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MicroRNA Regulatory Network Revealing the Mechanism of Inflammation in Atrial Fibrillation

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Atrial fibrillation (AF) is a highly prevalent condition associated with high morbidity and mortality that can cause or exacerbate heart failure and is an important risk factor for stroke. AF is the disorganized propagation of electrical activity in the atrium, which prevents organized contractions. However, the effect of microRNAs and the patterns of the regulatory network of AF remain vague.

Material/Methods: The mRNA expression data of atrial tissue splices from 3 conditions – permanent atrial fibrillation (AF), sinus rhythm (SR), and human left ventricular non-failing myocardium (LV) – were downloaded from GSE2240 and the differentially expressed genes (DEGs) between the 3 kinds of samples were calculated. Then we constructed 3 miRNA-DEGs networks and these networks were integrated to construct the final merged AF-related microRNA regulatory network. Finally, we constructed the miRNA-inflammation networks to detect the roles of miRNAs in inflammation development of AF.

Results: This network included 108 DEGs, and 27 microRNAs and DEGs are regulated by both microRNAs. We found that a sub-network composed by miR-124, miR-183, miR-215, miR-192, and a DEG of EGR1 were all represents in these 3 networks. Based on functional enrichment analysis, some biological process, such as energy and glucan metabolic process and heart and blood vessel development, were found to be regulated by miRNAs in AF. Some miRNAs, such as miR-26b and miR-355p, were involved in inflammation in AF.

Conclusions: In conclusion, the microRNA regulatory network sheds new light on the molecular mechanism of AF with this non-coding regulated model.

MeSH Keywords: Atrial Fibrillation • MicroRNAs • Neurogenic Inflammation

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Background

Atrial fibrillation (AF) is a highly prevalent condition associated with high morbidity and mortality, which can cause or exacerbate heart failure and is an important risk factor for stroke. AF is the disorganized propagation of electrical activity in the atrium, which prevents organized heart contractions. As a result, the atrial depolarization wave front, the P-wave, measured during sinus rhythm (SR), devolves into a series of fibrillatory waves in the surface electrocardiogram (ECG). AF is known to be progressive in nature [1,2].

Recently, microRNA has become a focus of many researchers. The microRNAs, which are 21–25-nucleotides-long non-coding RNA molecules, function in transcriptional and post-transcriptional regulation of gene expression and they are involved in various diseases. Recent studies have uncovered an important role of microRNAs (miRNAs) in regulating cardiac excitability and arrhythmogenesis in various cardiac diseases, including myocardial infarction [3], cardiac hypertrophy [4], diabetic cardiomyopathy [5], and atrial fibrillation (AF) [6,7]. The above studies have indicated the important roles of microRNAs in AF, but most of their underlying mechanisms are still unknown. Furthermore, the regulatory action of microRNAs in development from AF to SR has not been clearly defined.

In this study, we downloaded the mRNA expression data of atrial tissue splices from 3 conditions – permanent atrial fibrillation (AF), sinus rhythm (SR), and human left ventricular non-failing myocardium (LV). Then we calculated the differential expressed genes between theses 3 kinds of samples and constructed 3 miRNA-DEGs networks. Finally, we constructed the miRNA-inflammation networks to detect the roles of miRNAs in development of inflammation in AF.

Material and Methods

Microarray data and differentially expressed genes analysis

The mRNA expression data of atrial tissue was obtained from Gene Expression Omnibus (GEO, *http://www.ncbi.nlm.nih.gov/geo*) with GEO Series accession number GSE2240. This profile was based on human atrial tissue splices from 3 conditions – permanent atrial fibrillation (AF), sinus rhythm (SR), and human left ventricular non-failing myocardium (LV) [8]. Ten atrial fibrillation samples, 20 sinus rhythm samples, and 5 left ventricular non-failing myocardium samples were profiled using Affymetrix Human Genome U133A Array and Affymetrix Human Genome U133B Array, respectively [8]. For these 2 platforms, only genes contained in both platforms were retained for further study, and there are 4317 genes involved in this study. The fold change values were calculated for each gene in 3 comparisons (AF *vs.* SR, AF *vs.* LV, and SR *vs.* LV) in each platform. In each comparison, genes with absolute values of log2 (fold change value) greater than 1 in either platform were reported as differential expressed genes (DEGs). Finally, we obtained 14 DEGs from AF *vs.* SR, 118 DEGs from AF *vs.* LV, and 131 DEGs from SR *vs.* LV.

