNA network. This is thought to be the case owing to its regulation of protein-coding gene expression by functioning as miRNA sponges. However, functional roles and regulatory mechanisms of lncRNA-mediated ceRNA in cervical squamous cell carcinoma (CESC), as well as their use for potential prediction of CESC prognosis, remains unknown. The aberrant expression profiles of mRNA, lncRNA, and miRNA of 306 cervical squamous cancer tissues and three adjacent cervical tissues were obtained from the TCGA database. A lncRNA-mRNA-miRNA ceRNA network in CESC was constructed. Meanwhile, Gene Ontology (GO) and KEGG pathway analysis were performed using Cytoscape plug-in BinGo and DAVID database. We identified a total of 493 lncRNA, 70 miRNA, and 1921 mRNA as differentially expressed profiles. An aberrant lncRNA-mRNA-miRNA ceRNA network was constructed in CESC, it was composed of 50 DElncRNA, 18 DEMiRNA, and 81 DEmRNA. According to the overall survival analysis, 3 out of 50 lncRNA, 10 out of 81 mRNA, and 1 out of 18 miRNA functioned as prognostic biomarkers for patients with CESC (\( P \) value < 0.05). We extracted the sub-network in the ceRNA network and found that two novel IncRNA were recognized as key genes. These included IncRNA MEG3 and IncRNA ADAMTS9-AS2. The present study provides a new insight into a better understanding of the lncRNA-related ceRNA network in CESC, and the novel recognized ceRNA network will help us to improve our understanding of lncRNA-mediated ceRNA regulatory mechanisms in the pathogenesis of CESC.

Keywords
Cervical squamous cell carcinoma, competitive endogenous RNA, long noncoding RNAs
1 | INTRODUCTION

As the second most common type of cancer in females worldwide, cervical cancer carries a high risk of leading cause of mortality in females in developing countries. Cervical cancer has an estimated incidence of 530,000 new cases and 270,000 deaths, annually. At the time of diagnosis, 80% patients have already progressed into invasive cancer stages of cervical cancer. The age at diagnosis has slowly been decreasing. Moreover, cervical cancer still carries high risks of morbidity and mortality from metastasis and recurrence. Cervical cancer is an intricate disease, which involved in numerous reasons. There has been a great necessity and urgency in searching for novel treatment targets as well as prognosis biomarkers to improve the survival rate of cervical cancer patients.

To improve the prognosis and decrease mortality and morbidity of CESC, diagnostic biomarkers are critical for early detection and risk assessment of CESC, which can help us to select appropriate treatment. However, it has been widely accepted that CESC is a heterogeneous cancer in various aspects owing to its clinicopathological, molecular, and cellular heterogeneity. Therefore, identification of potential molecular biomarkers or therapeutic targets to conquer CESC is urgently required. Recently, accumulating evidence has suggested that, rather than being transcriptional "dark matter," many non-coding RNA (lncRNA) serve as master regulators that affect the expression levels of dozens or even hundreds of target genes. Since the discovery of ceRNA regulation in human cells, multiple studies reported that lncRNA, miRNA, and other RNA act as natural miRNA sponges to suppress miRNA function. LncRNA functions as ceRNA to communicate with mRNA by competing for shared miRNA. In the study, we first acquired the aberrant expression profiles of lncRNA, miRNA, and mRNA between 360 CESC patients and 4 non-tumor samples. After which, the aberrant lncRNA-miRNA-mRNA ceRNA network was constructed in CESC. A total of 3 out of 50 lncRNA, 10 out of 81 mRNA, and 1 out of 18 miRNA functioned as prognostic biomarkers for patients with CESC according to the overall survival analysis. This is the first study to investigate the cancer specific lncRNA from the TCGA and lncRNA-mediated ceRNA network that was constructed in CESC. The present study results can be used to help clinicians to elaborate the function of lncRNA through lncRNA-miRNA-mRNA ceRNA network in CESC and provide novel lncRNAs as potential diagnostic biomarkers.

