

## Original Article

# Potential dysfunction of inflammatory factors in patients with paroxysmal atrial fibrillation undergoing catheter radiofrequency ablation: a bioinformatics analysis

Jingjing Li<sup>1</sup>, Zhaoxin Li<sup>1</sup>, Linlin Zheng<sup>2</sup>

<sup>1</sup>Emergency Department of Weifang Traditional Chinese Medicine Hospital, Weifang 261041, Shandong, China;

<sup>2</sup>Department of Ultrasound, Anqiu Hospital of Traditional Chinese Medicine, Anqiu 262100, Shandong, China

Received February 26, 2020; Accepted March 20, 2020; Epub May 15, 2020; Published May 30, 2020

**Abstract:** Paroxysmal atrial fibrillation (PAF) is one of the common arrhythmias in found adults. Radiofrequency catheter ablation (RFCA) is the main method to treat arrhythmias. However, the mechanism of dysfunction of inflammatory factors in paroxysmal atrial fibrillation during surgery has not been clearly elucidated in previous studies. Therefore, this study is based on the dysfunction module of paroxysmal atrial fibrillation mediated by multiple regulators in order to predict its potential dysfunction mechanisms. First, we combine differential analysis, co-expression analysis and enrichment analysis, and construct protein interaction networks, regulator prediction, and network connectivity analysis. Subsequently, the function and path network of the integrated modules are analyzed. Finally, we performed Pivot analysis of ncRNA and TF. Results A total of 804 differentially expressed and persistently dysfunctional genes and 12 co-expression modules were obtained. Importantly, we identified three different sets of gene modules in the protein interaction network (including the inflammation module, the expression disorder module and the synthesis module of surgical state diseases). They are mainly involved in protein polyubiquitination, post-translational protein modification and SCF-dependent proteasomal ubiquitin-dependent protein catabolic process and other functional pathways. Second, using crosstalk analysis, we found a complex relationship between module 3 and module 5, while there is a simple crosstalk relationships between other modules. In addition, 23 endogenous genes (such as CUL1, UBE2D2 and NEDD4) were selected through a network connectivity analysis. In total, 1716 ncRNAs (including FENDRR, microRNA-300 and microRNA-186-5p) and 136 transcription factors (including BRCA1, CEBPD and MYB) were also obtained. These crucial regulators might be related to the dysfunction mechanism of paroxysmal atrial fibrillation. Therefore, radiofrequency ablation for paroxysmal atrial fibrillation may provide a new research method for patients.

**Keywords:** Inflammatory factors, catheter radiofrequency ablation, paroxysmal atrial fibrillation, dysfunction module, potential dysfunction mechanism

## Introduction

Atrial fibrillation is a common persistent arrhythmia throughout the world. It has a high incidence and can cause a series of complications when it is serious [1]. On the one hand, atrial fibrillation (AF) is a progressive disease, initially caused by triggering activity; and by AF changing to sustained AF, it is gradually becoming one of the main burdens of the health care system [2, 3]. On the other hand, chronic atrial fibrillation can be classified as paroxysmal, persistent and permanent atrial fibrillation [4].

Paroxysmal atrial fibrillation (PAF) accounts for about half of all cases of atrial fibrillation, and is considered the early stage of disease [5]. Paroxysmal atrial fibrillation is a common clinically related arrhythmia. Effective cure of paroxysmal atrial fibrillation is essential to reduce the risk of stroke and heart failure [6, 7]. Frozen headache accompanied by recurrent attacks of paroxysmal atrial fibrillation occurs simultaneously; so it can be inferred that frozen drinks are a initiator of arrhythmia, which has been confirmed by Lugovskaya et al. [8]. In addition, the heart is regulated by the external and inter-

nal autonomic nervous system, so the autonomic nervous system also plays an important role in the occurrence of atrial fibrillation [9]. According to the research of many scholars, catheter ablation is an important treatment of atrial fibrillation, and also the only operation that has proved to be curative in a large proportion of patients so far [10, 11]. In clinical trials, CF-guided radiofrequency catheter ablation has also been shown to be very suitable for the treatment of paroxysmal atrial fibrillation [12]. This irrigation CF-sensor catheter is safer and more effective in the treatment of PAF, and unintentional device-related adverse events can occur, so its use in the treatment of paroxysmal atrial fibrillation is more specific [13]. Pulmonary vein isolation is the main method of catheter ablation for paroxysmal atrial fibrillation, which is the cornerstone of current atrial fibrillation ablation technology. It is the most effective independent surgery in paroxysmal atrial fibrillation patients [12, 14]. Radiofrequency ablation (RFA) antiarrhythmic drugs (AADS) is a first-line treatment for paroxysmal atrial fibrillation, so providing RFA as a first-line treatment for patients with high level of symptoms is very reasonable [15]. As radiofrequency ablation is a common method of catheter ablation, improving its mapping methods can improve the success rate of catheter ablation of paroxysmal atrial fibrillation, and also help to improve the success rate of these complex operations [16].

In recent years, inflammatory factors have also been found to play a key role in the etiology of early onset and recurrence of atrial fibrillation [17]. Atrial fibrillation may occur and persist as a result of atrial remodeling caused by inflammation. Inflammatory cytokines such as serum amyloid A continue to increase in patients with atrial fibrillation, indicating that inflammatory factors are crucial in atrial fibrillation [18]. In addition, Kornej et al. have shown that catheter ablation of atrial fibrillation is associated with inflammation, endothelial damage and increased risk of thrombosis [19]. As far as the relationship between inflammatory cytokines and atrial fibrillation, the patient's risk of the two are closely related; on the one hand, circulating inflammatory factors such as increased CRP and IL-6 increases the recurrence of atrial fibrillation catheter ablation. On the other hand, other inflammatory markers, such as

white blood cells and transforming growth factor, are also important in the occurrence and recurrence of atrial fibrillation [20]. In fact, the inflammation pathway can also be considered as a target for the treatment of atrial fibrillation in an effort to reduce the clinical consequences of thromboembolism and improve the adverse consequences of atrial fibrillation [21]. In Pan J's conclusion, metoprolol can effectively reduce the incidence of atrial fibrillation and inflammatory cytokine levels, thereby improving heart rate function and quality of life of patients [22]. In addition to inflammatory factors, abnormal activation of other signal transduction and transcription activating factors has also been found to contribute to the promotion of atrial fibrosis, leading to the onset of atrial fibrillation [23].

