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Integrated analysis of circular RNA-associated ceRNA network in cervical cancer

Observational Study

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Abstract

Background: Circular RNAs (circRNAs) have displayed dysregulated expression in several types of cancer. Nevertheless, their function and underlying mechanisms in cervical cancer remains largely unknown. This study aimed to describe the regulatory mechanisms in cervical cancer.

Methods: We downloaded the circRNAs expression profiles from Gene Expression Omnibus database, and RNAs expression profiles from The Cancer Genome Atlas database. We established a circRNA-miRNA-mRNA and circRNA-miRNA-hubgene network. The interactions between proteins were analyzed using the STRING database and hubgenes were identified using MCODE plugin. Then, we conducted a circRNA-miRNA-hubgenes regulatory module. Functional and pathway enrichment analyses were conducted using R packages "Clusterprofile".

Results: Six circRNAs, 15 miRNAs, and 158 mRNAs were identified to construct the ceRNA network of cervical cancer. PPI (protein-protein interaction) network and module analysis identified 7 hubgenes. Then, a circRNA-miRNA-hubgene subnetwork was constructed based on the 1 DEcircRNAs, 3 DEmiRNAs, and 3 DEmRNAs. The KEGG pathway analysis indicated DEmRNAs are involved in progesterone-mediated oocyte maturation, cell cycle, and oocyte meiosis.

Conclusion: These ceRNAs are critical in the pathogenesis of cervical and may serve as future therapeutic biomarkers.

Abbreviations: CC = cervical cancer, circRNAs = circular RNAs, DEmiRNAs = differentially expressed miRNAs, DEmRNAs = differentially expressed mRNAs, FC = fold change, GEO = Gene Expression Omnibus, GO = GO, MREs = miRNA binding sites, PPI = protein–protein interaction, TCGA = The Cancer Genome Atlas.

Keywords: cervical cancer, circRNA, competitive endogenous RNA, microRNA

1. Introduction

Cervical cancer (CC) is one of the most common female genital malignant tumors, with high incidence and high mortality. There were approximately 500,000 new-diagnosed cases and 250,000 deaths.[1,2] The primary treatment of early-stage cervical cancer is surgery followed by chemotherapy or chemoradiation. However, in the event of tumor recurrence, patients with cervical cancer have a poor prognosis because of limited clinical strategies. Moreover, nearly one-third of patients die from recurrence or progression of the disease. Therefore, it is critical to investigate the molecular mechanisms involved in the development and progression of cervical cancer.[3,4]

Circular RNAs (circRNAs) are a class of noncoding RNAs with continuous, covalently closed circular structures. Owing to its absence of 3', 5' end and poly A tail, circRNAs can avoid the degradative effect of exonuclease and RNase R.[5,6] Compared with linear RNA, circRNAs are more conservative and stable and show cell-specific, tissue-specific and stage-specific.[7,8] With the development of high-throughput sequencing technologies and analysing, scientists gradually realize that circRNAs play important regulatory roles in the development of tumor, such as non-small cell lung cancer, colorectal cancer, and esophageal squamous cell carcinoma.[9–11] It has been demonstrated that circRNAs act as competitive endogenous RNAs (ceRNAs), namely microRNA sponges, regulating target gene expression. They could also serve as transcriptional regulator or protein-binding RNA, or even be directly translated into proteins under certain circumstances.[12–14] However, the expression and function of circRNAs in CC have rarely been explored.

In this study, circRNA microarray and RNA-Seq was used to screen CC tissues and pair-matched adjacent normal tissues to find the differential expressed circRNAs (DEcircRNAs) and their targets, by the aim to investigate potential markers for the progression of CC and elucidate the possible mechanism involved for new insights of molecular therapy.

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2. Materials and methods

2.1. Data acquisition and processing

The circRNA expression profile of GSE102686 were downloaded from the GEO database, including 5 cervical tissues and 5 normal tissues. The mRNA expression profile (306 cervical tissues and 3 normal tissues) and miRNA expression profiles (309 cervical tissues and 3 normal tissues) were obtained from The Cancer Genome Atlas (TCGA) database. Neither ethical approval nor informed consent was required in this study because of the public-available data.

