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Circular RNAs in atrial fibrillation: From bioinformatics analysis of circRNA-miRNA-mRNA network to serum expression

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ABSTRACT

Atrial fibrillation (AF) is a common arrhythmia in clinical practice, and its incidence is increasing year by year, which seriously affects the survival and prognosis of patients. In recent years, circRNAs has played an important role in the diagnosis and treatment of AF. The purpose of this study was to search for differentially expressed circRNAs(DEcircRNAs) in the serum of AF patients by analyzing the expression profile of existing chips, combining bioinformatics technology and in vitro experiments, and to explore the regulatory mechanism of circRNAs in the occurrence and development of AF. By using the AF datasets in the Gene expression omnibus (GEO) database, serum samples of patients with AF were collected, and the expression level of selected circRNAs was verified by qPCR. We found that the expression of four circRNAs was increased in the serum of patients with AF, suggesting that these four DEcircRNAs may be used as auxiliary diagnostic markers for AF. Bioinformatics predicts the related signaling pathways that differentially expressed genes may regulate in the occurrence and development of AF, providing a new theoretical basis for the molecular mechanism of the occurrence of atrial fibrillation and auxiliary diagnostic targets.

1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice, and its incidence is increasing year by year, which has a higher risk of sudden death [1,2]. The risk factors of AF are closely related to cardiovascular diseases, among which organic or functional heart problems are more common. Furthermore, age, gender and genetic factors are also important factors leading to the occurrence of AF [3,4]. In addition, Coronary artery bypass grafting (CABG), mainly uses the body's own blood vessels or vascular substitutes to connect the distal end of the narrowed or blocked coronary artery to the aorta, allowing blood to bypass the narrowed or blocked place and reach the ischemic site. Improve the blood supply of the myocardium, thereby alleviating the symptoms of angina pectoris and improving heart function [5,6]. However, AF is a relatively common arrhythmia in the early stage after coronary artery bypass grafting, and despite great advances in medical technology and postoperative care, the overall incidence of post-operative AF has not improved significantly [7,8]. Therefore, it is of great clinical significance to study the underlying mechanism of the occurrence and development of AF.

CircRNAs are a class of non-coding RNAs, which are formed by laroses connecting the upstream 5′ and downstream 3' ends to form a ring structure, and play an important regulatory role in many biological functions. Due to their unique circular structure, circRNAs are not susceptible to the influence of exonuclease and are stable in a variety of biological samples, making them potential biomarkers for auxiliary diagnosis and prognostic monitoring of a variety of diseases [9,10]. At present, the development of high-throughput sequencing technology and the advancement of bioinformatics analysis have laid the foundation for the research of circRNAs in AF [11,12]. Therefore, in-depth exploration of the regulatory pathways and mechanisms of circRNAs in AF provides a new basis and target for the diagnosis and treatment of AF, which has great clinical application value and prospects.

Our hypothesis in this study was that the differentially expressed circRNAs in serum may be an influential factor in the occurrence of AF. We analyzed the circRNAs microarray expression profiles of serum samples from 15 patients with AF after CABG and myocardial tissue from 3 patients with AF, and screened out 9 differential expressed circRNAs (Table 1). Combined with real-time fluorescence quantitative PCR (RT-PCR), we determined 4 circRNAs with increased expression in serum of newly diagnosed AF patients. Considering that these DEcircRNAs are increased in the serum of patients with AF after CABG and

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Table 1
Differentially expressed circRNAs.

circRNA	circBase ID	Gene symbol	Position	Genomic Length
CircTADA2A	hsa_circ_0043278	TADA2A	chr17:35797838–35800763	2925
Circ RPPH1	hsa_circ_0000511	RPPH1	chr14:20811282–20811431	149
Circ RPPH1	hsa_circ_0006853	RPPH1	chr14:20811282–20811360	78
Circ RPPH1	hsa_circ_0000514	RPPH1	chr14:20811305–20811436	131
Circ ZNF646	hsa_circ_0000691	ZNF646	chr16:31093273–31093358	85
Circ RPPH1	hsa_circ_0000512	RPPH1	chr14:20811282–20811436	154
Circ TADA2A	hsa_circ_0006220	TADA2A	chr17:35800605–35800763	158
Circ RPPH1	hsa_circ_0000515	RPPH1	chr14:20811305–20811534	229
Circ FAM120B	hsa_circ_0001666	FAM120B	chr6:170626457-170639638	13181

Table 2
Primer sequences used for qRT-PCR analysis of circRNA levels.

Gene name	Primer sequences (F:5′-3′)	Primer sequences (R:5′-3′)
hsa_circ_0043278	AGCCATTCCATTTCACTACTTCA	TCCTGCCAATTTCCAAAGCC
hsa_circ_0000511	GAACAGACTCACGGCCAGCGAAGTGAGTTC	GAACTCACTTCGCTGGCCGTGAGTCTGTTC
hsa_circ_0001666	GATGACCATTCCAGATCCTTTTTCAAGAGA	AAAGGATCTGGAATGGTCATCTTTTT
hsa_circ_0006220	CTACCCTGCTGAACCTGAAACA	TTCTCACACTCCTCCTTGGTCTT
GAPDH	CCCTTCATTGACCTCAACTA	TGGAAGATGGTGATGGGATT

also in the serum of patients with newly diagnosed AF, we hypothesized that these DEcircRNAs may be involved in the occurrence and progression of AF. Therefore, we used bioinformatics to construct competitive endogenous RNA (ceRNA) models of these DEcircRNAs to predict the potential regulatory mechanisms in the occurrence of AF, in order to provide new ideas for the diagnosis and treatment of AF.