Here, we propose a comprehensive analysis to explore the potential dysfunction mechanism of inflammatory factors in paroxysmal atrial fibrillation after radiofrequency catheter ablation. These findings not only provide a new insight into the therapeutic effect of catheter ablation on paroxysmal atrial fibrillation, but also provide abundant resources to further design experiments.

### Materials and methods

#### *Analysis of data resources and differential expressions*

We collected paroxysmal atrial fibrillation Expression Omnibus (GEO) from the NCBI gene database disease samples [24], and NO GSE-75092 microarray expression data set. The difference between the two groups was analyzed for the collected disease samples, and the R language limma package [25] was used to calculate the difference.

#### *Co-expression analysis and identification related functional modules*

First, Weighted Gene Expression Network Analysis (WGCNA) was used to analyze 5791 gene expression profiles associated with paroxysmal atrial fibrillation (PAF) [26] to find synergistic gene modules. Second, weighting coefficient calculation of any two genes (human factor) by taking the correlation coefficient between the N-power correlation value of the correlation coefficient. Then, hierarchical clustering tree by

the correlation between genes. Different branches of the cluster tree represent different gene modules, and different colors represent different modules.

### *Protein interaction network identification disorder module*

Observing the target interaction of genes in the module is helpful to understand the core molecules driving module function and dysfunction. We collected 299 inflammatory factor-related genes and 656 paroxysmal atrial fibrillation-related genes from NCBI-Gene and OMIM databases, respectively. Based on String database, we constructed a protein interaction network (PPIs) [27] for each module. Twelve co-expressed modules and genes related to inflammatory factors and diseases were introduced into the protein interaction network to identify the different roles played by different modules.

### *Identification of functional impairment modules and enrichment analysis of functions and pathway*

The language we used was R cluster probe bag [28], in order to enrich and analyze functions ( $p$ -value < 0.01,  $q$  value < 0.01) and KEGG pathway ( $p$ -value < 0.05,  $q$  value < 0.2). According to the enrichment analysis, we determined that inflammatory factor dysfunction module may occur in paroxysmal atrial fibrillation operation.

### *Inter-module crosstalk and internal driving force analysis*

We generated a random network 1000 by using Python and string (score > 950) [29], while maintaining the same size of the network, each node maintains a constant degree. Second, in order to get the interaction times between the interaction times, the interaction times between the important modules and the interaction times under the random background are statistically compared, using the random network. The logarithm of interactions between modules is called crosstalk. The methods to calculate crosstalk are: the number of interaction networks  $N$  random among modules larger than the real network in the context of a random network. When the  $p$  value is less than 0.05, there is interaction between the module's crosstalk ( $P=n/N$ ). Then, Cytoscape revealed clear crosstalk, and directly observed the com-

plex regulatory relationship between the modules [30]. Further, Cytoscape networks (including computational communications) for display and analysis. Finally, communication with the strongest gene is selected to adjust the process module core molecule, and determines the intrinsic gene. These genes could be key factors in molecular surgical treatment of paroxysmal atrial fibrillation.

### *Identification of transcription factors and ncRNA regulation of modules*

The Internet TRRUST V2 database [31] with predictive analysis was used for all the people in the transcription factor target data download. Human ncRNA protein data (score > 0.5) was download by RAID2.0 prediction database [32]. Then, pivot analysis was performed in these transcription factors and ncRNAs. The importance of the driving module pivoting means was to search and analyze the interaction between at least two pairs and calculate the driver hypergeometric test module and the target interaction. TF and RNA ( $P < 0.01$ ) is the fulcrum important regulation module. Finally, for statistical analysis, the hub is identified as the core hub.

## **Result**

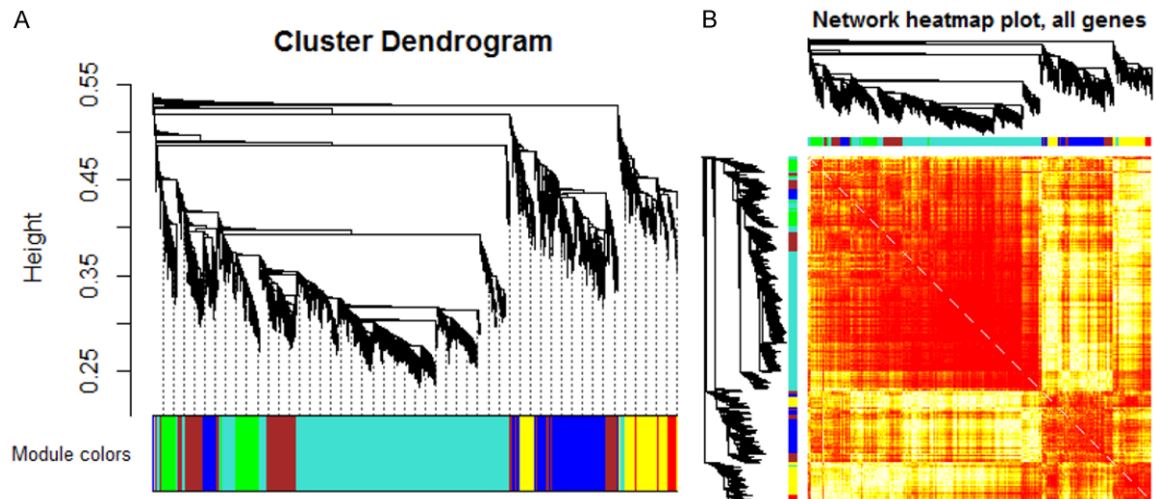
### *Differential expression of genes related to paroxysmal atrial fibrillation*

In order to explore the potential dysfunction mechanism of inflammatory factors in paroxysmal atrial fibrillation (PAF) after radiofrequency catheter ablation (RFCA), we selected two groups of gene expression profiles related to PAF to conduct an in-depth study. The difference in genes between the two groups were 4632 and 2023, respectively. In addition, we screened two groups of differentially expressed genes with positive or negative expression values, for a total of 804 (Table S1). This group of genes are believed to be genes with persistent disorders during surgery.