2.2. Identification of DEGs

We applied Limma package to identify differentially expressed circRNAs (DEcircRNAs) with thresholds of |log2 fold change (FC)| >2 and adjusted *P* value <.01. Additionally, the edgeR package was used to screen differentially expressed miRNA (DEmiRNA) and mRNA (DEmRNA) with thresholds of |log 2 (FC)| >2 and adjusted *P* value <.05.

2.3. Construction of the ceRNA network

We used the Cancer-specific CircRNA (http://gb.whu.edu.cn/CSCD/) database to predict the miRNA binding sites (MREs). Only overlapping genes were selected as candidate target miRNAs. These target miRNAs were further screened by the DEmiRNAs. Then, we used miRTarBase and TargetScan databases to identify miRNA-targeted mRNAs.[15,16] Only mRNAs recognized by all 2 databases were considered as candidate mRNAs and intersected with the DEmRNAs to determine the DEmRNAs that were targeted by the DEmiRNAs. Basing on the DEmiRNA-DEcircRNA and DEmiRNA–DEmRNA interactions, we constructed circRNA-miRNA-mRNA regulatory network, which was visualized using Cytoscape 3.7.0 software.

2.4. Construction of PPI network

To assess the interactions between DEmRNAs, we established a protein–protein interaction (PPI) network by the Search Tool for the Retrieval of Interacting Genes (STRING). The cut-off criteria were a combined score of > 0.9 for a PPI network and a node degree of ≥6 for screening hub genes. Cytoscape 3.7.0 was used for visualization. We used the MCODE app to extract hub genes from the PPI network.[17]

2.5. Functional enrichment analysis

To assess the main function of the DEmRNAs in the ceRNA network in tumorigenesis, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were conducted using the clusterProfiler package of R software.[18] *P* value <.05 was set as the cutoff criterion.

3. Results

3.1. Identification of differentially expressed circRNA, mRNA, and miRNA

A total of 7 the differentially expressed circRNAs (DEcircRNAs) were screened from GSE102686 dataset, including of 2 upregulated and 5 downregulated circRNAs (Fig. 1). In addition, 124 DEmiRNAs (67 upregulated and 57 downregulated miRNAs) and 2368 mRNAs (1049 upregulated and 1319 downregulated mRNAs) from RNA-Seq between CC tissues and normal cervival tissues were screened (Fig. 2A and B). The basic information of the 7 circRNAs is shown in Table 1. The basic structural patterns of the 7 circRNAs are listed in Figure 3.

3.2. Construction of the ceRNA network

The potential target miRNAs of 7 DEcircRNAs were retrieved from the CSCD online database. A total of 342 circRNA-miRNA