2. Materials and methods

2.1. Collection and processing of gene expression profile data

The GSE129409 and GSE97455 datasets were obtained from the Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo) database. The GSE129409 dataset collected the heart tissues from three AF patients and three healthy controls and profiled their circRNA expressions with circRNA Microarray. The GSE97455 dataset contains 15 plasma samples with postoperative AF and 15 plasma samples without postoperative AF. The R software (version 3.6.3) was used to process and analyze the original data. The limma package was used to perform background correction on the original data. The DESeq package was employed to detect DEcircRNAs with thresholds of $|\log2FC| \geq 1$ and P-value$\leq$0.05. False discovery rate (FDR) was used to correct the statistical significance of all p-values.

2.2. Sample collection and storage

20 serums of AF patients and 20 serums of healthy donors were obtained from the Aoyang Hospital affiliated to Jiangsu University. In this study, all patients were newly diagnosed with AF, and the control group was healthy people. Specimens were collected from January 2021 to May 2021. Serum samples were divided into RNase-free tubes and store at −80 °C until use to extract total RNA.

2.3. RNA extraction, reverse transcription, and quantitative real-time polymerase chain reaction

Total RNA was extracted using the serum RNA extraction Kit (Bio-Teke), and complementary DNA (cDNA) was synthesized by reverse transcription Kit (Thermo Fisher Scientific) and specific primers. The relative expression level of circRNAs was determined by Roche LightCycler 480. The internal control GAPDH was used to standardized the expression of circRNAs, and the relative expression were calculated by the $2^{-\Delta\Delta Ct}$ methods. Primer sequences are provided in Table 2.

2.4. Functional and pathway enrichment analysis

The target genes of DEcircRNAs were predicted using the Cancer Specific CircRNA Database (CSCD, http://gb.whu.edu.cn/CSCD/) based on the validated target module. The target genes of each circRNAs were subjected to Gene Ontology (GO) functional enrichment analysis and kyoto Encyclopedia of Genes and Genomes (KEGG) pathways enrichment analysis was performed using the ClusterProfiler package of R software. P-value<0.05 was considered significant.

2.5. Construction of ceRNA regulatory network

Based on ceRNA theory, CircInteractome database was used to predict miRNAs that have regulatory relationships with circRNAs. miRDB database was used to predict mRNAs that have regulatory relationships with miRNAs. Meanwhile, differentially expressed miRNAs in GSE68475 and mRNAs in GSE64904 were analyzed. The predicted results were respectively intersected with the differentially expressed miRNAs and mRNAs screened from the databse, and the regulatory networks of differentially expressed circRNAs, miRNAs and mRNAs were visualized using Cytoscape software.

2.6. Statistical analysis

SPSS statistics software version 20.0 was served as the statistical analysis. Mean ± standard deviation was used to represent measurement data with normal distribution. T-test was used to compare and analyze the data subject to normal distribution.

3. Results

3.1. Identification of differentially expressed genes (DEGs) in AF

We obtained the circRNA Microarray from datasets GSE129409 and GSE97455 in the GEO database. The dataset GSE12949 collected the heart tissues from three AF patients and three healthy controls, the

