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ORIGINAL ARTICLE

Molecular Network-Based Identification of Circular RNA-Associated ceRNA Network in Papillary Thyroid Cancer

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Abstract

Circular RNAs (circRNAs) have displayed dysregulated expression in several types of cancer. Nevertheless, their function and underlying mechanisms in papillary thyroid cancer (PTC) remains largely unknown. This study aimed to describe the regulatory mechanisms in PTC. The expression profile of circRNA was download from the Gene Expression Omnibus (GEO) database. The mRNA and miRNA data of PTC was downloaded from The Cancer Genome Atlas (TCGA) database. The circRNA-miRNA-mRNA network by Cytoscape. 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. Gene Ontology (GO) and Kyoto Encyclopedia of Gene and Genomes (KEGG) pathway analysis were conducted using R packages "Clusterprofile". We identified 14 differential expression circRNAs (DEcircRNA), 3106 differential expression mRNAs (DEmRNA), 142 differential expression miRNAs (DEmiRNA) and in PTC. Twelve circRNAs, 33 miRNAs, and 356 mRNAs were identified to construct the ceRNA network of PTC. PPI network and module analysis identified 5 hubgenes. Then, a circRNA-miRNA-hubgene subnetwork was constructed based on the 2 DEcircRNAs, 3 DEmiRNAs, and 4 DEmRNAs. GO and KEGG pathway analysis indicated DEmRNAs might be associated with PTC onset and progression. These ceRNAs are critical in the pathogenesis of PTC and may serve as future therapeutic biomarkers.

Keywords Papillary thyroid cancer · circRNA · Competitive endogenous RNA · microRNA

Introduction

An estimated 53,990 new cases of thyroid cancer will be diagnosed in the United States in 2018 [1]. Its incidence rate rose rapidly in recent decades [2]. Papillary thyroid carcinoma (PTC) is the most frequent type of differentiated thyroid cancer, accounting approximately 90% of all the cases [3]. The primary treatment of PTC is still surgical resection, with or without adjuvant radioactive iodine therapy. Despite the rate of survival for PTC being favorable, the risk of recurrence ranges from 5% to 21% in PTC [4, 5]. Therefore, there is a great need for better understanding of the molecular mechanisms of PTC carcinogenesis and novel biomarkers for improving the diagnosis and prognosis of PTC.

As a novel non-coding RNA, circular RNAs (circRNAs) are conserved between different species [6, 7]. CircRNAs are formed by back-splicing covalently joined 3′- and 5′- ends, which makes them resistant to exonucleases and more stable than linear RNA [8, 9]. Like long non-coding RNA (lncRNAs), circRNA could decrease the cytoplasmic levels of target microRNAs (miRNAs) by absorbing the miRNAs, thus liberating mRNA transcripts targeted by aforementioned miRNAs [6, 7]. Accumulating evidence indicated that circRNAs as novel diagnostic and prognostic markers in multiple tumors, such as hepatocellular carcinoma, gastric cancer, and glioblastoma [10–12]. 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

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circumstances [13–15]. However, the expression and function of circRNAs in papillary thyroid cancer (PTC) have rarely been explored. However, little is known about the functions of circRNAs in papillary thyroid cancer (PTC) carcinogenesis.

In the present study, circRNA microarray and RNA-Seq was used to screen PTC 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 PTC and elucidate the possible mechanism involved for new insights of molecular therapy.

Materials and Methods

Data Collection

The papillary thyroid cancer (PTC) genes expression profiles were obtained from GEO (https://www.ncbi.nlm.nih.gov/geo/) databases and the mRNA and miRNA data of PTC was downloaded from TCGA (https://portal.gdc.cancer.gov). The circRNA expression profile of GSE102686 were obtained from GEO database, including 6 PTC tissues and 6 normal tissues. A total of 567 mRNA samples (509 PTC samples and 58 normal samples) and 572 miRNA samples (509 PTC samples and 58 normal samples) from TCGA database.