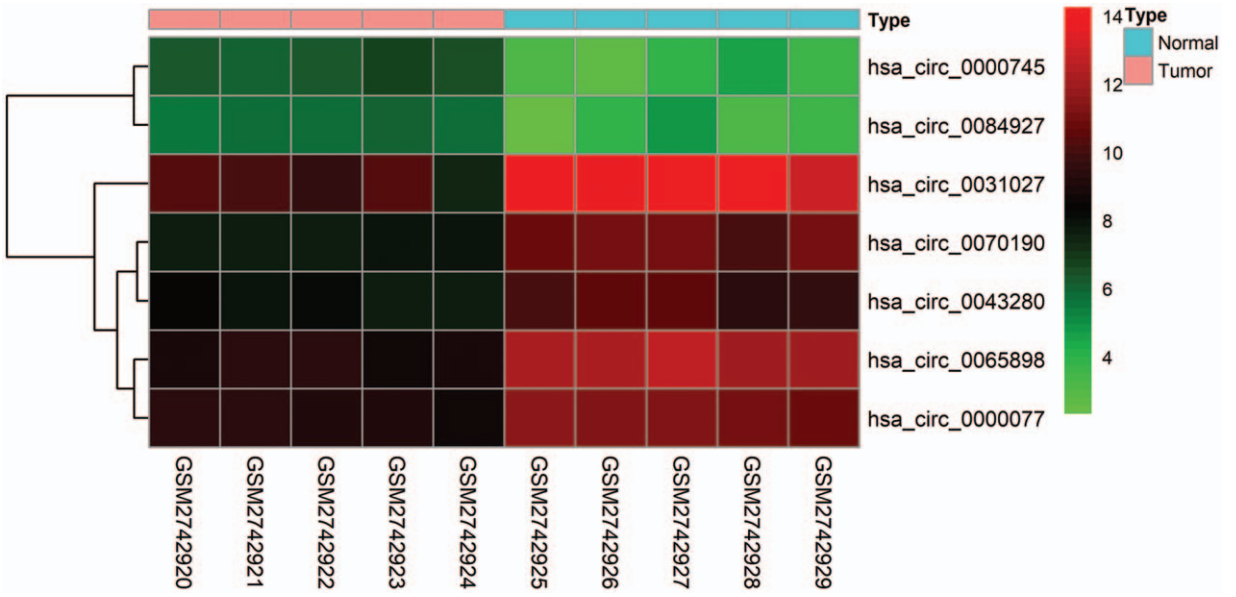

Figure 1. Heatmap of the differentially expressed circular RNAs.

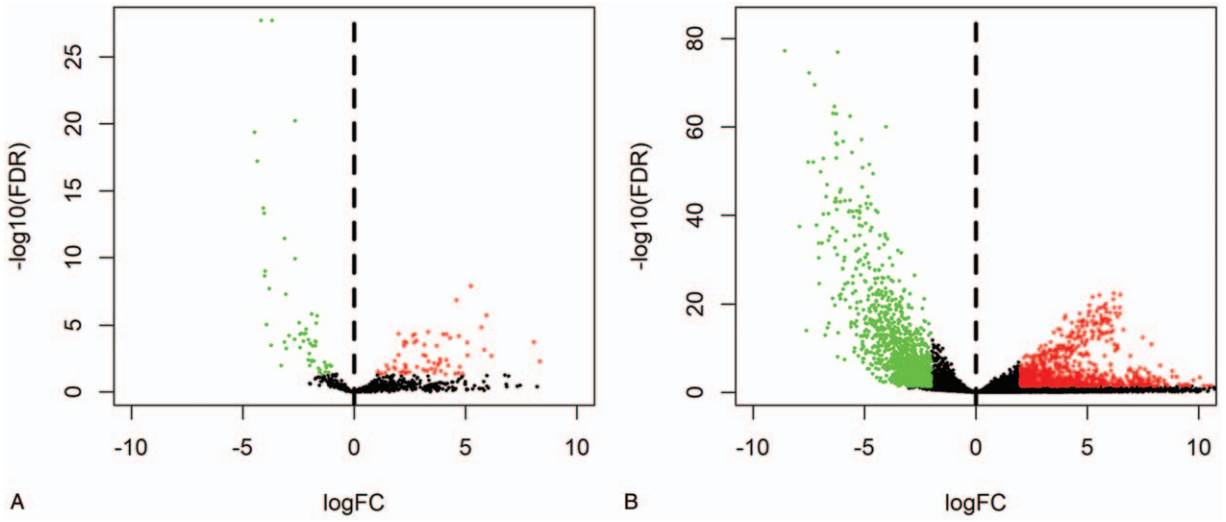

Figure 2. Volcano plot of differentially expressed miRNAs (A) and mRNAs (B).

Table 1

Basic characteristics of the 7 differently expressed circRNAs.

circRNA ID	Position	Genomic length	Strand	Best transcript	Gene symbol	Regulation
hsa_circ_0000745	chr17:20107645–20109225	1580	+	NM_001033554	SPECC1	Up
hsa_circ_0084927	chr8:95676924–95677424	500	+	NM_017697	ESRP1	Up
hsa_circ_0000077	chr1:62171487–62175109	3622	–	NM_032027	TM2D1	Down
hsa_circ_0043280	chr17:35797838–35804870	7032	+	NM_001488	TADA2A	Down
hsa_circ_0070190	chr4:79747190–79772210	25020	+	NM_198892	BMP2K	Down
hsa_circ_0065898	chr3:51454240–51456330	2090	–	NM_014703	VPRBP	Down
hsa_circ_0031027	chr13:114164552–114193822	29270	+	NM_017905	TMCO3	Down