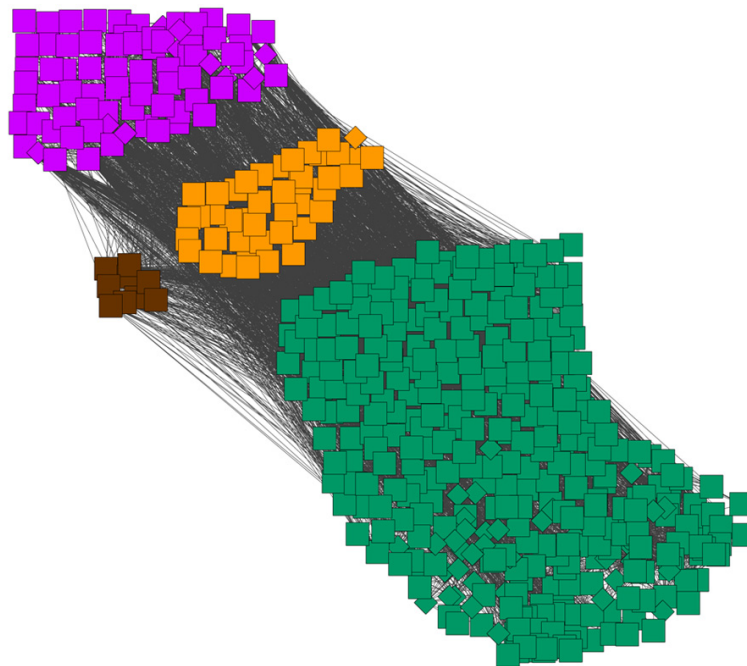
### *Differential gene co-expression in paroxysmal atrial fibrillation*

Through the difference of gene expression between the two groups, we obtained the disorder-related genes of paroxysmal atrial fibrillation under surgery. However, the regulatory

## Potential dysfunction of inflammatory factors in patients



**Figure 1.** Clustering Module of Co-expression Relations of Genes Associated with Paroxysmal Atrial Fibrillation. A. According to the co-expression relationship of differentially expressed genes, 12 modules are clustered, one color represents one module. B. Thermogram of Modular Gene Expression in Samples. The disease samples of paroxysmal atrial fibrillation showed the phenomena of grouping expression intuitively.



**Figure 2.** Protein Interaction Network Map (PIN) characterizing the underlying pathogenesis of paroxysmal atrial fibrillation (PAF). Coffee represents the genes related to inflammatory factors, green represents the first group of differentially expressed genes, purple represents the second group of differentially expressed genes, and yellow represents the two groups of differentially expressed genes.

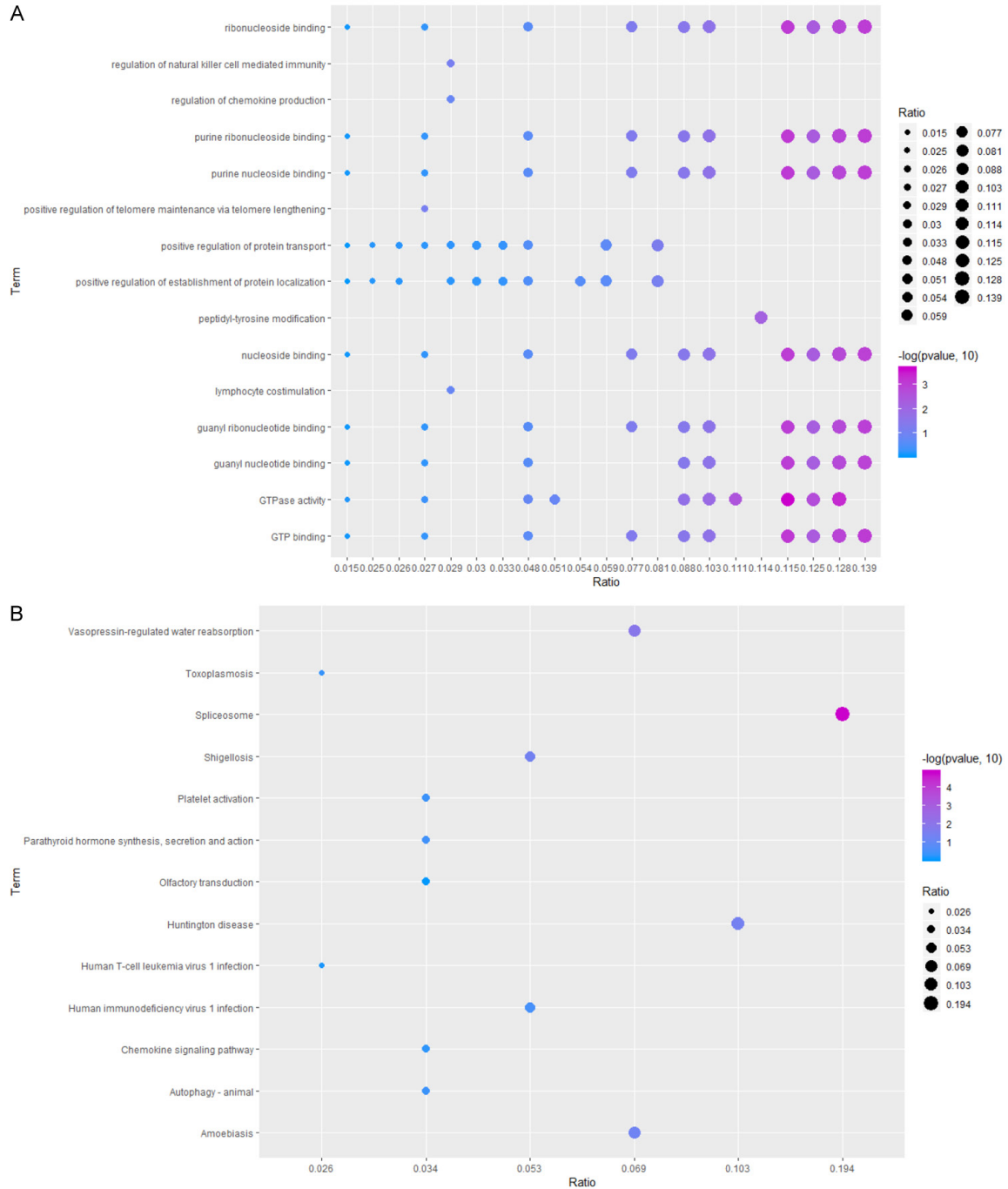
mechanism remained unclear. The expression profiles of paroxysmal atrial fibrillation disease samples were co-expressed by WGCNA. A total of 12 modules containing co-expressed genes were found (Figure 1A, 1B). These 12 modules