2 | MATERIALS AND METHODS

2.1 Patient datasets

The mRNA and miRNA expression and corresponding clinical information of PDAC patients were obtained from the TCGA data portal (https://tcga-data.nci.nih.gov/tcga/), which was imputed on IlluminaHiSeq RNA-Seq platform, containing 306 CESC sample tissues and four adjacent non-tumor pancreatic tissues. Both mRNA/miRNA profile data and clinical characteristics of PDAC are publicly available and available on open-access. Therefore, approval by a local ethics committee was not needed.

2.2 Acquisition and analysis of expression profiles

The differential expression lncRNA (DElncRNA), miRNA (DEmiRNA), and mRNA (DEmRNA) between CESC and adjacent tissue were calculated using R/Bioconductor package of edgeR. The differentially expressed genes (DEGs) of data sets with llog2 fold change ≥2.0 and a P-value less than 0.05 was considered as the selection criteria for subsequent analysis.

2.3 Identification of differentially expressed lncRNA

We obtained the lncRNA expression data by repurposing the probes in the mRNA expression profiles to lncRNA based on the annotations from the GENCODE project (http://www.gencodegenes.org). The transformed data (antisense, lncRNA, and sense_intronic) was considered as lncRNA.

2.4 Prediction of lncRNA-miRNA and miRNA-mRNA interactions

First, it should be stated that, the data of lncRNA-miRNA interactions was downloaded from a highly reliable online miRNA reference database of miRcode (http://www.mircode.org). The integrated lncRNA-miRNA pairs were predicted using miRcode, combining with the selected miRNA. Second, the prediction of targeted mRNA of miRNA was retrieved from three databases: miRTarBase, miRanda, and Targetscan. Finally, we established matched DElncRNA-DEmiRNA and DEmiRNA-DEmRNA pairs.

2.5 Reconstruction of the lncRNA-miRNA-mRNA ceRNA network

The DElncRNA-DEmiRNA-DEmRNA pairs were reconstructed by assembling all co-expression competing triplets. The ceRNA network was visualized using Cytoscape 3.3.2.
Simultaneously, the sub-network of the DElncRNA-DEmiRNA-DEmRNA ceRNA network was estimated using Cytoscape plug-in MCODE.

2.6 | Functional enrichment analysis

To understand the underlying biological processes and pathways of aberrantly expressed mRNA in the lncRNA-miRNA-mRNA network, Gene Ontology (GO) Biological Process term and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis was conducted using Cytoscape plug-in ClueGo\(^\text{19}\) and DAVID (database for annotation, visualization, and integrated discovery; https://david.ncifcrf.gov/). GO enrichment analysis was based on the threshold of \(P\)-value < 0.05 and enrichment score >1.0. Significant enrichment results were visualized using Cytoscape software 3.3.0.

2.7 | Statistical analysis

For overall survival analysis, the log-rank test was employed to analyze the difference between CESC and normal samples among DElncRNA, DEmiRNA, and DEmRNA. A \(P\)-value less than 0.05 was considered as statistically significant.

3 | RESULTS

3.1 | Differentially expressed lncRNA, miRNA, and mRNA

The expression profiles of mRNA, miRNA, and lncRNA between 304 CESC samples and four nonmalignant samples was calculated. We discovered that a total of 1921 mRNA, 493 lncRNA, and 70 miRNA were differentially expressed (log2 fold change \(\geq 2.0\) and FDR adjusted \(P\) less than 0.05). Of these, 712 mRNA, 128 lncRNA, and 33 miRNA were over-expressed. A total of 1209 mRNA, 365 lncRNA, and 37 miRNA were under-expressed. The heat map of clustering analysis of the analyzed RNA are shown in Figure 1–3.