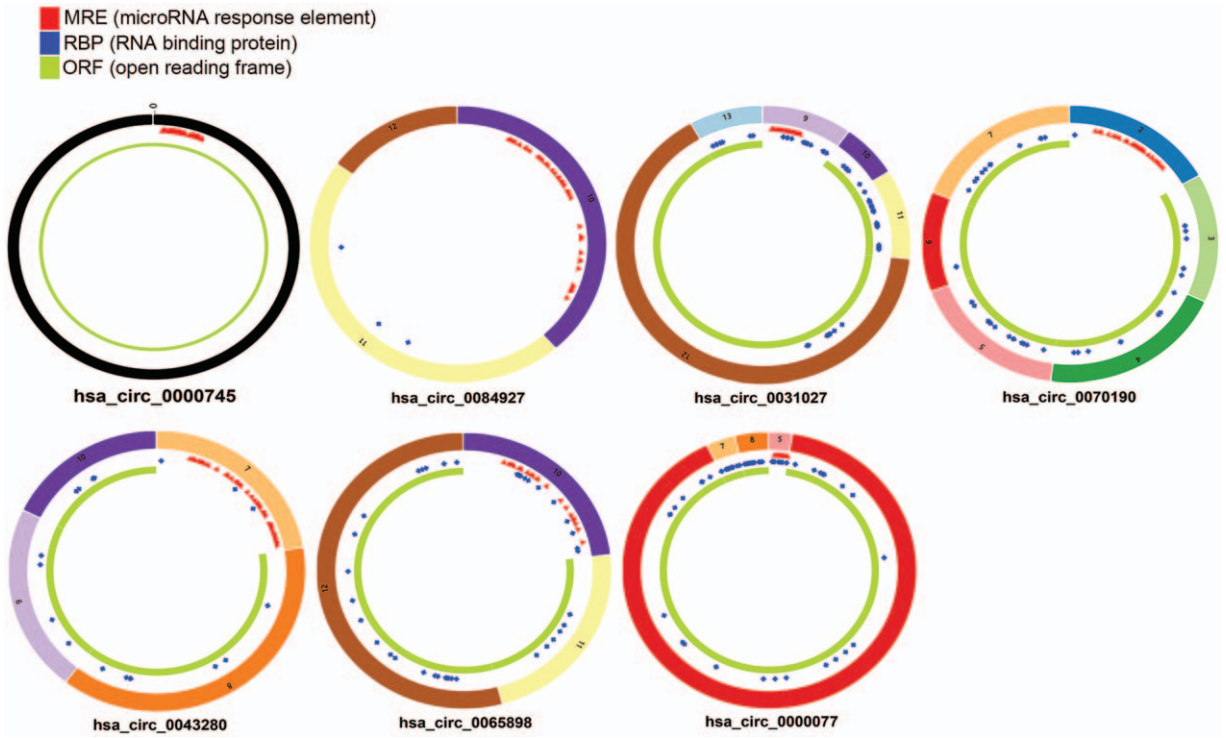

Figure 3. Structural patterns of the 7 circular RNAs: (A) hsa_circ_0000745, (B) hsa_circ_0084927, (C) hsa_circ_0031027, (D) hsa_circ_0070190, (E) hsa_circ_0043280, (F) hsa_circ_0065898, (G) hsa_circ_0000077.