Explore the Differentially Expressed Genes

The Limma package was used to screen differentailly expressed circRNAs (DEcircRNAs) between PTC tissue and adjacent normal tissue from GEO database (P value <0.01 and $|\log_2 FC| > 2$). Additionally, we used the edgeR package to screen differentially expressed miRNA (DEmiRNA) and mRNA (DEmRNA) with thresholds of $|\log_2(FC)| > 1$ and P value <0.05.

Construction of the ceRNA Network

The Cancer-Specific CircRNA (http://gb.whu.edu.cn/CSCD/) database was used to predict the correlations of miRNA and circRNA. These target miRNAs were further screened by the differently expressed miRNAs (DEmiRNAs) from TCGA database.

In addition, miRNA-targeted mRNAs were retrieved from miRTarBase and TargetScan databases [16, 17]. Only mRNAs recognized by all two databases were considered as candidate mRNAs and intersected with the DEmRNAs to screen out the DEmRNAs targeted by the DEmiRNAs. The ceRNA network was constructed by 3.7.0 software by the correlations between DEcircRNA, DEmiRNA and DEmRNA.

Construction of PPI Network

To assess the interactions between DEmRNAs, we established a PPI network by the Search Tool for the Retrieval of Interacting Genes (STRING). A combined score of >0.9 was considered significant. Cytoscape 3.7.0 was used for visualization. We used the MCODE app to extract hub genes from the PPI network.