3.2 | Construction and analysis of lncRNA-miRNA-mRNA ceRNA network

The lncRNA-miRNA-mRNA ceRNA network was established based on the relationship between DElncRNA, DEmiRNA, and DEmRNA. In the ceRNA network, we identified a total of 50 lncRNA nodes, 18 miRNA nodes, 81 mRNA nodes, and 2484 edges as differentially expressed profiles. The network is
presented in Figure 4. We noticed that DElncRNA ADAMTS9-AS2 interacted with as many as 13 DEmiRNA, including: hsa-mir-145, hsa-mir-182, hsa-mir-31, hsa-mir-96, hsa-mir-106a, hsa-mir-140, hsa-mir-141, hsa-mir-143, hsa-mir-183, hsa-mir-200a, hsa-mir-204, hsa-mir-205, and hsa-mir-32. Therefore, lncRNA ADAMTS9-AS2 may greatly contribute to the pathogenesis of CESC.

3.3 Prognostic overall survival assessment of lncRNA, miRNA, and mRNA

A total of 3 out of 50 DElncRNAs including AC097717.1, C20orf203, and EMX2OS were significantly associated

| GO id       | GO terms                                           | Ontology source            | Gene count | Genes                                      | P value   |
|-------------|----------------------------------------------------|----------------------------|------------|--------------------------------------------|-----------|
| GO:0009612  | Response to mechanical stimulus                    | GO_BiologicalProcess-GOA_23.02.2017_10h01 | 8          | BAK1, BCL2, DLC1, FOXO1, LRRK2, MYB, PDGFD, TXNIP | 210.0E-9  |
| GO:0033002  | Muscle cell Proliferation                          | GO_BiologicalProcess-GOA_23.02.2017_10h01 | 9          | CCNB1, FGF2, IGFBP5, MYB, PDGFD, TGFBR2, TGFBR3, THBS1, ZFPM2 | 71.0E-9   |
| GO:0048144  | Fibroblast Proliferation                           | GO_BiologicalProcess-GOA_23.02.2017_10h01 | 4          | [BAK1, BCL2, E2F1, PMAIP1]                  | 28.0E-6   |
| GO:0000083  | Regulation of transcription involved in G1/S transition of Mitotic cell cycle | GO_BiologicalProcess-GOA_23.02.2017_10h01 | 5          | CCNB1, E2F1, MYB, PDGFD, PDGFRA              | 4.3E-6    |
| GO:0070059  | Intrinsic apoptotic signaling pathway in response to endoplasmic reticulum stress | GO_BiologicalProcess-GOA_23.02.2017_10h01 | 5          | CCNB1, E2F1, MYB, PDGFD, PDGFRA              | 4.3E-6    |
with overall survival ($P < 0.05$) and exhibited positive effects. A total of 10 out of 81 mRNA significantly correlated with CESC overall survival ($P < 0.05$). Four DElncRNA of high expression (BCL2, E2F1, HMGGB3, and RASSF2), and 6 DElncRNA of low level expression (ERG, FASN, PTPRM, TBX2R, ULBP2, and ZCCHC24) were significantly related to the progression of CESC overall survival. Only 1 DEmiRNA (hsa-mir-14) was significantly associated with CESC overall survival ($P < 0.05$) (See Figure 5).

### 3.4 Functional prediction of lncRNA-miRNA-mRNA ceRNA network

In order to predict the function of aberrantly expressed genes in the ceRNA network, the intersection mRNA was analyzed by Cytoscape plug-in ClueGo and DAVID. Therefore, 81 DEmRNA were conducted to analyze their functions. The results revealed that enrichment of 140 GO categories occurred in the biological process (see Figure 6 and Table 1). The top 5 GO terms were a response to mechanical

**FIGURE 5** Kaplan-Meier survival curves of 10 DElncRNA, 3 DElncRNA, and DEmiRNA for the overall survival in CESC
stimulus, regulation of transcription involved in the G1/S transition of mitotic cell cycle, intrinsic apoptotic signaling pathways in response to endoplasmic reticulum stress, fibroblast proliferation, and muscle cell proliferation. KEGG analysis, focusing on the biological pathways, showed that 12 pathways were significantly enriched, particularly apoptosis, miRNAs in cancer, cell cycle, p53 signaling pathway, and prostate cancer pathways (Table 2). The mentioned pathways are exhibited in Figure 7.