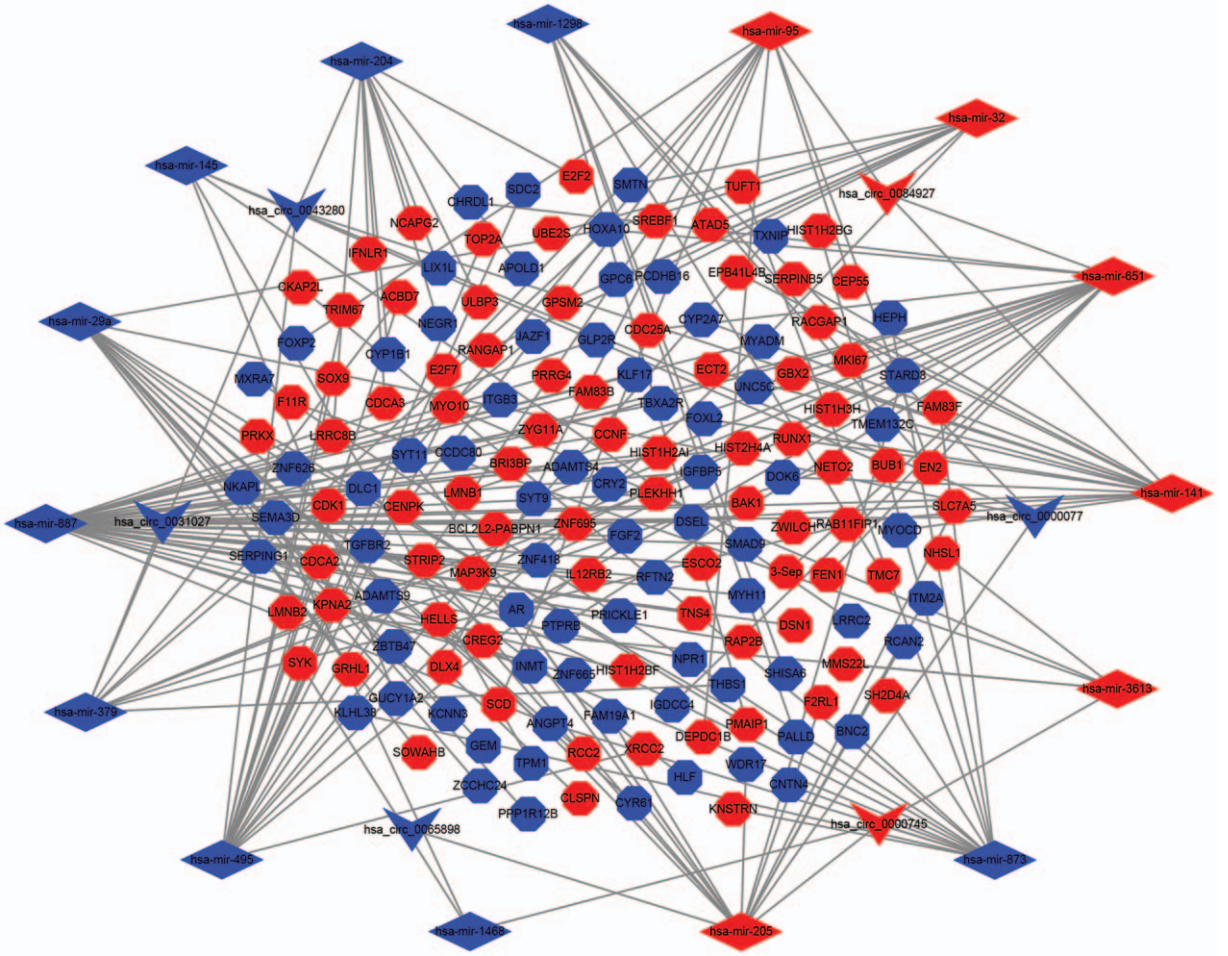

Figure 4. The ceRNA network of circRNA-miRNA-mRNA in CC. V indicate circRNA, diamond indicate miRNA, and octagon indicate mRNA. The nodes highlighted in red and blue represent upregulation and downregulation, respectively.

pairs were identified. After intersecting with the DEmiRNAs, only 21 circRNA–miRNA pairs, including 6 circRNAs and 15 DEmiRNAs, remained. Furthermore, 1739 mRNAs predicted by 2 databases (miRTarBase and TargetScan) were identified. Then, the 1739 targeted mRNAs were compared to the 2368 DEmRNAs and only overlapping genes were selected as candidate genes. The results indicated that 158 DEmRNAs were involved in ceRNA network. Finally, we constructed a ceRNA network based on 6 circRNAs, 15 miRNAs, and 158 mRNAs (Fig. 4).