Then we calculated the expression correlation values between DEGs and other genes for each condition, using Pearson correlation coefficient method. In each comparison, if the correlation value of 1 pair of genes (1 DEG and another gene) was less than 0.5 in one condition and more than 0.8 in another conditions or vice versa, this pair was identified as a differential co-expression pair.

Heapmap.2 in gplots package was used to describe the expression landscape of all samples in each platform.

Functional enrichment analysis

To implement functional annotation with different regulatory networks, we used the database for annotation, visualization, and integrated discovery (DAVID) tool [9]. DAVID is a high-throughput and integrated data-mining environment and can analyses a given gene list derived from genomic experiments [9]. DAVID was used for pathway enrichment analysis based on hypergeometric distribution. P-value less than 0.05 was chosen as the cutoff criterion for statistically significant GO terms related to AF and SR.

Construction the microRNA-DEGs network

To construct microRNA-DEGs networks, we downloaded the experimentally verified associations between human microRNAs and their targets from miRTarBase, which has accumulated more than 50 000 miRNA-target interactions collected by manually surveying pertinent literature after systematic data mining of the text [10]. This dataset contained miRNA-target interactions consisting of 963 miRNAs and 12518 mRNAs. We mapped the DEGs between the 3 kinds of samples into the above interactions and extracted the corresponding miRNA-DEG interactions. Finally, we constructed 3 miRNA-DEGs networks.

Construction of the microRNA-inflammation network

To construct the microRNA-inflammation networks, a set of inflammation genes was obtained from the Gene Ontology categories "inflammatory response" (GO: 0006954) and "regulation of inflammatory response" (GO: 0050727), namely the human inflammation gene set containing 231 genes. Then the 231 genes were intersected with the DEGs of AF *vs.* SR, AF *vs.* LV, and SR *vs.* LV. Finally, the miRNAs which regulated 3 sets of overlapped genes were extracted and the microRNA-inflammation networks were constructed. These 3 networks were visualized by Cytoscape.

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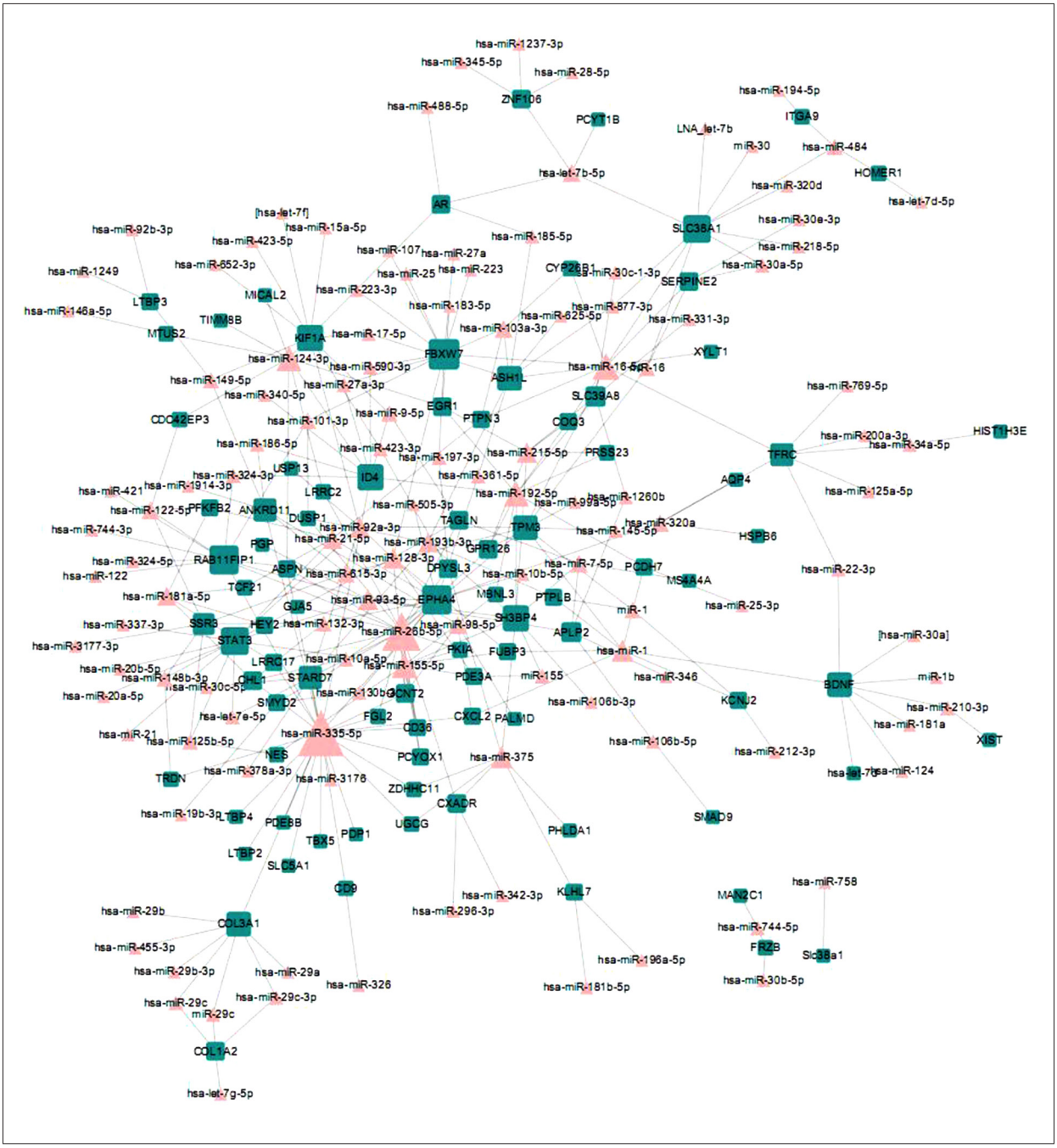