3.5 | Key lncRNA-miRNA-mRNA in sub-network

We analyzed the hub gene in the ceRNA network using Cytoscape plug-in MCODE. A total of 10 nodes could be selected hub nodes, including lncRNA MEG3, lncRNA ADAMTS9-AS2, hsa-mir-141, hsa-mir-96, RECK, ZFPM2, OSBPL3, RPLR, AP1S2, and TPM2. The sub-network is shown in Figure 8.

4 | DISCUSSION

Cervical cancer in females contributes to the second highest number of deaths in the world, exceeded only by breast cancer. Cervical cancer carries a high risks of morbidity and mortality. It goes without saying that recurrence and metastasis are the most significant challenge to overcome in the treatment of cervical cancer. Therefore, looking for available biomarker markers of cervical cancer is essential for improving its prognosis in patients. At present, an increasing amount of evidence indicates that lncRNA plays an important molecular role in apoptosis, proliferation, progression, metastasis, invasion, and relapse and relapse of tumor. LncRNAs acts as the potential biomarkers for diagnosis and prognosis in various cancers. Numerous studies have indicated that the dysregulated lncRNA expression profiles are associated with the development of various cancers, includes CESC, as well as respective patients survival rate. This hence uncovers the potential for lncRNA to be utilized as a potential prognostic cancer biomarker. Recent studies have reported that lncRNA can regulate miRNA abundance by binding and sequestering them, making lncRNA the titular name of miRNA sponges. Meanwhile, lncRNA also regulates the expression of target mRNA. Based on the theory Salmena proposed; a competing endogenous RNA (ceRNA) hypothesis that lncRNA functions as ceRNA to react with mRNA by competing for shared miRNA. Experimental evidence indicates that lncRNA, that harbors similar sequences to its targeted miRNA, can sequester miRNA away from mRNA. LncRNA CASC2 up-regulates PTEN as a ceRNA of miR-21 and plays an

| GO id       | KEGG terms         | Ontology source | Gene count | Genes                                      | P value   |
|-------------|---------------------|-----------------|------------|--------------------------------------------|-----------|
| GO:0004215  | Apoptosis           | KEGG_01.03.2017 | 3          | BAK1, BCL2, PMAIP1                         | 1.3E-3    |
| GO:0005206  | MicroRNAs in cancer | KEGG_01.03.2017 | 13         | BAK1, BCL2, CCNE1, CCNE2, CDC25A, E2F1,    | 44.0E-9   |
|             |                     |                 |            | KIF23, PDGFRA, RECK, THBS1, ZEB1, ZEB2,    |           |
|             |                     |                 |            | ZFPM2                                      |           |
| GO:0004110  | Cell cycle          | KEGG_01.03.2017 | 6          | CCNB1, CCNE1, CCNE2, CDC25A, CHEK1, E2F1  | 150.0E-6  |
| GO:0004115  | p53 signaling pathway | KEGG_01.03.2017 | 7          | CCNB1, CCNE1, CCNE2, CHEK1, PMAIP1, RRM2,  | 290.0E-9  |
|             |                     |                 |            | THBS1                                      |           |
| GO:0005215  | Prostate cancer     | KEGG_01.03.2017 | 8          | AKT3, BCL2, CCNE1, CCNE2, E2F1, FOXO1,     | 83.0E-9   |
|             |                     |                 |            | PDGF, PDGFRA                               |           |