3.3. Construction of PPI network and module analysis

Based on the DEmRNAs, PPI network was conducted, involving 57 nodes and 90 edges (Fig. 5A). To explore the hubgenes in the process of PDAC carcinogenesis, the degree, betweenness centrality, key circRNA-miRNA-mRNA regulatory module was extracted using MCODE approach from the PPI network. The significant module contains 7 nodes and 21 edges. These hubgenes were *CDK1*, *BUB1*, *CENPK*, *ZWILCH*, *DSN1*, *RCC2*, and *RANGAP1* (Fig. 5B). Then, we established a circRNA-miRNA-hugene subnetwork (Fig. 6), including 3 subnetwork regulatory modules (hsa_circ_0084927-hsa-mir-141-ZWILCH, hsa_circ_0084927-hsa-mir-32-RANGAP1, and hsa_circ_0084927-hsa-mir-95-CENPK).

3.4. Functional enrichment analysis of DEmRNA

According to GO analysis, we found that the most enriched GO terms in biological process were sister chromatid cohesion, sister chromatid segregation, nuclear chromosome segregation, and chromosome segregation; in terms of cellular components (CC), DEmRNAs were mostly enriched in chromosomal region. Among the 7 molecular function terms, the most enriched GO term was RNA polymerase II carboxy-terminal domain kinase activity ($P < .05$). The top 5 GO terms are indicated in Table 2. Moreover, KEGG pathway analysis indicated that most of DEmRNAs are involved in progesterone-mediated oocyte maturation, cell cycle, and oocyte meiosis.

4. Discussion

With the continuous maturity and development of bioinformatics, scientists gradually realize that circRNA is a novel noncoding RNA which have conserved sequence and can stably express in mammals. CircRNAs can regulate the expression of gene at transcriptional or posttranscriptional.[19,20] Many studies have revealed the abnormal expression and regulation of circRNAs can affect the occurrence and course of cancers,[21,22] and thus have the potential to serve as biomarkers of malignancies.[23–25] However, the exact role of circRNAs in CC remains largely unclear. In this study, we firstly integrated circRNA, miRNA, and