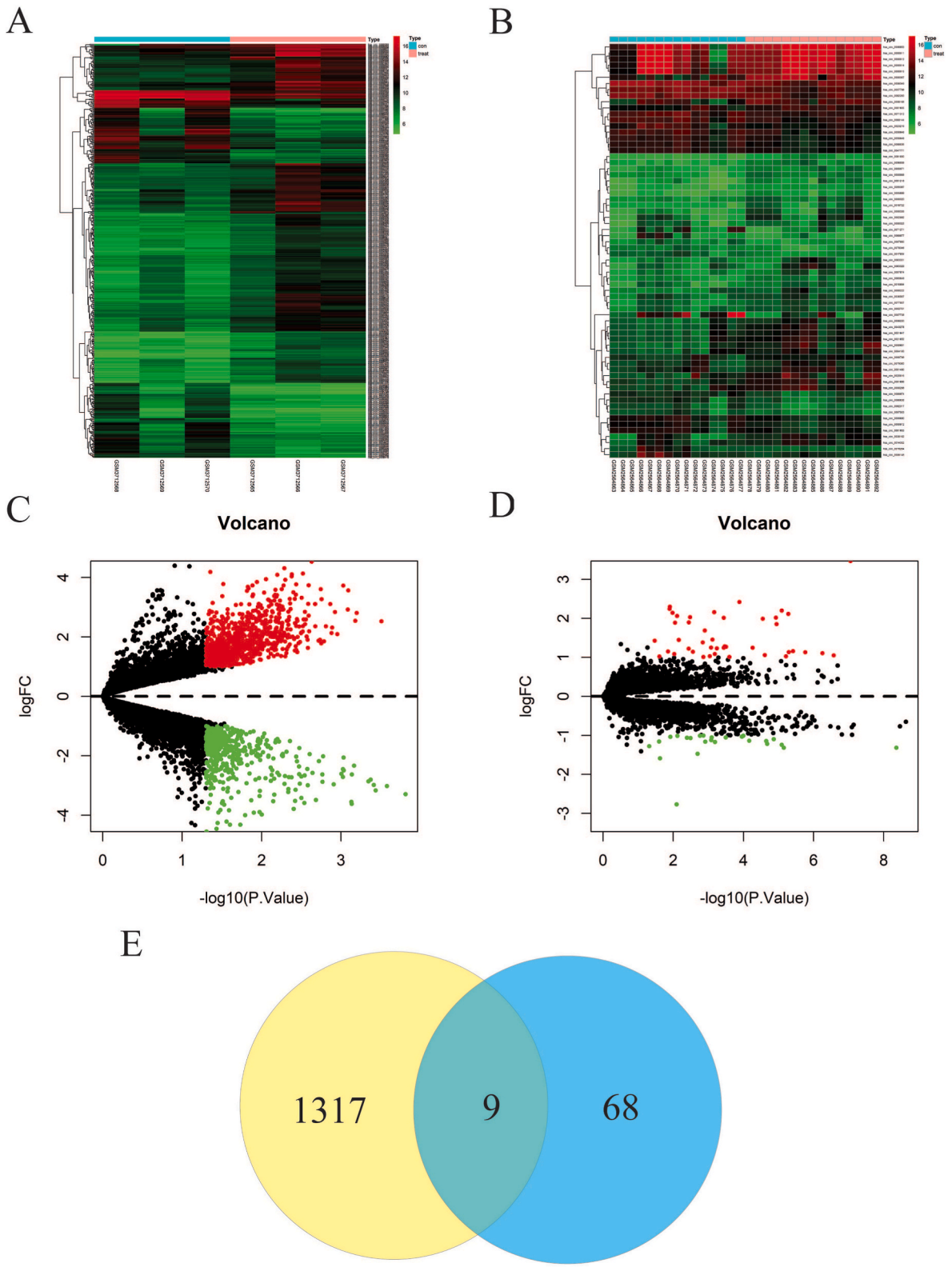

Fig. 1. DEcircRNAs in AF. A,C: volcano maps and heat maps of the DEcircRNAs in GSE129409; B,D: volcano maps and heat maps of the DEcircRNAs in GSE97455; E: The Venn diagram indicated that 9 circRNAs were found AF.

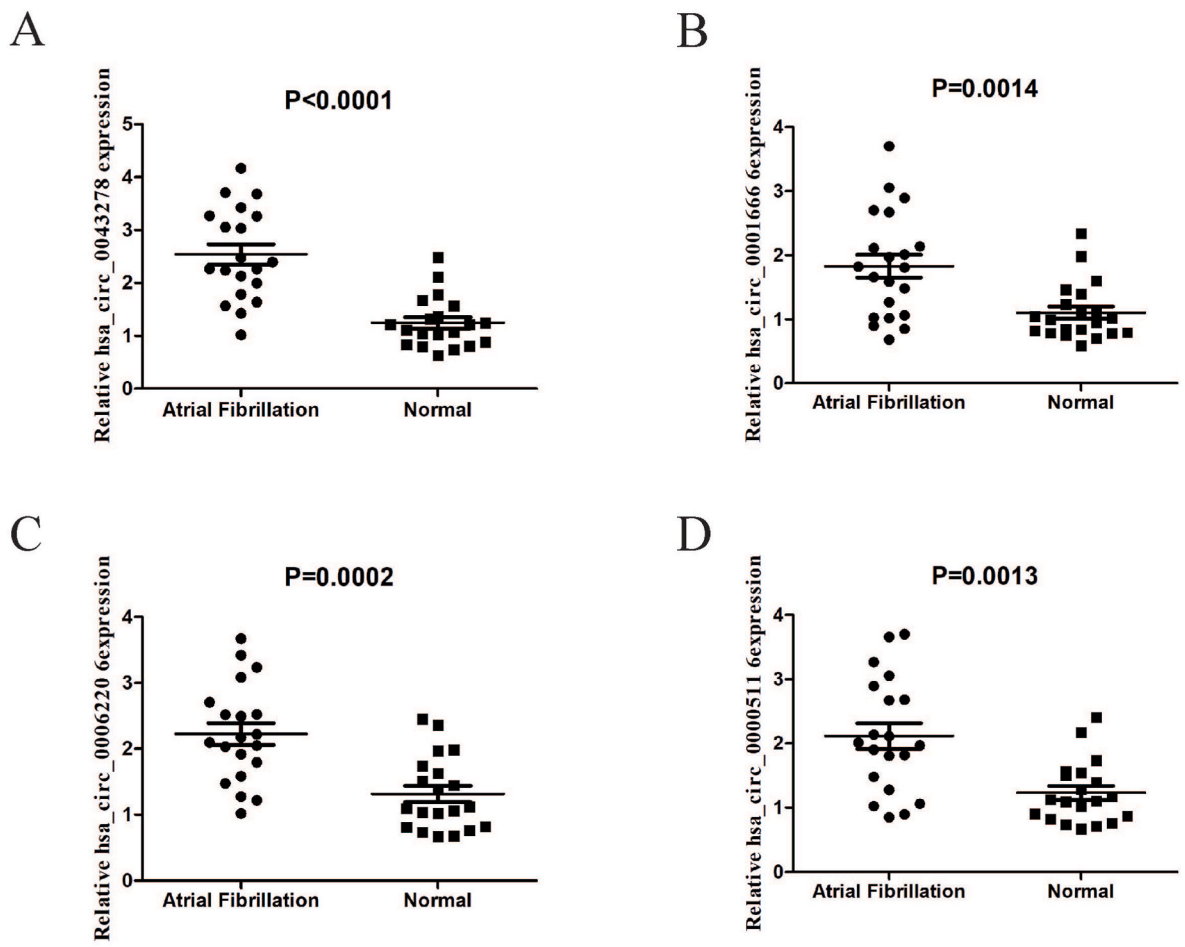

Fig. 2. 4 DEcircRNAs in the serum of patients with AF. A: hsa_circ_0043278 was increased in AF; B: hsa_circ_0001666 was increased in AF; C: hsa_circ_0006220 was increased in AF; D: hsa_circ_0000511 was increased in AF.