Figure 1. MiRNA-DEGs network of AF and LV. The rectangle nodes represent DEGs and the triangle nodes represent miRNAs.

Results

Differentially expressed genes analysis between 3 samples

To identify the differentially expressed genes (DEGs) of AF *vs.* SR, AF *vs.* LV, and SR *vs.* LV, we obtained the microarray dataset GSE2240 of 3 samples from the GEO database (*http://www.ncbi.nlm.nih.gov/geo/*). We then used fold change method to identify DEGs of AF *vs.* SR, AF *vs.* LV and SR *vs.* LV. A total of 14, 118, and 131 genes were considered differentially expressed in AF *vs.* SR, AF *vs.* LV and SR *vs.* LV, respectively (see Material and Methods).

MiRNA-DEGs network

To obtain this network, we first constructed the experimental verified interactions between miRNA and mRNAs. After mapping the DEGs between the 3 kinds of samples into the above

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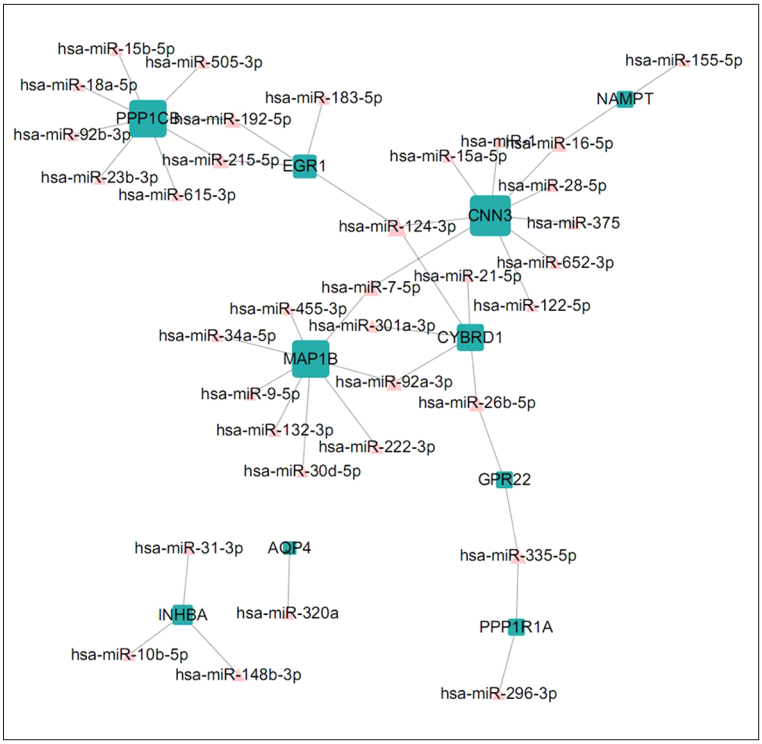

Figure 2. MiRNA-DEGs network of AF and SR. The rectangle nodes represent DEGs and the triangle nodes represent miRNAs.