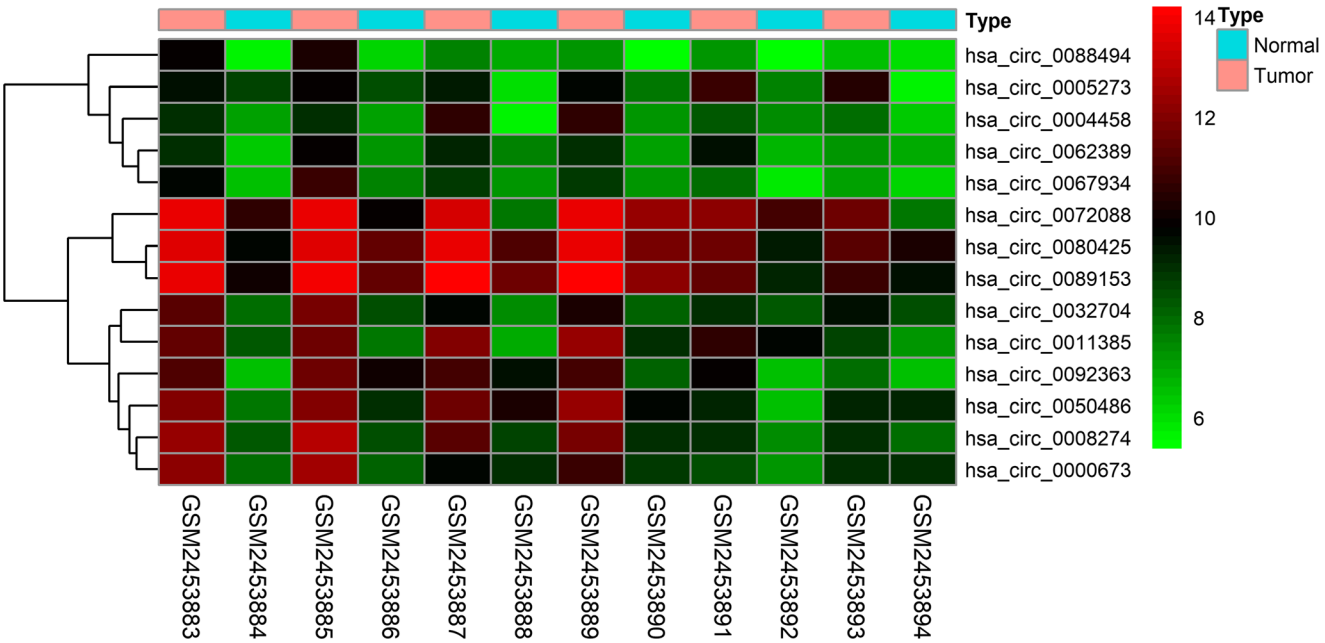

Fig. 1 Heatmap of the differentially expressed circRNAs

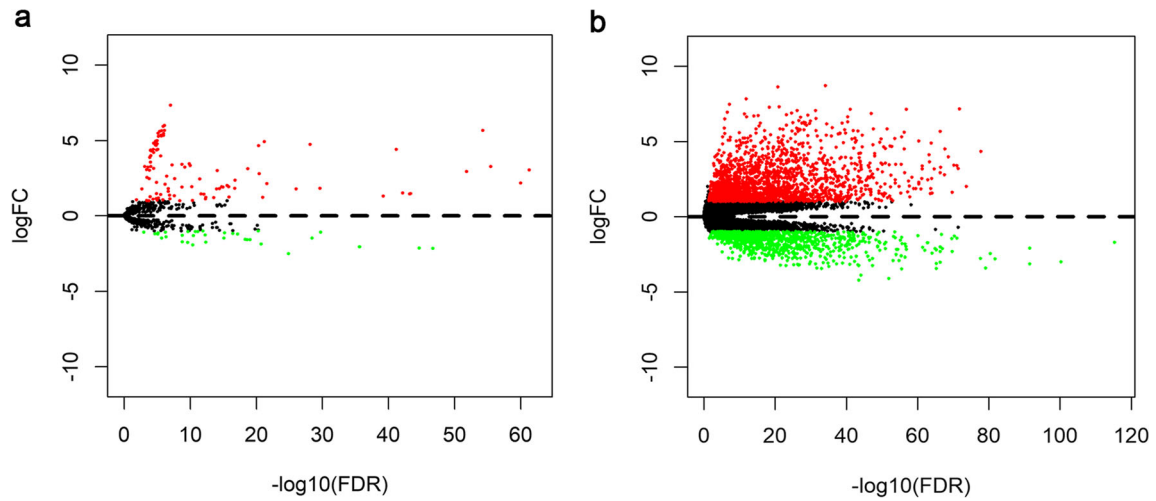

Fig. 2 Volcano plot of differentially expressed miRNAs (**a**) and mRNAs (**b**)