may represent different mechanisms mediating the potential dysfunction of inflammatory factors in paroxysmal atrial fibrillation during radio-frequency catheter ablation.

### *Construction of protein interaction networks in paroxysmal atrial fibrillation*

To further clarify the gene disorder networks in patients with paroxysmal atrial fibrillation undergoing radio-frequency catheter ablation under inflammatory microenvironment, we constructed a protein interaction network PPIs using functional modules derived from co-expression analysis. In total, 14184 interaction pairs of 527 module genes were obtained (Figure 2). In addition, we integrated genes related to paroxysmal atrial fibrillation and inflammatory factors into the network module. The genes of the same module are clustered together and distinguished by color. Three modules were identified, including the inflammation module, the PAF imbalance module and the synthesis module.

# Potential dysfunction of inflammatory factors in patients



**Figure 3.** Modular genes are involved in the function and pathway identification of paroxysmal atrial fibrillation dysfunction modules. A. GO functional enrichment analysis of module genes (excerpts). The darker the color, the stronger the significance of enrichment. The larger the circle, the larger the proportion of module genes in GO functional entry genes. B. KEGG pathway enrichment analysis of modular genes (excerpts). The darker the color, the stronger the significance of enrichment. The larger the circle, the larger the proportion of module genes to KEGG pathway entry genes.

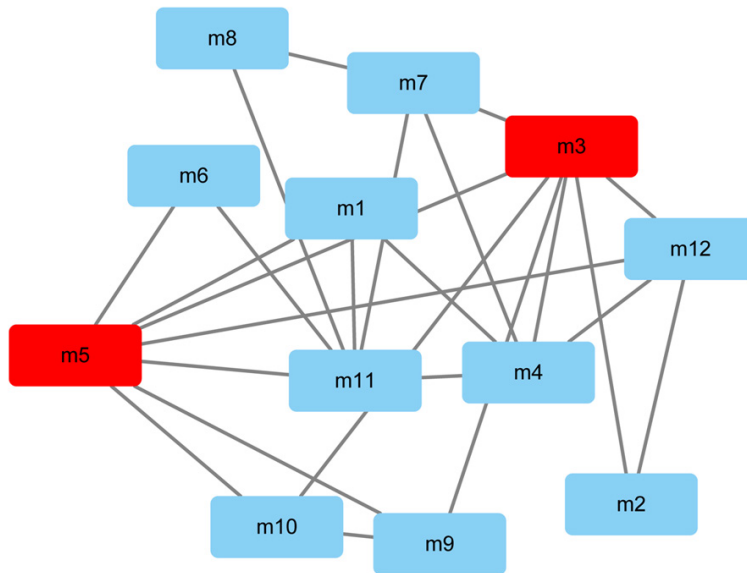
## Identification of dysfunction modules in paroxysmal atrial fibrillation

Dysfunction modules in paroxysmal atrial fibrillation results found 11083 functions and 386

KEGG pathways were enriched (Figure 3A, 3B; Table S2). There are 1202 molecular functions (MF), 109 cell components (CC) and 8784 biological processes (BP). It is noteworthy that these signaling pathways, protein polyubiquiti-



## Potential dysfunction of inflammatory factors in patients



**Figure 4.** Cross talk analysis between paroxysmal atrial fibrillation modules, the red part represents a complex crosstalk relationship.

nation, post-translational protein modification and SCF-dependent proteasomal ubiquitin-dependent protein catabolic process might be the core signaling pathways in disorder mechanisms. Above all, these signaling pathways may correlate with the imbalance mechanism of inflammatory factors in paroxysmal atrial fibrillation during surgery.

### *Modular interaction analysis of paroxysmal atrial fibrillation*

To explore the crosstalk relationship between modules, it is helpful to deepen our understanding of the potential dysfunction mechanism of module regulation of paroxysmal atrial fibrillation. Therefore, we conduct cross talk analysis among modules based on the relationship between module genes. The results show that there is a complex interaction between module 3 and module 5 (**Figure 4**). This crosstalk may play a driving role and regulate the imbalance mechanisms of inflammatory factors in paroxysmal atrial fibrillation.