dataset GSE97455 contained 15 patients without postoperative (isolated off-pump coronary artery bypass grafting) AF and 15 patients with postoperative AF. With the cutoff criteria set at P value < 0.05 and $|\log2FC|>1$, we identified 1317 DEcircRNAs in dataset GSE129409 and 68 DEcircRNAs in dataset GSE97455. The expression volcano maps and heat maps of the DEcircRNAs are shown in Fig. 2A–D. Furthermore, we draw a Venn diagram to find the common changed circRNAs and 9 circRNAs were observed to be improved in the datasets GSE129409 and GSE97455 (Fig. 1, Table 1). Through comparative analysis of these datasets, we hypothesized that these 9 DEcircRNAs may serve as auxiliary diagnostic markers for monitoring the occurrence and recurrence of AF.

3.2. qRT-PCR validation of differentially expressed circRNAs

qRT-PCR was used to verify the relative expression levels of 9 differentially expressed circRNAs (hsa_circ_0043278, hsa_circ_0000511, hsa_circ_0006853, hsa_circ_0000514, hsa_circ_0000691, hsa_circ_0000512, hsa_circ_0006220, hsa_circ_0000515 and hsa_circ_0001666) in the serum of patients with AF, and the results showed that the expression levels of 4 circRNAs (hsa_circ_0043278, hsa_circ_0000511, hsa_circ_0006220 and hsa_circ_0001666) in the serum of patients with AF were higher than that of normal control group, and the differences were statistically significant. In the future, we will conduct in-depth studies on these 4 differentially expressed circRNAs (Fig. 2A–D).

3.3. GO and KEGG pathway analysis

In order to study the regulatory mechanism of differentially expressed circRNAs in patients with AF and the occurrence of AF, we used the CSCD database to predict the downstream target genes with potential regulatory relationship with circRNAs, and predicted the regulatory pathways that circRNAs may participate in through GO and KEGG pathway analysis (Figs. 3 and 4).

3.4. ceRNA regulatory network

Most circRNAs are mainly located in cytoplasm, so circRNAs can compete with endogenous RNA as a miRNA molecular sponge to regulate miRNA target gene expression. Based on ceRNA theory, circRNA-miRNA-mRNA ternary interaction network is constructed and prognostic analysis is performed. Screening a new target for prognosis assessment after clinically assisted diagnosis of AF. First, 41 DEmiRNAs in the tissues of patients with AF were screened out using dataset GSE68475, and 132 DEmRNAs in the serum of patients with AF were screened out using dataset GSE64904. Then, we used CircInteractome