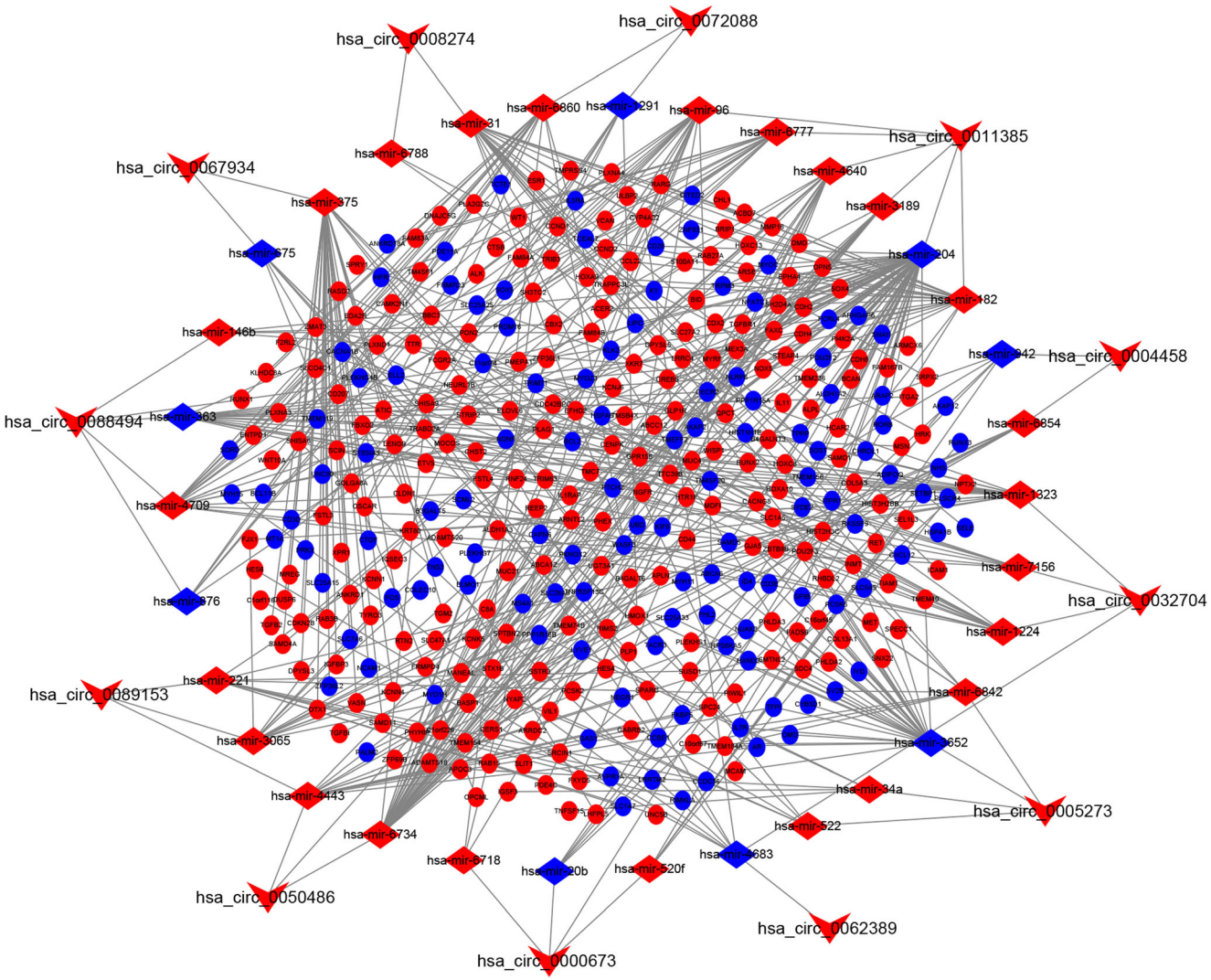

Fig. 3 The ceRNA network of circRNA-miRNA-mRNA in PTC. V indicate circRNA, diamond indicate miRNA, and ellipse indicate mRNA. The nodes highlighted in red and blue represent up-regulation and down-regulation, respectively