### *The ncRNA and TF mediating paroxysmal atrial fibrillation dysfunction module*

Transcriptional regulation of genes in the development of disease is crucial, and non-coding RNA are also important to predict the module dysfunction caused by ncRNA regulatory fac-

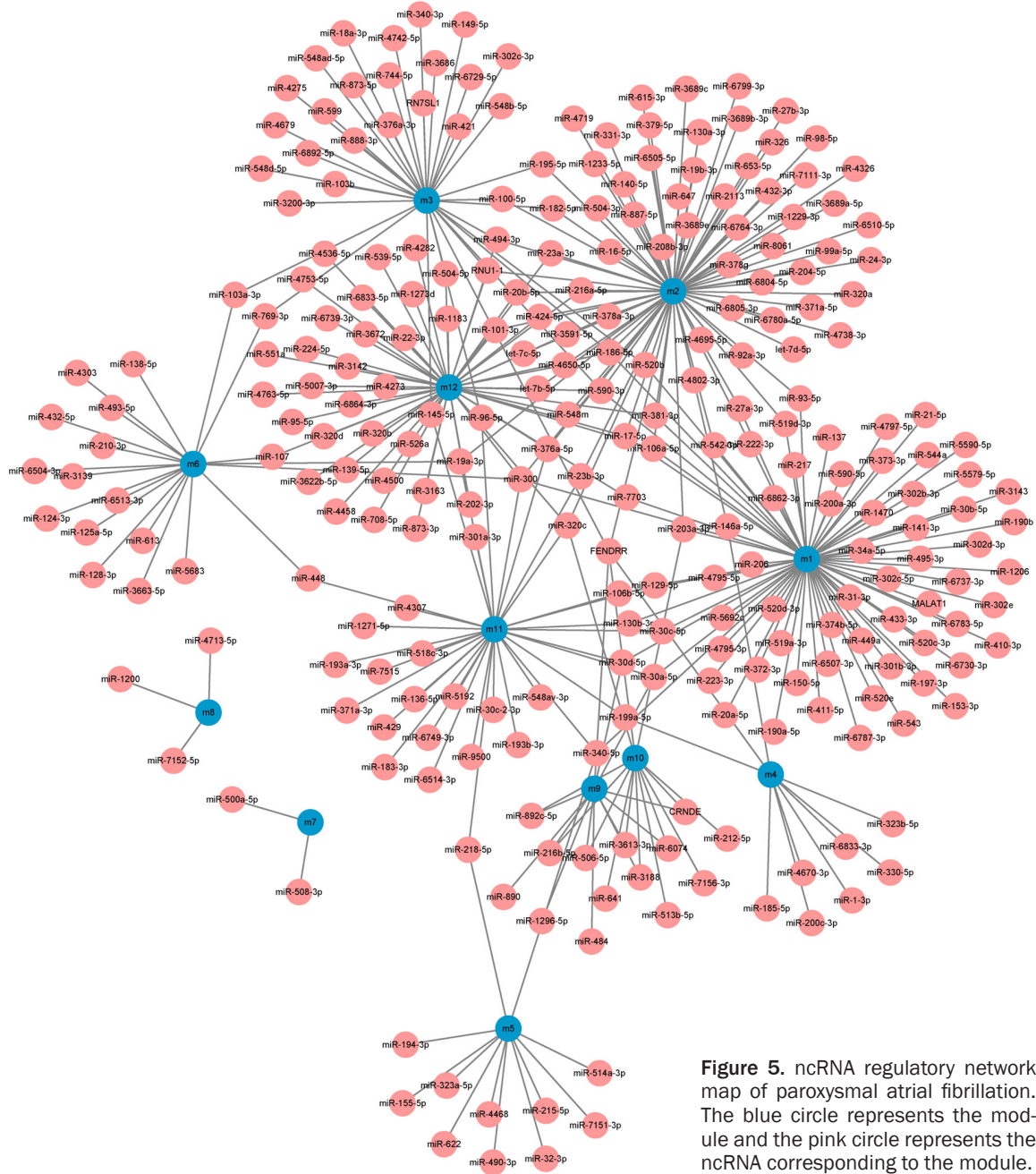
tors. We analyzed the relationship between critical and non-coding RNA gene targeting. We obtained 1716 ncRNAs with regulatory effects on these modules, involving 2951 ncRNA module interaction pairs (**Figure 5**). Statistical analysis showed that the modules of small RNA-146B-5P dysfunction have a strong regulatory role and may become the core of ncRNA. miR-300 also plays an important role in regulating 5 dysfunctional modules and dysfunctional modules. Next, we predicted from the analysis using pivot transcription factor gene module. The results show that the mechanism of 136 dysfunctions of the transcription

factor of paroxysmal atrial fibrillation, the pivot block 193 relates to the interaction with a significant role in transcriptional regulation (**Figure 6**). Statistical analysis shows that STAT1 and CITA have significant regulatory effects on a dysfunctional module. These data suggest that transcription factors are critical functions of paroxysmal atrial fibrillation barriers mechanisms. These transcription factors may be the core transcription factors of paroxysmal atrial fibrillation. Besides, we analyzed the network connection through functional modules and identified 20 key endogenous genes, including CUL1, UBE2D2 and NEDD4. These genes have a high intrinsic connectivity network module, as well as the mechanism underlying dysfunction paroxysmal atrial fibrillation playing a significant regulatory role.

## Discussion

Atrial fibrillation is one of the common persistent arrhythmias in found clinical practice, and its risk factors include stroke and heart failure [33]. Paroxysmal atrial fibrillation is a significant manifestation of atrial fibrillation. More and more evidence shows that catheter ablation is superior to antiarrhythmic drugs in controlling atrial fibrillation [10]. On the other hand, according to Lesaka et al., inflammation plays an important role in the etiology of early recurrence of atrial fibrillation (ERAF) [17]. Although