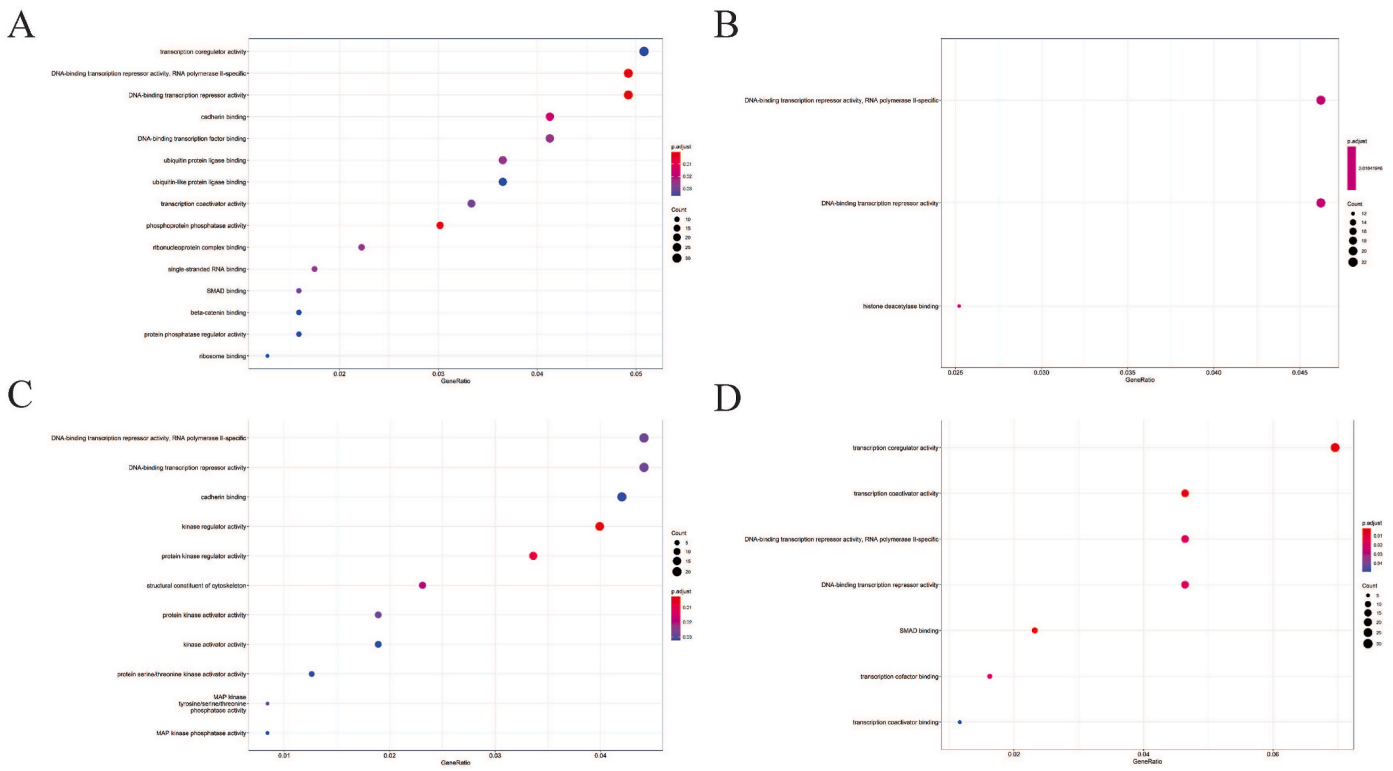

Fig. 3. GO analysis of 4 DEcircRNAs. A: GO analysis of hsa_circ_0043278; B: GO analysis of hsa_circ_0001666; C: GO analysis of hsa_circ_0006220; D: GO analysis of hsa_circ_0000511.

database to predict the miRNAs that have regulatory relationships with circRNAs, and intersected the differential miRNAs screened by GSE68475 to obtain a total of 8 DEmiRNAs. Similarly, we used miRDB database to predict mRNAs that have regulatory relationships with miRNAs, and took intersection with differential mRNAs screened by GSE64904. Finally, 4 circRNAs, 8 miRNAs and 35 mRNAs were constructed for ceRNA network (Figs. 5 and 6, Table 3).

4. Discussion

AF is the most common persistent arrhythmia. The incidence of AF increases with age. When AF occurs, blood is easy to stagnate in the heart chamber and form thrombus. Once the thrombus falls off, it can flow to the whole body with the blood, resulting in vascular embolism and even life-threatening. At present, AF is mainly treated by drug therapy, electrical cardioversion and surgery, but the prognosis of patients is still not ideal. With the rapid development of high-throughput sequencing technology and bioinformatics analysis, circRNAs played an important regulatory role in the occurrence and development of human diseases. The ceRNA hypothesis, originally proposed by Salmena et al., suggests that miRNAs can affect RNA expression at the post-transcriptional level by binding to target genes, and conversely, target genes can affect miRNAs [13]. At present, a variety of ceRNAs have been found, including mRNA, circRNA, and lncRNA. All of them contained miRNA response elements (MREs). circRNA, as a new research hotspot in the ceRNA family, also has MREs, which can competitively inhibit the function of miRNA and play the role of RNA sponge, blocking and inhibiting the binding of miRNA and target genes, thereby leading to mutual regulation. CircRNAs can be stably expressed in all kinds of samples due to their unique ring structure, and there are differences in expression among different patients, which is expected to be a new strategy for the diagnosis and treatment of AF (Fig. 7). Liu et al. using bioinformatics tools as well as literature review, constructed the circRNA-miRNA-mRNA ceRNA network related to AF fibrosis. qPCR valiated the expression of hsa_circ_0000672 in peripheral blood monocytes of patients with persistent AF was significantly higher than that of controls. The dual luciferase activity experiment confirmed that hsa_circ_0000672 functioned as a sponge for miR-516a-5p and regulated the expression of its target gene TRAF6. hsa_circ_0000672 may indirectly regulate TRAF6 by absorbing miR-516a-5p as ceRNA to participate in atrial fibrosis [14]. Wu et al. found that hsa_circ_0099734 was significantly less expressed in atrial tissue of patients with AF than in normal tissue. Mechanistic studies have shown that has_circ_0099734 can competitively bind miR-499-5p to promote the expression of Kcnd1, Kcnd3, Scn5a and Kcnn3, thereby playing a protective role in the development of AF [15]. In addition, circRNA was associated with cardiac fibrosis and plays an important role in the malignant progression of AF. By analyzing the differentially expressed circRNA in the plasma of 6 patients with persistent AF and 6 patients with paroxysmal AF, hsa_circ_0004104 was confirmed to be down-regulated in patients with persistent AF. Mechanism study found that hsa_circ_0004104 was negatively correlated with TGF-β1. While TGF-β1 is a known marker of atrial fibrosis, low expression of has_circ_0004104 may affect myocardial fibrosis by regulation, possibly by targeting the MAPK and TGF-β