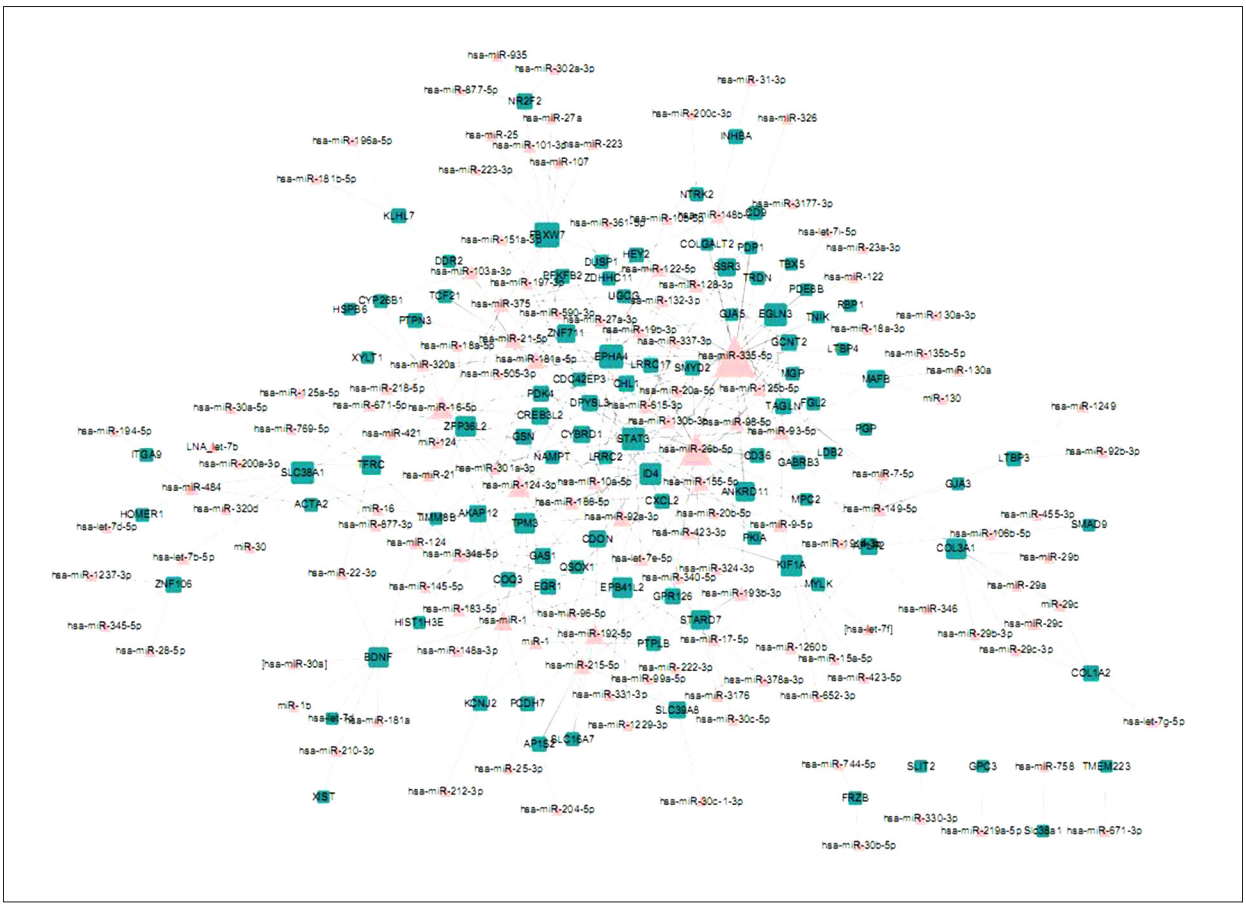

Figure 3. MiRNA-DEGs network of LV and SR. The rectangle nodes represent DEGs and the triangle nodes represent miRNAs.

