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Identification of microRNA-mRNA interactions in atrial fibrillation using microarray expression profiles and bioinformatics analysis

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Abstract. The present study integrated microRNA (miRNA) and mRNA expression data obtained from atrial fibrillation (AF) tissues and healthy tissues, in order to identify miRNAs and target genes that may be important in the development of AF. The GSE28954 miRNA expression profile and GSE2240 mRNA gene expression profile were downloaded from the Gene Expression Omnibus. Differentially expressed miRNAs and genes (DEGs) in AF tissues, compared with in control samples, were identified and hierarchically clustered. Subsequently, differentially expressed miRNAs and DEGs were searched for in the miRecords database and TarBase, and were used to construct a regulatory network using Cytoscape. Finally, functional analysis of the miRNA-targeted genes was conducted. After data processing, 71 differentially expressed miRNAs and 390 DEGs were identified between AF and normal tissues. A total of 3,506 miRNA-mRNA pairs were selected, of which 372 were simultaneously predicted by both miRecords and TarBase, and were therefore used to construct the miRNA-mRNA regulatory network. Furthermore, 10 miRNAs and 12 targeted mRNAs were detected, which formed 14 interactive pairs. The miRNA-targeted genes were significantly enriched into 14 Gene Ontology (GO) categories, of which the most significant was gene expression regulation (GO 10468), which was associated with 7 miRNAs and 8 target genes. These results suggest that the screened miRNAs and target genes may be target molecules in AF development, and may be beneficial for the early diagnosis and future treatment of AF.

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Introduction

Atrial fibrillation (AF), which is the most common type of arrhythmia, is characterized by an irregular and rapid heartbeat. AF has strong associations with other cardiovascular diseases, including heart failure, coronary artery disease, valvular heart disease, diabetes mellitus, and hypertension (1). The prevalence of AF within a population increases with age, and 8% of people over 80 years old have AF (2). AF accounts for 1/3 of hospital admissions for cardiac rhythm disorders, and the rate of admissions for AF has risen in recent years (3).

The molecular mechanisms underlying AF-associated cardiovascular risk factors have gained attention in recent years, since a clear understanding of these mechanisms is essential for further AF management. Regulation of gene expression by microRNAs (miRNAs) has also garnered much attention. miRNAs belong to a class of endogenous small regulatory RNA molecules, which target mRNAs and trigger either translational suppression or mRNA degradation (4). Abnormal expression of several miRNAs has been reported to be associated with various types of disease, including AF (5). Luo *et al* (6) demonstrated that miR-26 family members were significantly downregulated in left atrial appendages from a canine model of AF (miR-26a), and in right atrial appendages from patients with AF (miR-26a and miR-26b). Gene expression profiling has also been used to investigate various types of disease, and a range of gene signatures have been identified using DNA chips (7). Chen *et al* (7) identified 31 differentially expressed genes, which were associated with transcriptional regulation, signal transduction, and structural components, in a porcine model of AF using a low-density cDNA array. This study indicated that four and a half LIM domains 1 and cardiac ankyrin repeat protein may have important regulatory roles in AF activation.

miRNAs, as important regulators of mRNAs, are excellent biomarkers for disease development. mRNA and miRNA markers always function through relationship networks. It has previously been reported that miRNA-1 levels are markedly reduced in human AF, which may contribute to upregulation of Kir2.1 subunits, leading to increased cardiac

inward-rectifier potassium current (I_{K1}) (8). Furthermore, miR-26 has been suggested as a potentially important regulator of potassium channel, inwardly rectifying subfamily J, member 2 gene expression and, via I_{K1}, a determinant of AF susceptibility (6).

The present study aimed to screen the differentially expressed miRNAs and genes (DEGs) in AF tissues compared with control samples, using expression profile data downloaded from an online database (GSE28954 and GSE2240). In addition, a regulatory network was constructed using Cytoscape and a functional analysis of miRNA-targeted genes was performed. The results of the present study may help elucidate the mechanisms underlying AF pathogenesis and contribute to the improvement of AF treatment.

Materials and methods

Datasets. A dataset containing mRNA gene expression profiles for 10 patients with AF and 10 control samples (9,10) was downloaded from the Gene Expression Omnibus (GEO) deposited on the public National Center for Biotechnology Information database (accession number: GSE2240) (http://www.ncbi.nlm.nih.gov/geo/). U133A and U133B microarray chips (Affymetrix, Inc., Santa Clara, CA, USA), together representing 44,928 probe sets, were used to analyze each human heart sample. A dataset containing miRNA expression profiles for 10 patients with AF and 5 healthy control samples (11) was downloaded from the GEO (accession number: GSE28954). miRNA expression profiling was conducted using the 15 human samples (10 AF and 5 healthy controls) using microarrays covering whole miRNAs from Agilent Technologies (Human miRNA Microarrays: G4470B, cat. no. 019118 and V3, cat. no. 021827; Santa Clara, CA, USA). According to the original data, all studies were approved by the appropriate Human Ethics Committees and informed consent was obtained from all of the patients.