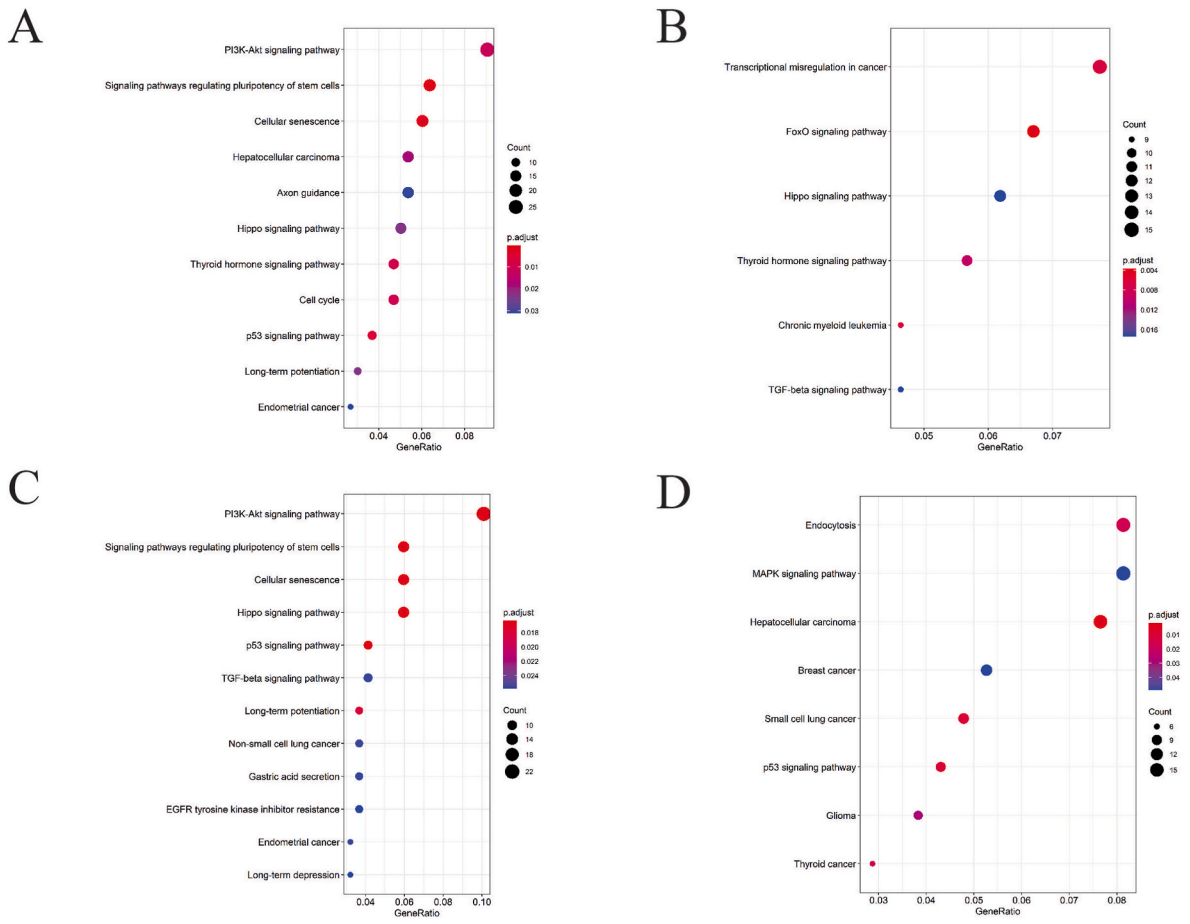

Fig. 4. KEGG analysis of 4 DEcircRNAs. A: KEGG analysis of hsa_circ_0043278; B: KEGG analysis of hsa_circ_0001666; C: KEGG analysis of hsa_circ_0006220; D: KEGG analysis of hsa_circ_0000511.

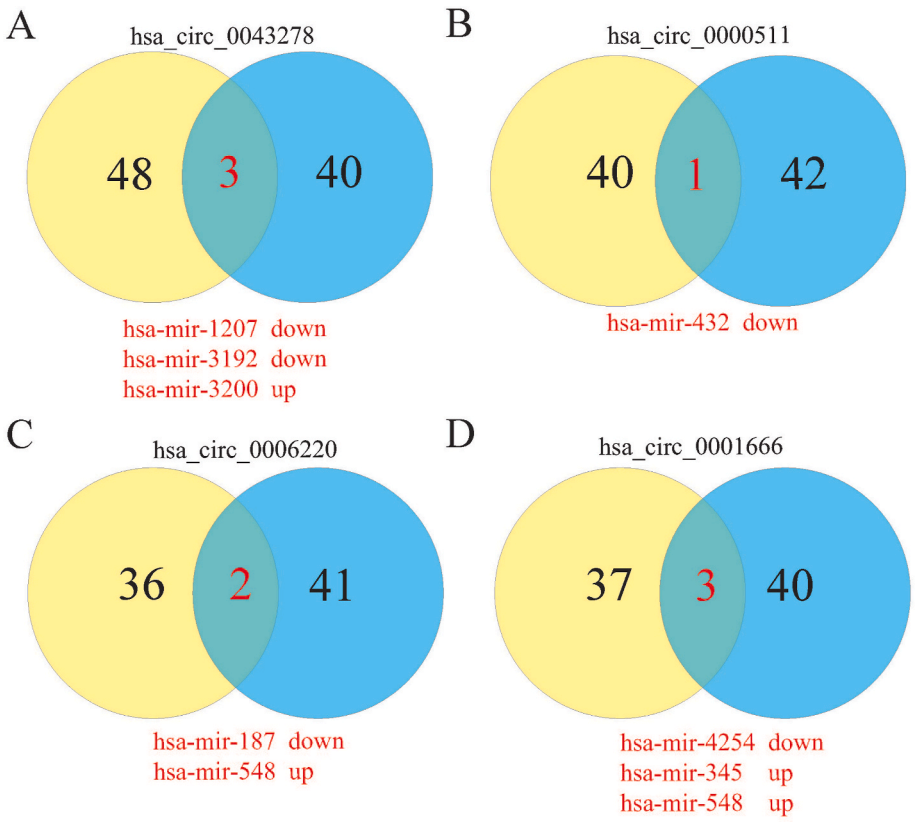

Fig. 5. Venn diagram for circRNAs and miRNAs. A: CircInteractome database and GSE68475 to predict the hsa_circ_0043278's miRNAs; B: CircInteractome database and GSE68475 to predict the hsa_circ_0000511's miRNAs; C: CircInteractome database and GSE68475 to predict the hsa_circ_0006220's miRNAs; D: CircInteractome database and GSE68475 to predict the hsa_circ_0001666's miRNAs.

pathways. These studies suggest that has_circ_0004104 is of great significance in predicting the malignant progression of AF [16]. Zhang et al. found that circCAMTA1 was upregulated in atrial muscle tissue from patients with AF and in angiotensin-II (Ang-II) -treated human atrial fibroblasts (HAFs). In vitro and in vivo experiments showed that knockdown of circCAMTA1 significantly inhibited Ang–II–induced HAFs proliferation and decreased the expression of atrial fibrosis-related genes, while reducing the incidence and duration of AF. The mechanism study showed that circCAMTA1 promoted Ang–II–induced atrial fibrosis by down-regulating the inhibitory effect of miR-214-3p on the expression of transforming growth factor β receptor 1 (TGFBR1). circCAMTA1/miR-214-3p/TGFBR1 axis may be a new target for the clinical treatment of AF [17].