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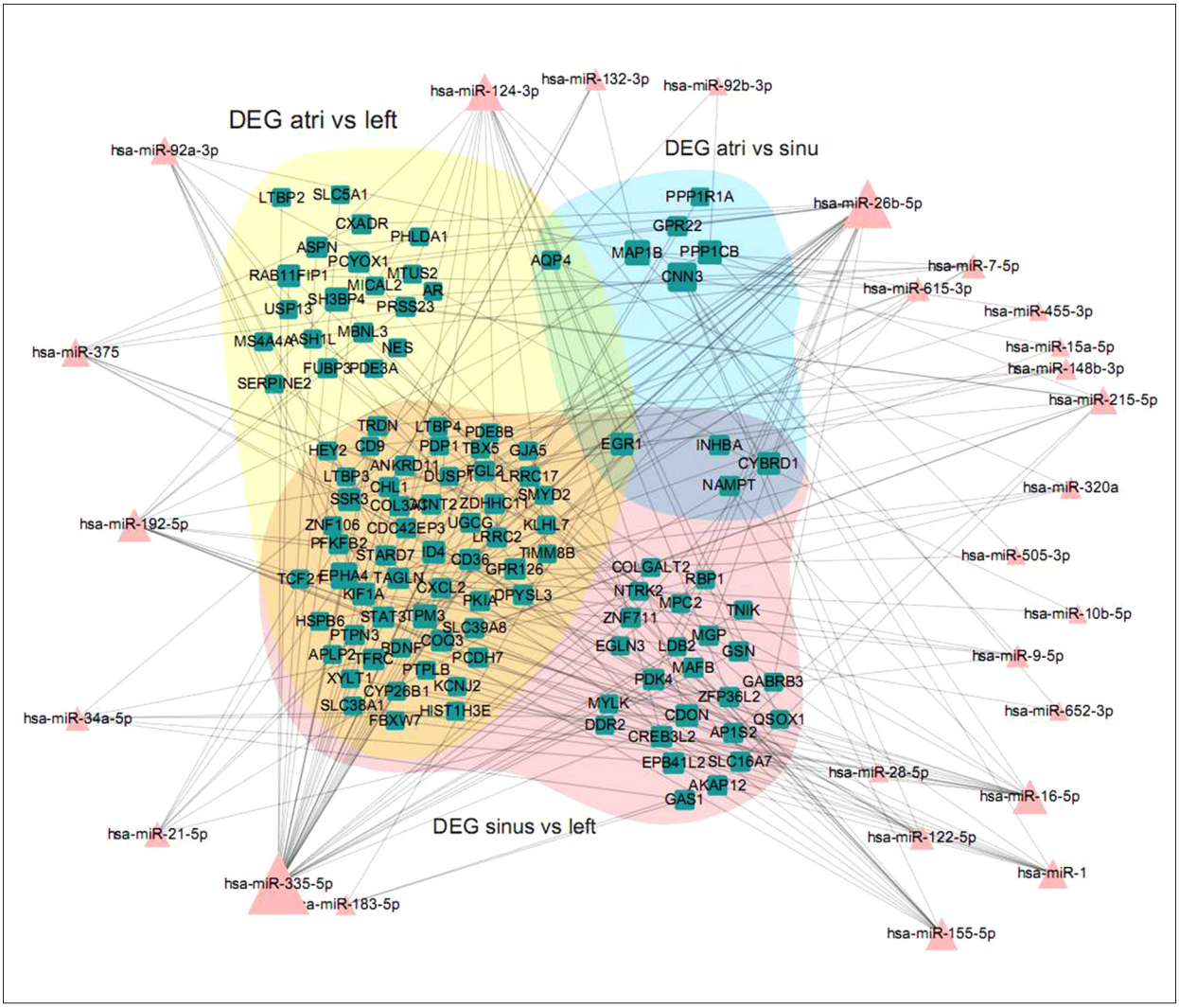

Figure 4. The merged miRNA-DEGs network.

interactions, we obtained 3 miRNA-DEGs networks: AF *vs.* SR, AF *vs.* LV, and SR *vs.* LV (Figures 1–3). In these networks, triangle nodes represent miRNAs and rectangle nodes represent DEGs. In the AF *vs.* SR network, there were 45 nodes and 44 edges. In the AF *vs.* LV network, there were 212 nodes and 304 edges. The SR *vs.* LV network consisted of 235 nodes and 345 edges. Finally, the 3 networks were integrated to detect the miRNAs, which involved the development from non-failing myocardium to atrial fibrillation (AF) and sinus rhythm (SR) (Figure 4). We found that a sub-network composed by miR-124, miR-183, miR-215, miR-192, and a DEG of EGR1 were all represents in the above 3 networks.

Functional enrichment analysis

To explore the biological functions of different sets of DEGs, we conducted GO functional enrichment analysis to the 3 sets of DEGs. Tables 1–3 showed the significant enriched GO terms of AF *vs.* SR, AF *vs.* LV, and SR *vs.* LVy. Some biological terms, such as regulation of heart growth (GO: 0060420), were related to both atrial fibrillation and sinus rhythm.