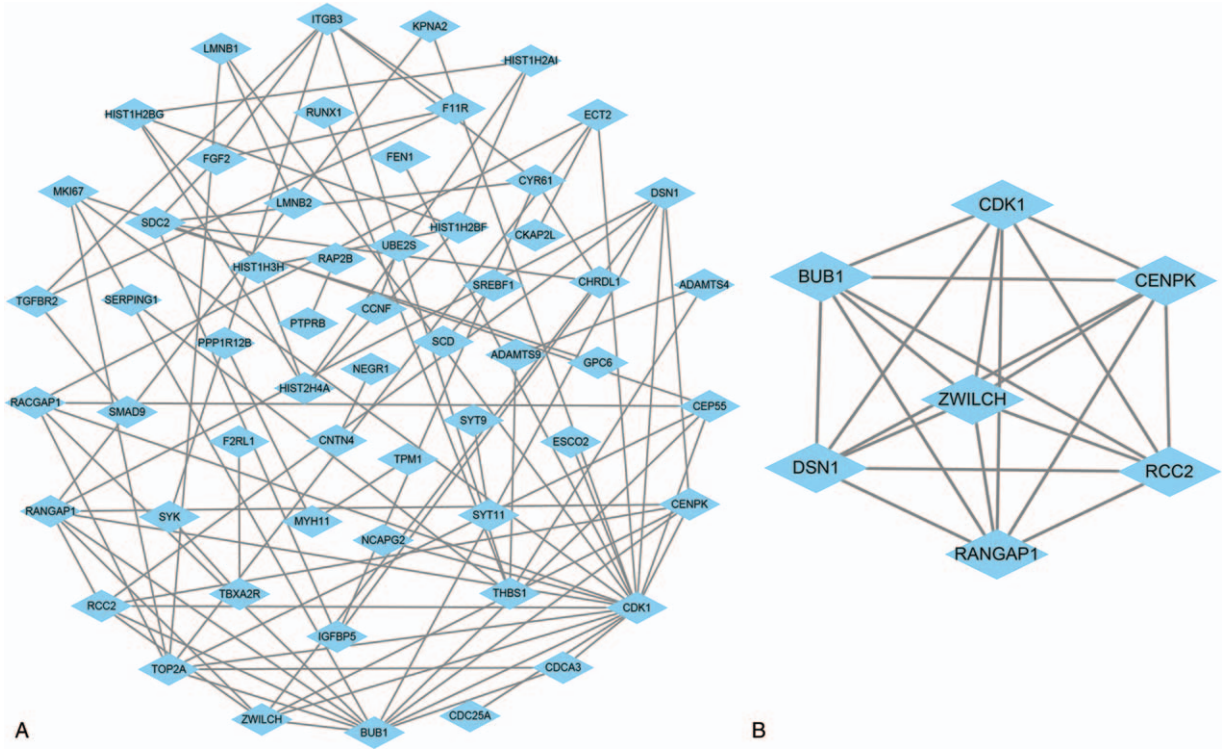

Figure 5. Identification of hubgenes from the protein–protein interaction (PPI) network with the MCODE algorithm. (A) PPI network of 158 genes. (B) PPI network of 7 hubgenes that extracted from (A).

mRNA data between CC tissues and nontumor tissues from GEO and TCGA database and constructed the circRNA-miRNA-mRNA regulatory network.

Several studies have indicated that circRNA have displayed dysregulated expression in CC and is linked to the pathogenesis and prognosis, and is considered to be a tumor-related biomarker.[26–28] Zhang et al[26] showed that hsa_circ_0023404 was significantly upregulated in CC tissues compared to cervical normal tissues. Elevated hsa_circ_0023404 expression was linked to worse survival, and hsa_circ_0023404 may serve as an independent prognostic biomarker. Silence of hsa_circ_0023404 reduced cell proliferation, induced cell cycle arrest, and inhibited cell migration and invasion. Furthermore, they found that hsa_circ_0023404 can regulate the expression of TFCP2 by sponging miR-136, leading to CC development and progression. Similarly, elevated circRNA8924 was observed in CC tissues and was associated with tumor size, FIGO staging, and myometrial invasion. The knockdown of circRNA8924 significantly inhibited the proliferation, migration, and invasion of CC cells.[27] In our study, a total of 6 circRNAs were identified involved in the ceRNA network. Hsa_circ_0000745 may serve as a diagnostic marker for gastric cancer.[29] Hsa_circ_0084927 has been found to be significantly upregulated in malignant pleural effusion by qRT-PCR.[30] However, none of the other 6 circRNAs have been reported in CC.

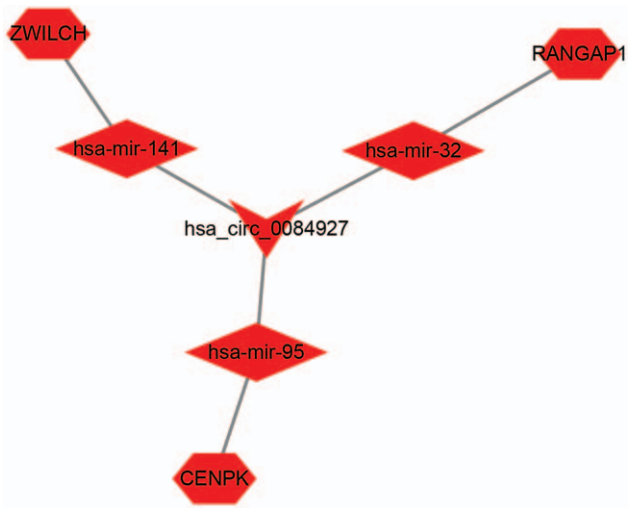

Figure 6. CircRNA-miRNA-hubgene network consisting of 1 cricRNA, 3 miRNAs, and 3 hubgenes.

miRNAs are a class of small (approximately 22 nucleotides in length) and highly conserved noncoding RNAs.[31] They can post-transcriptionally regulate gene expression by binding to 3' untranslated regions, resulting in translation repression or mRNA degradation.[32] MiRNAs play key roles in many biological processes, including cell proliferation, differentiation, development, immune response.[32,33] In this study, we indentified 15 DEmiRNAs in the ceRNA network. Some researchers have studied the binding of circRNAs to miRNAs and their interactions in CC.[28,34] Cai et al[34] indicated that hsa_circ_0000263 promoted CC cell proliferation, apoptosis, and migration by sponging miR-150–5p. Ma et al[28] reported that circRNA-000284 promotes progression of CC by sponging miR-506. In present study, we predicted the correlation between 6 circRNAs and 15 miRNAs involved in ceRNA network. Of these 15 miRNAs, 7 have been reported in CC.[35–41]

Table 2

The top 5 GO terms enriched by DEmRNA involved in the ceRNA network.