Our study mainly aims to screen out circRNAs related to the occurrence and development of AF, and provide new ideas and directions for the diagnosis and treatment. By analyzing the circRNAs expression levels in serum of patients with AF after CABG, we found 68 differentially expressed circRNAs, and we speculated that these DEcircRNAs might be involved in the occurrence of AF. Then, we analyzed the expression level of circRANs in cardiac tissue of patients with AF, and screened out more than 1317 DEcircRNAs. By comprehensive analysis of the two datasets, a total of 9 circRNAs were screened out with the same expression level in the two databases. RT-PCR was used to verify the expression levels of these circRNAs in serum of newly diagnosed patients with AF, and the results showed that the expression levels of 4 circRNAs were consistent with the sequencing results. Due to the particularity of the samples in these two datasets, the four differentially expressed circRNAs we screened and verified may be involved in the occurrence of AF, and can also be used to indicate the possibility of AF recurrence after CABG and guide clinical preventive measures to improve the prognosis of patients. In order to further investigate the potential regulatory mechanism of these 4 DEcircRNAs in the occurrence and development of AF, we performed the GO and KEGG pathway analyses of DEmRNAs in the ceRNA network. Using dataset GSE68475 and GSE64904 to screen out DEmiRNAs and DEmRNAs in the tissues and plasma of AF patients. DEcircRNAs may competitively bind miRNAs, thereby affecting the expression of downstream target genes, thereby regulating certain signaling pathways and affecting the prognosis of patients with AF. By analyzing the interaction between circRNA-miRNA-mRNA, and constructing the regulation model of ceRNA, it is expected to provide theoretical basis for the early diagnosis and prognosis monitoring of AF. Furthermore, as a drug carrier, nanomaterials have been widely studied in cancer therapy [18]. These materials not only have the advantages of stability and biocompatibility, but also have certain tumor targeting. In future studies, we will further expand the sample size and explore the reliability of these regulatory pathways through in vitro and in vivo experiments. At the same time, nanocarriers combined with circRNAs interference plasmids were used to target and efficiently transport plasmids to tumor sites, and it is expected that the circRNAs we screened can be better applied in clinical treatment and prognosis assessment.