MicroRNA-inflammation network

To explore the inflammation mechanism in the development of atrial fibrillation and sinus rhythm, we constructed a miRNA-inflammation network, in which the nodes represent inflammation-related DEGs and miRNAs and miR-355 and miR-26b emerged as hubs (Figure 5).

Discussion

In this study, based on the GSE2240 from GEO database, and microRNA-targets relationships from the miRTarBase database, 3 microRNA regulatory networks were constructed. Then the

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Table 1. The significantly enriched Go terms of DEGs between AF and LV.

Term	P value	Genes
GO: 0034404~nucleobase, nucleoside and nucleotide biosynthetic process	0.017073	NAMPT, ATP1B4, NME7
GO: 0034654~nucleobase, nucleoside, nucleotide and nucleic acid biosynthetic process	0.017073	NAMPT, ATP1B4, NME7
GO: 0006753~nucleoside phosphate metabolic process	0.037143	NAMPT, ATP1B4, NME7
GO: 0006073~cellular glucan metabolic process	0.03743	PPP1R1A, PPP1CB
GO: 0044042~glucan metabolic process	0.03743	PPP1R1A, PPP1CB
GO: 0006112~energy reserve metabolic process	0.044556	PPP1R1A, PPP1CB

Table 2. The significantly enriched Go terms of DEGs between AF and SR.

Term	P value	Genes
GO: 0060043~regulation of cardiac muscle cell proliferation	0.002554	TBX5, HEY2, CXADR
GO: 0055021~regulation of cardiac muscle growth	0.002554	TBX5, HEY2, CXADR
GO: 0055024~regulation of cardiac muscle tissue development	0.002554	TBX5, HEY2, CXADR
GO: 0007167~enzyme linked receptor protein signaling pathway	0.002662	EPHA4, FGF18, SMAD9, LTBP2, LTBP3, USP9Y, COL3A1, COL1A2, STAT3
GO: 0060420~regulation of heart growth	0.003051	TBX5, HEY2, CXADR
GO: 0016202~regulation of striated muscle tissue development	0.005113	TBX5, HEY2, MBNL3, CXADR
GO: 0009888~tissue development	0.017406	TCF21, FGF18, PGP, TBX5, UGCG, COL3A1, COL1A2, DHRS9, ENO3, CXADR, HOMER1
GO: 0001944~vasculature development	0.031215	TCF21, FGF18, HEY2, COL3A1, COL1A2, GJA5
GO: 0060044~negative regulation of cardiac muscle cell proliferation	0.034502	TBX5, CXADR
GO: 0001656~metanephros development	0.03786	TCF21, BDNF, SLC5A1
GO: 0009887~organ morphogenesis	0.043332	TCF21, FGF18, PGP, TBX5, HEY2, ANKRD11, COL1A2, TMEM176B, STAT3

3 networks were merged to a final microRNA regulatory network including 27 microRNAs and 108 DEGs.

At first, DEGs between atrial fibrillation (AF), sinus rhythm (SR), and human left ventricular non-failing myocardium (LV) were obtained. We found that a gene-EGR1 was continuously differentially expressed among the 3 kinds of samples. The early growth response transcription factor Egr-1 controls cell-specific responses to proliferation, differentiation, and apoptosis [11]. Although we did not find directed association between AF and EGR1, EGR-1 can up-regulate Siva-1 expression and induces cardiac fibroblast apoptosis. Furthermore, EGR-1 works as a master regulator that plays a key role in triggering inflammation-induced tissue injury after ischemia and reperfusion [12].

Then we implemented GO enrichment by the DAVID tool. We found that some terms related to heart and blood vessel development were detected, indicating that the early stage of heart development might be related to AF (Tables 1–3). Furthermore, some biological energy and glucan metabolic process were also found to be related to AF (Table 2). Some studies hypothesized that increased energy requirements in the atria during myocardial fibrillation lead to activation of anaerobic metabolism [13]. Dong et al. found that activation of β3-AR contributes to atrial metabolic remodeling via transcriptional down-regulation of the PGC-1α/NRF-1/Tfam pathway, which is involved in mitochondrial biogenesis and ultimately perturbs mitochondrial function in rapid pacing-induced AF [14].

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Table 3. The significantly enriched Go terms of DEGs between SR and LV.