## Potential dysfunction of inflammatory factors in patients

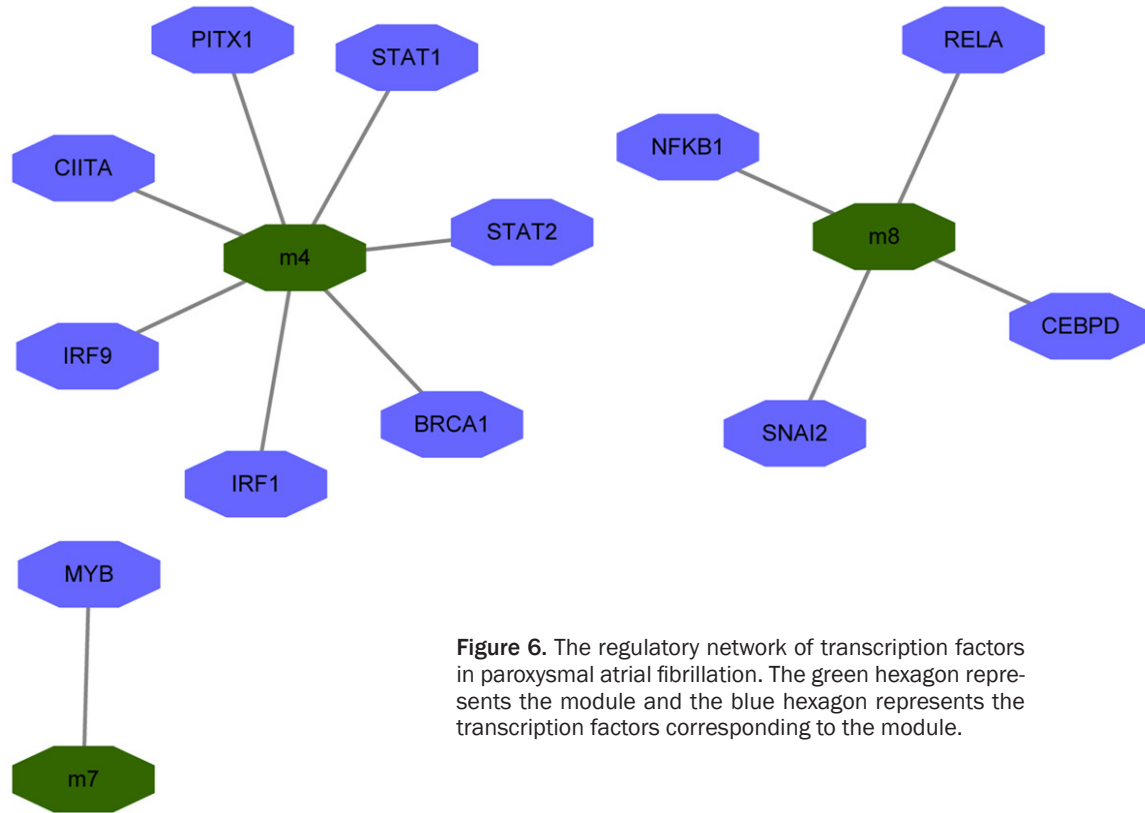


**Figure 5.** ncRNA regulatory network map of paroxysmal atrial fibrillation. The blue circle represents the module and the pink circle represents the ncRNA corresponding to the module.

in recent years, the exploration of paroxysmal atrial fibrillation has made some progress. However, the detailed mechanism remains unclear. Co-expression analysis, protein interaction network, transcription and post transcriptional regulation, and multidimensional module interaction analysis were used to explore the potential dysfunction mechanisms of inflammatory factors in patients with paroxysmal atrial fibrillation undergoing radiofrequency ablation.

To fully explore the potential dysfunction mechanism of paroxysmal atrial fibrillation, we first integrated two groups of related genes of paroxysmal atrial fibrillation under surgical condition and analyzed the differences. We screened 804 genes related to persistent disorders in the two groups. We found that KCNA5 is up-regulated in both groups of DEG, and the up-regulated multiple genes are large. In Sattiraju's study, KCNA5 mutation is a new risk deficiency

## Potential dysfunction of inflammatory factors in patients



**Figure 6.** The regulatory network of transcription factors in paroxysmal atrial fibrillation. The green hexagon represents the module and the blue hexagon represents the transcription factors corresponding to the module.

factor for atrial fibrillation, which plays an important role in the occurrence and development of atrial fibrillation [34]. Secondly, we found 12 co-expression modules, in which the genes are considered to be co-expressed. Subsequently, in view of the results of enrichment analysis, we found that the genes in the 12 modules obtained from paroxysmal atrial fibrillation mainly participate in protein polyubiquitination, post-translational protein modification and SCF-dependent proteasomal ubiquitin-dependent protein catabolic process and other functional pathways. We then found that STAT1 has an important regulatory role in the 12 dysfunction modules, suggesting that STAT1 has an important role in paroxysmal atrial fibrillation. Ctsai et al. concluded that STAT1 activation may lead to inflammation and structural changes, leading to atrial fibrillation [35]. In addition, CIITA has also been found to be associated with chronic inflammation. The down-regulation of CIITA and the interaction of transcription between cells are related to STAT1 expression [36]. Therefore, STAT1 and CITA may be the core transcription factors regulating the mechanism of paroxysmal atrial fibrillation disorder.

In addition, non-coding RNA is considered as the crucial regulator of the development and progression of the disease. According to the target relationship between ncRNA and genes, we made a pivot analysis. The results show that 1716 of the predicted, non-coding RNA modules played significant regulatory roles. On the one hand, miR-146b-5p was found to regulate these two dysfunctional modules.

According to Roldn et al., we found that miR-146b-5p is an important negative regulatory factor for inflammation, which can be used as a prognostic biomarker for atrial fibrillation [37]. Therefore, miR-146b-5p is considered as a key regulator in many aspects of paroxysmal atrial fibrillation and plays a key role in the disorder mechanism of the whole disease. On the other hand, miR-300 has been found to regulate five dysfunction modules, which are also the core regulators of diseases. Overexpression of miR-300 can inhibit cell apoptosis and enhance vascular endothelial cells in cell growth cycle, thereby reducing inflammation and playing a role in endothelial cells by regulating apoptosis and anti-apoptotic factors [38]. At the same time, we found that 20 endogenous genes may



be the main potential obstacles of inflammatory factors in surgical treatment of paroxysmal atrial fibrillation.