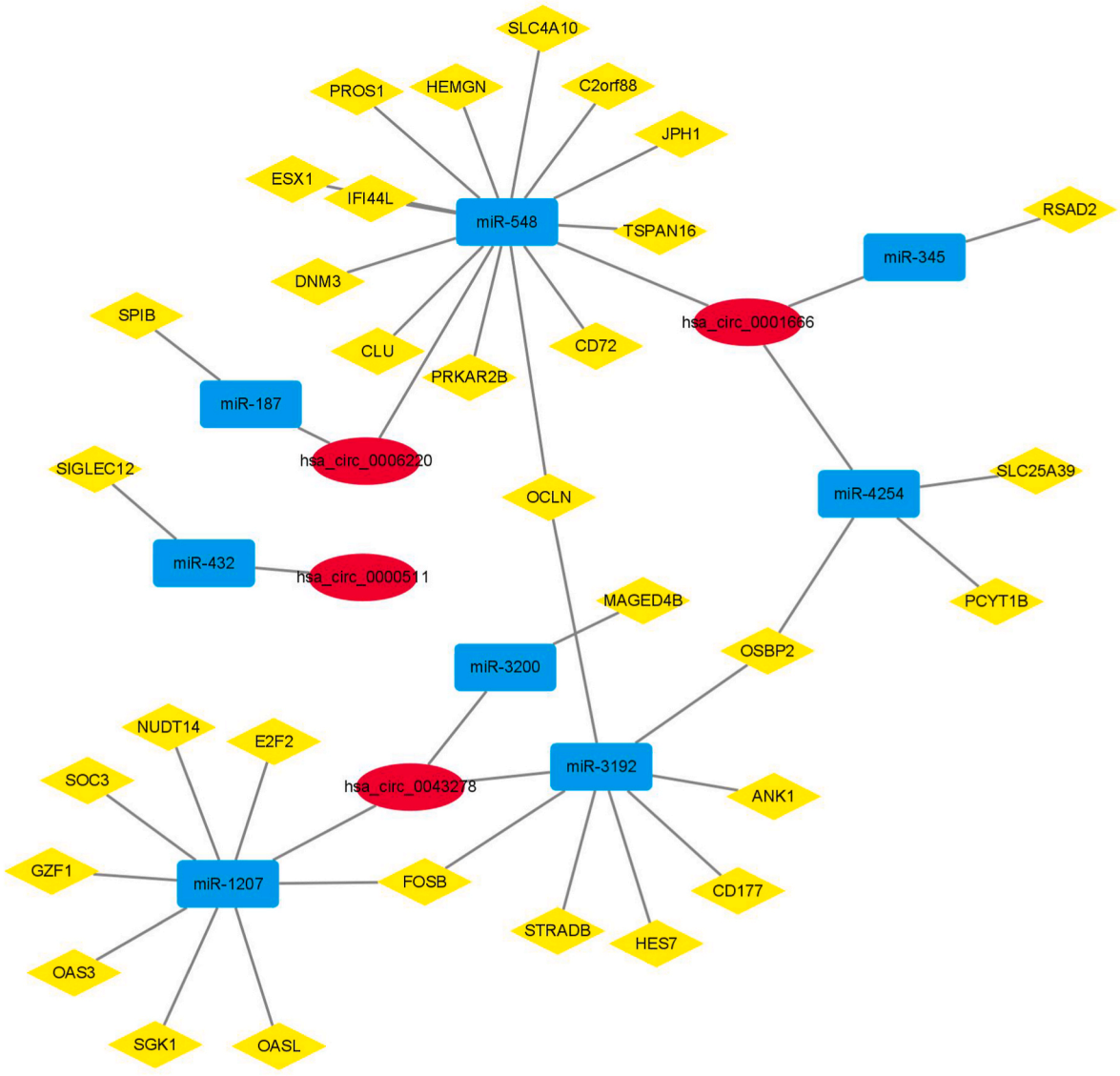

Fig. 6. The circRNA-miRNA-mRNA network of AF.

Table 3
The construction of ceRNA network through circRNAs-miRNAs-mRNAs.

circRNA	miRNA	mRNA
hsa_circ_0043278	miR-1207	OAS3,SGK1,FOSB, OASL,NUDT14,E2F2,SOCS3,GZF1
	miR-3192	STRADB,CD177,OCLN, OSBP2,ANK1,HES7,FOSB
	miR-3200	MAGED4B
hsa_circ_0000511	miR-432	SIGLEC12
hsa_circ_0006220	miR-187	SPIB
	miR-548	TSPAN16,PRKAR2B,OCLN, HEMGN,C2orf88,CLU, DNM3,PROS1,JPH1,ESX1,CD72,SLC4A10,IFI44L
hsa_circ_0001666	miR-4254	OSBP2,SLC25A39,PCYT1B
	miR-345	RSAD2
	miR-548	TSPAN16,PRKAR2B,OCLN, HEMGN,C2orf88,CLU, DNM3,PROS1,JPH1,ESX1,CD72,SLC4A10,IFI44L

5. Conclusions

In this study, we identified four circRNAs that are up-regulated in the plasma of AF patients by PCR, and the highly expressed circRNAs may have a certain role in the diagnosis and prognosis evaluation of AF. Combined with bioinformatics analysis, the ceRNA regulatory network of differentially expressed circRNAs (DEcircRNA) was constructed. GO functional enrichment and KEGG pathway showed that these DEcircRNAs affected the occurrence and development of AF mainly by participating in PI3K-AKT signaling pathway and MAPK signaling pathway. These findings provide a theoretical basis for us to further investigate circRNA as an adjuvant therapy in AF.

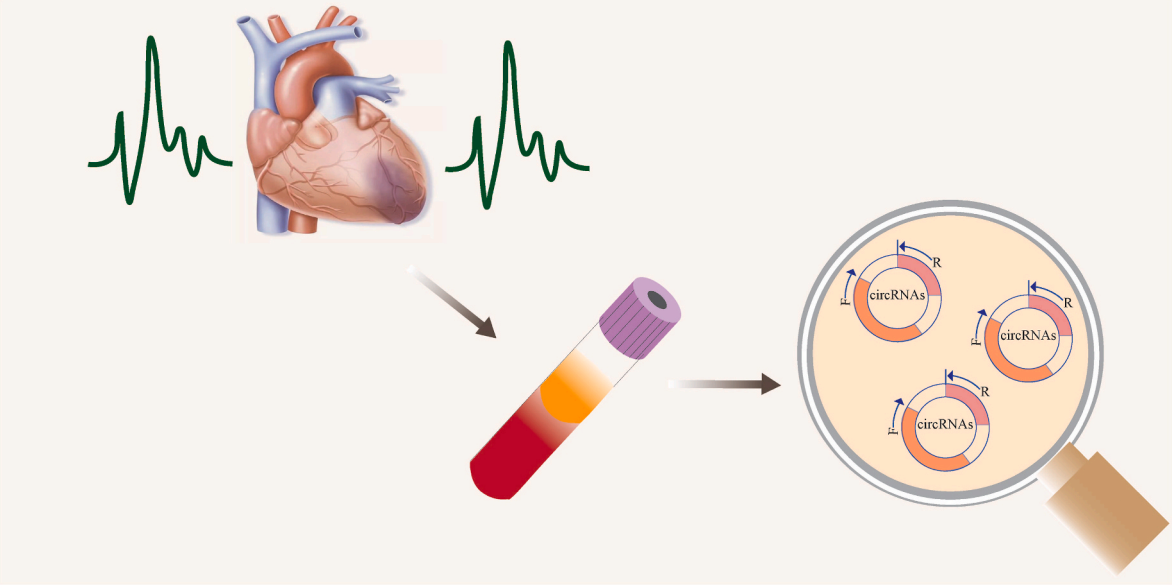

Fig. 7. DEcircRNAs may be involved in the occurrence and progression of AF.

Ethics statement

Approval was obtained from the Medical Ethics Committee of Aoyang Hospital affiliated to Jiangsu University.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Author contributions

D- JJ and X-ZQdesigned the study and wrote the manuscript. Z-JB, LJ and W-LL performed the experiments and analyzed the data. All authors contribute to this study and approved the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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