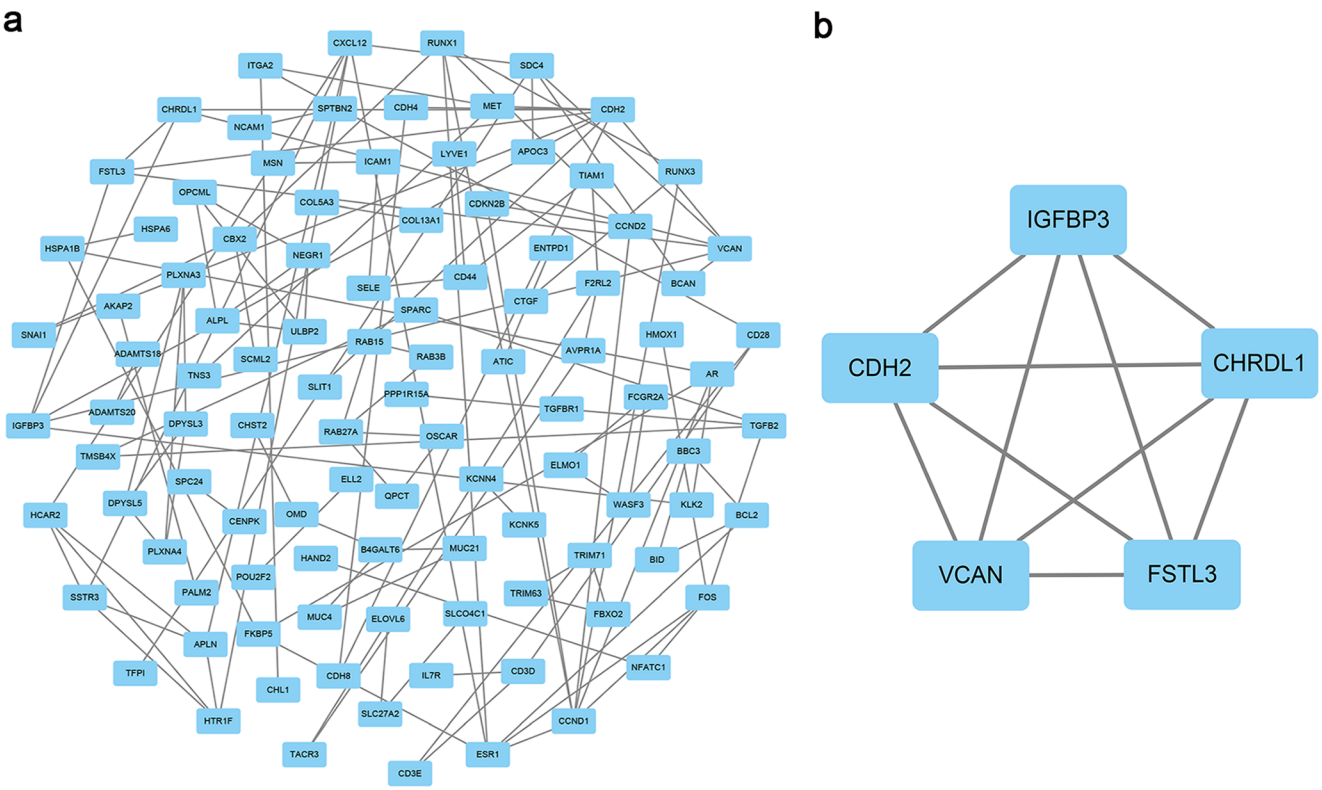

Fig. 4 Identification of hubgenes from the PPI network with the MCODE algorithm. **a**. PPI network of 356 genes. **b**, PPI network of 5 hubgenes that extracted from **a**

Functional Enrichment Analysis

To predict the function of the key circRNA, we performed Gene Ontology (GO) analysis with Gene Ontology Consortium and Kyoto Encyclopedia of Gene and Genomes (KEGG) pathway enrichment analysis using the clusterProfiler package of R software [18]. to analyze the target gene of key circRNA. The entry will be preserved if it was meaningful (*P* value <0.05).

Results

Identification of DEGs

The GSE93522 dataset from GEO was analyzed by the limma package in R (*P* value <0.01 and $\log_2|\text{fold change}| > 2$), we identified 14 upregulated DEcircRNAs (Fig. 1). In addition, a total of 142 DEmiRNAs (108 upregulated and 34 downregulated 57 miRNAs) and 3106 DEmRNAs (1989 upregulated and 1117 downregulated 1968 mRNAs) were identified from TCGA database between PTC tissues and normal thyroid tissues (Fig. 2a and b).

Construction of the ceRNA Network

The CSCD database was used to predict the potential target miRNAs of DEcircRNAs. A total of 616 circRNA-miRNA

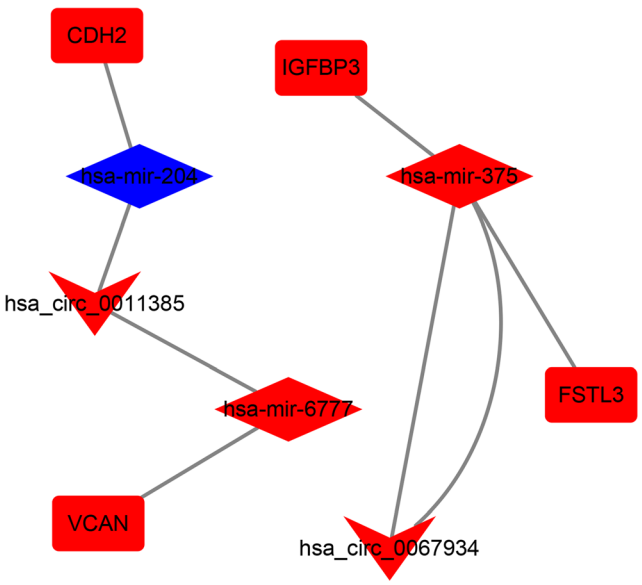

Fig. 5 CircRNA-miRNA-hubgene network. The network consisting of 2 cricRNAs, 3 miRNAs, and 4 hubgenes