A series of regulatory factors predict the potential dysfunction of the mechanism of paroxysmal atrial fibrillation. However, other unreported ncRNAs and transcription factors may play a role in the dysfunction mechanism of paroxysmal atrial fibrillation, which needs further exploration. Overall, our study is based on the mechanism of inflammatory cytokines in patients with paroxysmal atrial fibrillation undergoing radiofrequency ablation, in order to explore the potential of dysfunction. In the future, we will further explore the molecular mechanism in patient samples, which will provide a new pathway for the treatment of paroxysmal atrial fibrillation.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Zhaoxin Li, Emergency Department of Weifang Traditional Chinese Medicine Hospital, 1055 Weizhou Road, Weifang 26-1041, Shandong, China. Tel: +86-13561413073; Fax: +86-0536-8060186; E-mail: zangfudi83865-5250@163.com

### References

- [1] Xin Y, Zhao Y, Mu Y, Li Q and Shi C. Paroxysmal atrial fibrillation recognition based on multi-scale Renyi entropy of ECG. *Technol Health Care* 2017; 25: 189-196.
- [2] Margulescu AD and Mont L. Persistent atrial fibrillation vs. paroxysmal atrial fibrillation: differences in management. *Expert Rev Cardiovasc Ther* 2017; 15: 601-618.
- [3] Romero J, Gianni C, Di Biase L and Natale A. Catheter ablation for long-standing persistent atrial fibrillation. *Methodist Debaquey Cardiovasc J* 2015; 11: 87-93.
- [4] Mischke K, Knackstedt C, Marx N and Vollmann D. Insights into atrial fibrillation. *Minerva Med* 2013; 104: 119-130.
- [5] Howlett PJ, Hatch FS, Alexeenko V, Jabr RI, Leatham EW and Fry CH. Diagnosing paroxysmal atrial fibrillation: are biomarkers the solution to this elusive arrhythmia? *Biomed Res Int* 2015; 2015: 910267.
- [6] Wasserlauf J, Pelchovitz DJ, Rhyner J, Verma N, Bohn M, Li Z, Arora R, Chicos AB, Goldberger JJ, Kim SS, Lin AC, Knight BP and Passman RS. Cryoballoon versus radiofrequency catheter ablation for paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol* 2015; 38: 483-489.
- [7] Luik A, Kunzmann K, Hormann P, Schmidt K, Radzewitz A, Bramlage P, Schenk T, Schymik G, Merkel M, Kieser M and Schmitt C. Cryoballoon vs. open irrigated radiofrequency ablation for paroxysmal atrial fibrillation: long-term FreezeAF outcomes. *BMC Cardiovasc Disord* 2017; 17: 135.
- [8] Lugovskaya N and Vinson DR. Paroxysmal atrial fibrillation and brain freeze: a case of recurrent co-incident precipitation from a frozen beverage. *Am J Case Rep* 2016; 17: 23-26.
- [9] Choi EK, Zhao Y, Everett TH 4th and Chen PS. Ganglionated plexi as neuromodulation targets for atrial fibrillation. *J Cardiovasc Electrophysiol* 2017; 28: 1485-1491.
- [10] Haegeli LM and Calkins H. Catheter ablation of atrial fibrillation: an update. *Eur Heart J* 2014; 35: 2454-2459.
- [11] Santangeli P, Di Biase L, Burkhardt DJ, Horton R, Sanchez J, Bai R, Pump A, Perez M, Wang PJ, Natale A and Al-Ahmad A. Catheter ablation of atrial fibrillation: state-of-the-art techniques and future perspectives. *J Cardiovasc Med (Hagerstown)* 2012; 13: 108-124.
- [12] Lin H, Chen YH, Hou JW, Lu ZY, Xiang Y and Li YG. Role of contact force-guided radiofrequency catheter ablation for treatment of atrial fibrillation: a systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2017; 28: 994-1005.
- [13] Natale A, Reddy VY, Monir G, Wilber DJ, Lindsay BD, McElderry HT, Kantipudi C, Mansour MC, Melby DP, Packer DL, Nakagawa H, Zhang B, Stagg RB, Boo LM and Marchlinski FE. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. *J Am Coll Cardiol* 2014; 64: 647-656.
- [14] Khoueiry Z, Albenque JP, Providencia R, Combes S, Combes N, Jourda F, Sousa PA, Cardin C, Pasquie JL, Cung TT, Massin F, Marijon E and Boveda S. Outcomes after cryoablation vs. radiofrequency in patients with paroxysmal atrial fibrillation: impact of pulmonary veins anatomy. *Europace* 2016; 18: 1343-1351.
- [15] Raatikainen MJ, Hakalahti A, Uusimaa P, Nielsen JC, Johannessen A, Hindricks G, Walfridsson H, Pehrson S, Englund A, Hartikainen J, Kongstad O, Mortensen LS and Hansen PS; MANTRA-PAF investigators. Radiofrequency catheter ablation maintains its efficacy better than antiarrhythmic medication in patients with paroxysmal atrial fibrillation: on-