Categories	Terms	Description	*P*	*P* adjusted	Genes	Counts
BP	GO:0007062	Sister chromatid cohesion	1.19E-12	4.36E-10	ZWILCH/CENPK/BUB1/DSN1/RCC2/RANGAP1	6
	GO:0000819	Sister chromatid segregation	4.00E-11	7.35E-09	ZWILCH/CENPK/BUB1/DSN1/RCC2/RANGAP1	6
	GO:0098813	Nuclear chromosome segregation	1.82E-10	2.22E-08	ZWILCH/CENPK/BUB1/DSN1/RCC2/RANGAP1	6
	GO:0007059	Chromosome segregation	4.59E-10	4.21E-08	ZWILCH/CENPK/BUB1/DSN1/RCC2/RANGAP1	6
	GO:0007135	Meiosis II	7.40E-06	0.000453	BUB1/DSN1	2
CC	GO:0098687	Chromosomal region	7.14E-13	3.50E-11	ZWILCH/CDK1/CENPK/BUB1/DSN1/RCC2/RANGAP1	7
	GO:0000775	Chromosome, centromeric region	8.01E-12	1.96E-10	ZWILCH/CENPK/BUB1/DSN1/RCC2/RANGAP1	6
	GO:0000777	Condensed chromosome kinetochore	1.01E-10	1.64E-09	ZWILCH/CENPK/BUB1/DSN1/RANGAP1	5
	GO:0000779	Condensed chromosome, centromeric region	1.83E-10	2.24E-09	ZWILCH/CENPK/BUB1/DSN1/RANGAP1	5
	GO:0000776	Kinetochore	3.51E-10	3.44E-09	ZWILCH/CENPK/BUB1/DSN1/RANGAP1	5
MF	GO:0008353	RNA polymerase II carboxy-terminal domain kinase activity	0.006366	0.04637	CDK1	1
	GO:0035173	Histone kinase activity	0.007159	0.04637	CDK1	1
	GO:0030332	Cyclin binding	0.012303	0.04637	CDK1	1
	GO:0008536	Ran GTPase binding	0.013487	0.04637	RANGAP1	1
	GO:0004693	Cyclin-dependent protein serine/threonine kinase activity	0.013881	0.04637	CDK1	1

BP = biological process, CC = cellular component, MF = molecular function.

To further identify the key circRNAs participating in the regulatory network, we estibalished the PPI network, screening 7 hubgenes. Then, we established the circRNA-miRNA-hubgene network, including 3 circRNA-miRNA-mRNA axes. To understand the underlying biological processes and pathways between DEmRNAs in the ceRNA network, we performed the GO and KEGG enrichment analyses. The result indicated that the DEmRNAs were involved in many important tumor-associated biological functions.[42,43] However, our study presents several limitations. First, the dataset is relatively small. Second, these DEcircRNAs and their predicted interactions are needed to be validated by experimental methods. In the future, we will perform substantial experiments in vitro and in vivo to verify our findings.

5. Conclusions

We have screened several dysregulated circRNAs and established a circRNA-associated ceRNA network by bioinformatics analysis. The result demonstrated that hsa_circ_0084927 may play important roles in CC, which provides new insight into the pathogenesis and may offer potential therapeutic targets for CC.

Author contributions

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Validation: Jun Gong, Yin-zhi Wei.
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Writing – original draft: Jun Gong, Hui Jiang, Chang Shu, Mei-qin Hu, Yan Huang, Qin Liu, Rong-feng Li, Yin-zhi Wei.
Writing – review & editing: Jun Gong, Hui Jiang, Chang Shu, Mei-qin Hu, Yan Huang, Qin Liu, Rong-feng Li, Yin-zhi Wei.

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