pairs were identified. After intersecting with the DEmiRNAs, only 38 circRNA-miRNA pairs, including 12 circRNAs and 33 DEmiRNAs, remained. Furthermore, we used the miRTarBase and TargetScan databases to search for targeted mRNAs based on the 33 DEmiRNAs. Then, the targeted mRNAs were compared to the DEmRNAs and only overlapping genes were selected as candidate genes. The results indicated that 356 DEmRNAs were involved in ceRNA network. Finally, we constructed a ceRNA network based on 12 circRNAs, 33 miRNAs, and 356 mRNAs (Fig. 3).

PPI Network Construction

The STRING database was used to unveil the interrelationships among 356 DEmRNAs by constructing PPI networks. The combined scores >0.900 were selected for constructing PPI networks. After removing unconnected nodes, PPI network included 356 nodes and 683 edges (Fig. 4a). To explore the key circRNA-miRNA-mRNA regulatory modules in the process of PTC carcinogenesis, we used MCODE approach to extract hubgenes from the PPI network. The significant module containing 5 nodes and 10 edges. These hubgenes were IGFBP3, CDH2, CHRDL1, VCAN, and FSTL3 (Fig.4b). After excluding modules with inconsistent expression of circRNA and mRNA, we established a circRNA-miRNA-hubgene subnetwork (Fig. 5), including 4 subnetwork regulatory modules (hsa_circ_0011385-hsa-mir-204-CDH2, hsa_circ_0011385-hsa-mir-6777-VCAN, hsa_circ_0067934- hsa-mir-375-IGFBP3, and hsa_circ_0067934-hsa-mir-375-95-FSTL3).

Functional Enrichment Analysis of DEmRNA

According to GO analysis, we found that the most enriched GO terms in Biological Process (BP) were ossification and post-translational protein modification; In terms of cellular components (CC), DEmRNAs were mostly enriched in endoplasmic reticulum lumen; Among the 12 molecular function (MF) terms, the most enriched GO terms were fibronectin binding ($P < 0.05$). The top 5 GO terms are indicated in Table 1. Moreover, KEGG pathway analysis indicated that most of DEmRNAs are involved in p53 signaling pathway, cell adhesion molecules (CAMs), cellular senescence, and transcriptional misregulation in cancer.

Discussion

CircRNA is abundant in eukaryotic cells at a high degree conservative, structurally stable, with a certain degree of organization, timing and disease-specific [19, 20]. Based on these features, circRNAs have become new hotspots. CircRNAs can regulate the expression of gene at transcriptional or posttranscriptional [21, 22]. In recent years, an increasing number of researches have reported that the abnormal expression and regulation of circRNAs can affect the occurrence and course of cancers, thus have the potential to serve as biomarkers of malignancies [23, 24]. However, the exact role of circRNAs in PTC remains largely unclear. In this study, we firstly integrated circRNA, miRNA, and mRNA data between PTC tissues and non-tumor tissues from GEO and TCGA database and constructed the circRNA-miRNA-mRNA regulatory network.