## Potential dysfunction of inflammatory factors in patients

- treatment analysis of the randomized controlled MANTRA-PAF trial. *Int J Cardiol* 2015; 198: 108-114.
- [16] Steven D, Sultan A, Schaffer B, Servatius H, Hoffmann B, Luker J and Willems S. Catheter ablation of persistent and long-standing persistent atrial fibrillation. Strategies and results. *Herzschrittmacherther Elektrophysiol* 2013; 24: 15-18.
- [17] Miyazaki S, Kuroi A, Hachiya H, Nakamura H, Taniguchi H, Ichihara N, Takagi T, Iwasawa J and Iesaka Y. Early recurrence after pulmonary vein isolation of paroxysmal atrial fibrillation with different ablation technologies - prospective comparison of radiofrequency vs. second-generation cryoballoon ablation. *Circ J* 2016; 80: 346-353.
- [18] Cheng T, Wang XF, Hou YT and Zhang L. Correlation between atrial fibrillation, serum amyloid protein A and other inflammatory cytokines. *Mol Med Rep* 2012; 6: 581-584.
- [19] Kornej J, Dinov B, Blann AD, Rolf S, Arya A, Schmid J, Husser D, Hindricks G, Bollmann A and Lip GY. Effects of radiofrequency catheter ablation of atrial fibrillation on soluble P-selectin, von Willebrand factor and IL-6 in the peripheral and cardiac circulation. *PLoS One* 2014; 9: e111760.
- [20] Wu N, Xu B, Xiang Y, Wu L, Zhang Y, Ma X, Tong S, Shu M, Song Z, Li Y and Zhong L. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: a meta-analysis. *Int J Cardiol* 2013; 169: 62-72.
- [21] Guo Y, Lip GY and Apostolakis S. Inflammatory biomarkers and atrial fibrillation: potential role of inflammatory pathways in the pathogenesis of atrial fibrillation-induced thromboembolism. *Curr Vasc Pharmacol* 2015; 13: 192-201.
- [22] Pan J, Wang W, Wu X, Kong F, Pan J, Lin J and Zhang M. Inflammatory cytokines in cardiac pacing patients with atrial fibrillation and asymptomatic atrial fibrillation. *Panminerva Med* 2018; 60: 86-91.
- [23] Huang Z, Chen XJ, Qian C, Dong Q, Ding D, Wu QF, Li J, Wang HF, Li WH, Xie Q, Cheng X, Zhao N, Du YM and Liao YH. Signal transducer and activator of transcription 3/microRNA-21 feedback loop contributes to atrial fibrillation by promoting atrial fibrosis in a rat sterile pericarditis model. *Circ Arrhythm Electrophysiol* 2016; 9.
- [24] Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, Marshall KA, Phillippy KH, Sherman PM, Holko M, Yefanov A, Lee H, Zhang N, Robertson CL, Serova N, Davis S and Soboleva A. NCBI GEO: archive for functional genomics data sets—update. *Nucleic Acids Res* 2013; 41: D991-995.
- [25] Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W and Smyth GK. limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Res* 2015; 43: e47.
- [26] Langfelder P and Horvath S. WGCNA: an R package for weighted correlation network analysis. *BMC Bioinformatics* 2008; 9: 559.
- [27] Athanasios A, Charalampos V, Vasileios T and Ashraf GM. Protein-protein interaction (PPI) network: recent advances in drug discovery. *Curr Drug Metab* 2017; 18: 5-10.
- [28] Yu G, Wang LG, Han Y and He QY. clusterProfiler: an R package for comparing biological themes among gene clusters. *OMICS* 2012; 16: 284-287.
- [29] Hopf TA, Green AG, Schubert B, Mersmann S, Scharfe CPI, Ingraham JB, Toth-Petroczy A, Brock K, Riesselman AJ, Palmedo P, Kang C, Sheridan R, Draizen EJ, Dallago C, Sander C and Marks DS. The EVcouplings Python framework for coevolutionary sequence analysis. *Bioinformatics* 2019; 35: 1582-1584.
- [30] Carlin DE, Demchak B, Pratt D, Sage E and Ideker T. Network propagation in the cytoscape cyberinfrastructure. *PLoS Comput Biol* 2017; 13: e1005598.
- [31] Han H, Cho JW, Lee S, Yun A, Kim H, Bae D, Yang S, Kim CY, Lee M, Kim E, Lee S, Kang B, Jeong D, Kim Y, Jeon HN, Jung H, Nam S, Chung M, Kim JH and Lee I. TRRUST v2: an expanded reference database of human and mouse transcriptional regulatory interactions. *Nucleic Acids Res* 2018; 46: D380-D386.
- [32] Yi Y, Zhao Y, Li C, Zhang L, Huang H, Li Y, Liu L, Hou P, Cui T, Tan P, Hu Y, Zhang T, Huang Y, Li X, Yu J and Wang D. RAID v2.0: an updated resource of RNA-associated interactions across organisms. *Nucleic Acids Res* 2017; 45: D115-D118.
- [33] Mujovic NM, Marinkovic MM, Potpara TS and Geller L. Catheter ablation of lone atrial fibrillation. *Curr Pharm Des* 2015; 21: 591-612.
- [34] Olson TM, Alekseev AE, Liu XK, Park S, Zingman LV, Bienengraeber M, Sattiraju S, Ballew JD, Jahangir A and Terzic A. Kv1.5 channelopathy due to KCNA5 loss-of-function mutation causes human atrial fibrillation. *Hum Mol Genet* 2006; 15: 2185-2191.
- [35] Tsai CT, Lin JL, Lai LP, Lin CS and Huang SK. Membrane translocation of small GTPase Rac1 and activation of STAT1 and STAT3 in pacing-induced sustained atrial fibrillation. *Heart Rhythm* 2008; 5: 1285-1293.
- [36] Xia J, Fang M, Wu X, Yang Y, Yu L, Xu H, Kong H, Tan Q, Wang H, Xie W and Xu Y. A2b adenosine signaling represses CIITA transcription via an epigenetic mechanism in vascular smooth

## Potential dysfunction of inflammatory factors in patients

- muscle cells. *Biochim Biophys Acta* 2015; 1849: 665-676.
- [37] Roldan V, Arroyo AB, Salloum-Asfar S, Manzano-Fernandez S, Garcia-Barbera N, Marin F, Vicente V, Gonzalez-Conejero R and Martinez C. Prognostic role of MIR146A polymorphisms for cardiovascular events in atrial fibrillation. *Thromb Haemost* 2014; 112: 781-788.
- [38] Li Y, Ke J, Peng C, Wu F and Song Y. microRNA-300/NAMPT regulates inflammatory responses through activation of AMPK/mTOR signaling pathway in neonatal sepsis. *Biomed Pharmacother* 2018; 108: 271-279.