Term	P value	Genes
GO: 0009887~organ morphogenesis	3.74E-05	FGF18, MAFB, TBX5, MGP, GAS1, STAT3, SLIT2, TCF21, PGP, GPC3, SMARCD3, HEY2, ANKRD11, NTRK2, COL1A2, TMEM176B
GO: 0009888~tissue development	2.36E-04	FGF18, TBX5, COL3A1, UGCG, DHRS9, MGP, HOMER1, SLIT2, TCF21, PGP, GPC3, GSN, COL1A2, MYH11, ENO3, NR2F2
GO: 0001944~vasculature development	8.74E-04	TCF21, FGF18, HEY2, COL3A1, NTRK2, COL1A2, NR2F2, GJA5, SLIT2
GO: 0007167~enzyme linked receptor protein signaling pathway	0.001607	EPHA4, FGF18, SMAD9, LTBP3, USP9Y, COL3A1, NTRK2, COL1A2, DDR2, STAT3
GO: 0001568~blood vessel development	0.003407	FGF18, HEY2, COL3A1, NTRK2, COL1A2, NR2F2, GJA5, SLIT2
GO: 0001656~metanephros development	0.005137	TCF21, BDNF, GPC3, SLIT2
GO: 0022008~neurogenesis	0.008224	EPHA4, BDNF, GNAO1, MCOLN3, GSN, NTRK2, ID4, GAS1, NR2F2, NTM, STAT3, SLIT2
GO: 0048699~generation of neurons	0.013489	EPHA4, BDNF, GNAO1, MCOLN3, NTRK2, ID4, GAS1, NR2F2, NTM, STAT3, SLIT2
GO: 0006776~vitamin A metabolic process	0.014275	RBP1, CYP26B1, DHRS9
GO: 0001523~retinoid metabolic process	0.014275	RBP1, CYP26B1, DHRS9
GO: 0048729~tissue morphogenesis	0.014479	TCF21, PGP, GPC3, TBX5, COL1A2, SLIT2
GO: 0006721~terpenoid metabolic process	0.016753	RBP1, CYP26B1, DHRS9
GO: 0007166~cell surface receptor linked signal transduction	0.018533	FGF18, SMAD9, GNAO1, GPR126, GABRA4, ADAM23, LTBP3, USP9Y, CXCL2, COL3A1, AKAP12, NPY6R, HOMER1, FRZB, DDR2, STAT3, APLP2, INHBA, EPHA4, ITGA9, CDON, NTRK2, HEY2, COL1A2
GO: 0007417~central nervous system development	0.020067	SMAD9, GNAO1, ADAM23, GSN, MAFB, ID4, GAS1, NR2F2, APLP2
GO: 0042490~mechanoreceptor differentiation	0.022211	BDNF, MCOLN3, NTRK2
GO: 0007420~brain development	0.027914	SMAD9, GNAO1, MAFB, ID4, GAS1, NR2F2, APLP2
GO: 0035113~embryonic appendage morphogenesis	0.032187	TBX5, CYP26B1, GAS1, GJA5
GO: 0030326~embryonic limb morphogenesis	0.032187	TBX5, CYP26B1, GAS1, GJA5
GO: 0051146~striated muscle cell differentiation	0.033135	TBX5, CDON, MYH11, HOMER1
GO: 0060429~epithelium development	0.035001	TCF21, PGP, GPC3, TBX5, DHRS9, NR2F2
GO: 0007423~sensory organ development	0.03614	BDNF, MCOLN3, MAFB, NTRK2, GAS1, STAT3
GO: 0045597~positive regulation of cell differentiation	0.03614	INHBA, BDNF, CD36, SMAD9, TBX5, SLIT2
GO: 0043583~ear development	0.040179	BDNF, MCOLN3, MAFB, GAS1
GO: 0001822~kidney development	0.041242	TCF21, BDNF, GPC3, SLIT2
GO: 0035108~limb morphogenesis	0.044517	TBX5, CYP26B1, GAS1, GJA5
GO: 0030324~lung development	0.044517	TCF21, FGF18, TBX5, MGP
GO: 0002009~morphogenesis of an epithelium	0.04677	TCF21, PGP, GPC3, TBX5
GO: 0014047~glutamate secretion	0.046902	BDNF, NTRK2
GO: 0030323~respiratory tube development	0.047918	TCF21, FGF18, TBX5, MGP
GO: 0006720~isoprenoid metabolic process	0.047932	RBP1, CYP26B1, DHRS9