CircRNAs have been found to regulate thyroid cancer cell proliferation, apoptosis and invasion by targeting miRNAs. For example, circNEK6, plays a role as a miR-370-3p sponge to promote the progression of thyroid cancer through up-regulating FZD8 and activating Wnt signaling pathway [25]. Wei et al. [26] showed that circZFR was significantly

Table 1 The top 5 GO terms enriched by DEmRNA involved in the ceRNA network

Categories	Terms	Description	*P* value	P-adjusted	Genes	Counts
BP	GO:0001503	Ossification	9.44E-07	0.000119	IGFBP3/CHRDL1/VCAN/FSTL3	4
	GO:0043687	Post-translational protein modification	1.90E-06	0.00012	IGFBP3/CHRDL1/VCAN/FSTL3	4
	GO:0030514	Negative regulation of BMP signaling pathway	8.14E-05	0.003418	CHRDL1/FSTL3	2
	GO:0030510	Regulation of BMP signaling pathway	0.000249	0.007839	CHRDL1/FSTL3	2
	GO:0090101	Negative regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	0.00043	0.010833	CHRDL1/FSTL3	2
CC	GO:0005788	Endoplasmic reticulum lumen	3.08E-07	2.16E-06	IGFBP3/CHRDL1/VCAN/FSTL3	4
MF	GO:0001968	Fibronectin binding	1.26E-05	0.000177	IGFBP3/FSTL3	2
	GO:0019211	Phosphatase activator activity	0.002505	0.010361	IGFBP3	1
	GO:0048185	Activin binding	0.002733	0.010361	FSTL3	1
	GO:0031994	Insulin-like growth factor I binding	0.00296	0.010361	IGFBP3	1
	GO:0005540	Hyaluronic acid binding	0.005006	0.014016	VCAN	1

upregulated in PTC tissues compared to adjacent normal tissues. Elevated circZFR expression was negatively associated with clinical severity. Silence of circZFR reduced cell proliferation, migration and invasion of PTC cells. Furthermore, they found that circZFR can regulate the expression of C8orf4 by sponging miR-1261, leading to PTC development and progression. Similarly, Liu [27] found that circEIF6 acts as the sponge of miR-144-3p to promote the cisplatin-resistance of human thyroid cancer cells by autophagy regulation. In our study, a total of 14 circRNAs were identified involved in the ceRNA network. Among them, elevated hsa_circ_0004458 expression can promote progression of PTC by inhibition of miR-885-5p and activation of RAC1 [28]. In addition, dysregulated hsa_circ_0067934 and hsa_circ_0000673 expression are associated with the pathogenesis in gastric caner, esophageal squamous cell carcinoma, and hepatocellular carcinoma [29, 30]. However, none of the other 11 circRNAs have been reported.

MicroRNAs (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 (UTRs), resulting in translation repression or mRNA degradation [32]. It is known that the regulation of miRNAs is indispensable in tumor-related pathways, which are involved in oncogenesis and the development of tumors [33]. In this study, we indentified 33 DEmiRNAs in the ceRNA network. Several miRNAs have been reported to play important roles in the initiation and development of thyroid cancer, such as miR-96, miR-182, and miR-204 [34–36]. For example, miR-96 participates in the development and progression of PTC as an oncogene by inhibiting the FOXO1 and regulating AKT/FOXO1/Bim pathway [34]. Spitschak et al. [35] reported that miR-182 promotes medullary thyroid cancer invasion by linking RET oncogene activated NF-κB to loss of the HES1/Notch1 regulatory circuit.

To further identify the key circRNAs participating in the regulatory network, we estibalished the PPI network, screening 5 hubgenes. Then, we established the circRNA-miRNA-hubgene network, including 4 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 thyroid cancer-associated biological functions and pathways [37, 38].

Conclusions

Our study indicated that hsa_circ_0011385 and hsa_circ_0067934 may play important roles in PTC, which provides new insight into the pathogenesis and may offer potential therapeutic targets for PTC.

Author's Contributions Conceived and designed the experiments: QL, LZP, and JYM. Performed the experiments: QL, LZP, and MH. Analyzed the data: QL, LZP, and JYM. Contributed reagents/materials/analysis tools: QL, LZP, and MH. Wrote the paper: all authors.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Ethics Approval Ethical approval was not required in this study due to the public-available data.

Informed Consent The data did not include the use of human subjects or personal identifying information. Thus, no informed consent was required for this part of the study.

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