FIGURE 6 GO terms show as an interaction network using Cytoscape plug-in ClueGO
important role in cervical cancer sensitivity to DDP, and may
serve as a potential target for cancer diagnosis and treatment. Gao et al demonstrated that the tumor-promoting role of lncRNA PVT1, is that it acts as competing endogenous RNA (ceRNA), or a molecular sponge in negatively modulating miR-424. This tumor-promoting role of lncRNA PVT1 might provide a novel therapeutic target for cervical cancer. However, a comprehensive analysis of CESC-related lncRNA and miRNA in a whole genome-wide, especially based on high through detection with large-scale sample size, has always been lacking. Therefore, it is crucial to explore the functional roles and regulatory mechanisms of the lncRNA-miRNA-mRNA ceRNA network in the development of CESC. In this presented study, a total of 494 lncRNAs, 70 miRNA, and 1921 mRNA differentially expressed profiles were identified from the TCGA database. An aberrant lncRNA-mRNA-miRNA ceRNA network was constructed in CESC. The lncRNA-miRNA-mRNA ceRNA network was composed of 50 DElncRNAs, 18 DEmiRNA, and 81 DEMRNA. We extracted the sub-network in the ceRNA network and found that four nodes were recognized as key genes, including: lncRNA MEG3, lncRNA ADAMTS9-AS2, hsa-mir-141, and hsa-mir-96. As for lncRNA MEG3, several studies have suggested its involvement in various cancers via acting on cell apoptosis, including cervical cancer. The lncRNA ADAMTS9-AS2, hsa-mir-141, and hsa-mir-96 can also be regarded as potential biomarkers for CESC. Hsa-mir-141 and hsa-mir-96, lncRNA ADAMTS9-AS2 originally served as prognostic predictors, providing reasonable implications in future clinical practice regarding targeted treatment of CESC. Three out of 50 lncRNAs, 10 out of 81 mRNAs, and 1 out of 18 miRNAs functioned as prognostic biomarkers for patients with CESC according to the overall survival analysis ($P$ value < 0.05). GO analysis and KEGG pathway analysis have been used to evaluate the biological functions enriched among differentially expressed coding genes. The results of DEmRNA related GO analysis revealed that enrichment of 140 GO categories in the biological process was significant with $P$-value < 0.05. These significant GO terms involved a response to mechanical stimulus, regulation of transcription involved in the G1/S transition of mitotic cell cycle, intrinsic apoptotic signaling pathway in response to endoplasmic reticulum stress, fibroblast proliferation, and muscle cell proliferation. The pathway analysis further demonstrated that 12 pathways were enriched, and primarily involved: apoptosis, miRNAs in cancer, cell cycle, p53 signaling pathway, and prostate cancer pathways.

Among these key lncRNA, several studies have reported that lncRNA MEG3 played crucial roles in the development of various cancers, such as: non-small cell lung cancer, cervical cancer, colorectal cancer, esophageal cancer. The lncRNA MEG3 had effects to suppress cervical cancer by regulation of PI3K/AKT/Bcl-2/Bax/P21 and PI3K/AKT/MMP-2/9 signaling pathways. However, only two studies demonstrated that lncRNA ADAMTS9-AS2 was associated with development of gliomas, and colorectal cancer. However, the contribution of lncRNA ADAMTS9-AS2 to the development of CESC is still not certain from the current
available study. Further studies should be performed to address these issues. According to the lncRNA-miRNA-mRNA sub-network, we speculated that downregulated-lncRNA ADAMTS9-AS2 might have a role in altering the upregulated-hsa-mir-141 and upregulated-hsa-mir-96. Recent studies demonstrated that miR-141 downregulated-TM4SF1 expression to inhibit invasion and migration of prostate cancer cells. Wang Y suggested that hsa-miR-96 may affect the growth of bladder cancer cells by up-regulating IRS1 and MAP4K1 levels, functioning as a promising diagnostic marker in human bladder urothelial carcinomas. Based on these findings, lncRNA ADAMTS9-AS2 may be involved in the invasion and migration of CESC. These results also indicated that lncRNA ADAMTS9-AS2 and MEG3 is a critical lncRNA in the development of CESC.

In summary, we first reconstructed the lncRNA-miRNA-mRNA ceRNA network, and analyzed the lncRNA related ceRNA in the development of CESC. Our results demonstrated that lncRNA plays an important role in the development of CESC. Two novel lncRNA ADAMTS9-AS2 and MEG3 may be chosen as key lncRNA. Further studies are needed to explore the biological mechanisms of these two lncRNAs in CESC.

AUTHORS’ CONTRIBUTION

Authors JKS, AZY, JGZ, and JGL wrote the main manuscript text. XHY, ZC, and ELJ prepared Figures 1–8. XHY and ELJ contributed on data analysis and all authors reviewed the manuscript.

CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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