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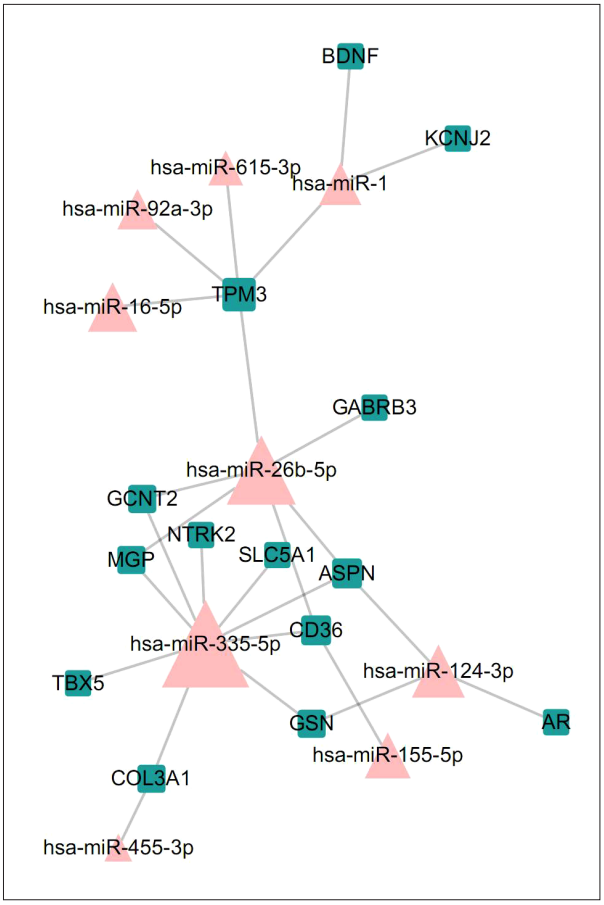

Figure 5. The miRNA-inflammation network. The triangle nodes represent miRNAs and the rectangle nodes represent DEGs which were also related to inflammation.

In the integrated network, we also noticed that in this miRNA synergistic regulatory network some nodes were connected to many other kinds of nodes. For miRNA nodes, miR-355 was the most frequently connected node. miR-355 is over-expressed in human breast cancer and is related to lymph node metastasis and poor patient prognosis. However, to the best of our knowledge, there were no direct reports about miR-355 and AF. This miRNA might be a potential novel regulator in AF. Furthermore, miR-26b also regulated many DEGs and was found to play important roles in cardiovascular diseases. For example, some new miRs were found to modulate physiological cardiac hypertrophy, particularly miR-26b [15]. Furthermore, miR-26b can regulate GATA4 expression, which plays a fundamental role in myocyte growth and survival, via a post-transcriptional mechanism during cardiac hypertrophy [16]. On the other hand, some DEGs were also simultaneously regulated by many miRNAs. For example, CNN3 was regulated by up to 9 miRNAs. Perez-Ilzarbe et al. found that CNN3 was related to paracrine effects of human skeletal myoblasts transplanted in infarcted myocardium [17]. We also noticed that DEGEGR1 was continuously differentially expressed among the 3 kinds of samples. Four miRNAs – miR-124, miR-192, miR-183, and miR-215 – regulated this DEG. Of these miRNAs, microRNA-124 controls the proliferative, migratory, and inflammatory phenotype of pulmonary vascular fibroblasts [18]. Long-term doxorubicin treatment can induce up-regulation of miR-215 in the rat heart [19].

Finally, we constructed an AF-related miRNA-inflammation network in which DEGs were also related to inflammation. The presence of inflammation in the heart or systemic circulation can predict the onset of AF and recurrence in the general population, as well as in patients after cardiac surgery, cardioversion, and catheter ablation [20]. Inflammation also modulates calcium homeostasis and connexins, which are associated with triggers of AF and heterogeneous atrial conduction [20,21]. Also, the noncoding RNAs seem to participate in vascular homeostasis, inflammation, and platelet function [7]. In our network, some DEGs, such as TPM3, and some miRNAs, such as miR-26b and miR-355p, emerged as hubs, indicating that the miRNA-DEGs regulating these relations also play a key role in inflammation in AF.

Conclusions

We constructed an atrial fibrillation- and sinus rhythm-related microRNA regulatory network and revealed the potential mechanism of development of atrial fibrillation and sinus rhythm on the transcriptional regulation level. Furthermore, we identified some crucial regulators in atrial fibrillation and sinus rhythm. Our research may provide important insights into the inflammation mechanism of AF and SR and potentially serve as a reference for the therapeutic strategies of angiocardiopathy.

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