Data processing and significance analysis. The raw miRNA and mRNA microarray data of all AF and control samples were normalized simultaneously using the robust multiarray average (RMA) method (12), implemented in R/Bioconductor project (https://www.bioconductor.org/). DEGs between AF and control samples were calculated using the significance analysis of microarray (SAM) method (13). Furthermore, each miRNA expression comparison was tested between AF patients and healthy controls using Student's t-test (14), and raw P-values were adjusted using the Benjamini-Hochberg method (15). Fold changes between the two groups were also calculated. A false discovery rate (FDR)<0.05 from Student's t-test, and P<0.05 from SAM were used to identify differentially expressed miRNAs and DEGs.

Hierarchical cluster analysis of selected miRNAs and genes. The hierarchical cluster analysis of differentially expressed miRNAs was performed using CLUSTER3.0 (16), and the hierarchical clustering heat-map was visualized by TreeView (17).

Identification of potential target genes of miRNAs. The candidate target genes of the identified miRNAs were predicted using miRecords (18) (http://mirecords.biolead.org/; no longer accessible) and TarBase (19) (http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=tarbase/index/). The miRNAs differentially expressed between AF patients and healthy controls were searched for in the miRecords database and TarBase, which contains validated miRNA-target interactions. In addition, the probability of a miRNA-target interaction existing between differentially expressed miRNAs and DEGs was predicted by miRecords (score ≥50, energy ≤-20). The untranslated region (UTR) location was also predicted.

Table I. Selected miRNA-mRNA pairs.

Diff. miRNAs	Diff. & validated targets	miRNA-mRNA expression
hsa-miR-186	AKAP12	Up-down
hsa-miR-101	ARID1A	Up-down
hsa-miR-221	BNIP3L	Up-down
hsa-miR-34b*	CREB1	Up-down
hsa-miR-146a	EGFR	Up-down
hsa-miR-146a	ERBB4	Up-down
hsa-miR-221	FOXO3	Up-down
hsa-miR-424	PIAS1	Up-down
hsa-miR-221	PIK3R1	Up-down
hsa-miR-29b	PIK3R1	Up-down
hsa-miR-221	TIMP3	Up-down
hsa-miR-31	YY1	Up-down
hsa-miR-34a	YY1	Up-down
hsa-miR-214	ZBTB20	Up-down

Diff., differentially expressed; miRNA/miR, microRNA; Up, upregulated; down, downregulated.

Construction of a miRNA-target network. miRNAs regulate target gene expression via mRNA degradation or translational inhibition (20,21). The expression of miRNA-targeted genes that are regulated by mRNA degradation are negatively correlated with the expression of miRNA regulators. Therefore, a miRNA-mRNA regulatory network was constructed containing the paired miRNA-mRNA expression profiles, and the putative target genes of miRNAs were predicted. Predictive and validated miRNA-mRNA pairs were extracted from the miRecords database and TarBase, and only the miRNA-mRNA pairs predicted by both miRecords database and TarBase were retained. Subsequently, a miRNA-mRNA regulatory network was constructed via Cytoscape (22).

Functional analysis of targeted genes from the network. To obtain a better understanding of the biological function of miRNAs and their target genes in AF, a functional analysis of the miRNA-targeted genes was carried out using the Database for Annotation, Visualization and Integrated Discovery (23) (https://david.ncifcrf.gov/). FDR<0.05 was set as the cut-off criterion.

Table II. Enriched GO terms of target genes.

GO term ID	FDR	Description	Target genes
10468	0.00895	Gene expression	ZBTB20, ERBB4, YY1, CREB1, BNIP3L, ARID1A, PIAS1, FOXO3
19219	0.00973	Nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	ZBTB20, ERBB4, YY1, CREB1, AKAP12, ARID1A, PIAS1, FOXO3
48522	0.00115	Positive regulation of cellular process	EGFR, ERBB4, CREB1, BNIP3L, AKAP12, ARID1A, PIAS1, FOXO3, PIK3R1
48518	0.00115	Positive regulation of biological process	EGFR, ERBB4, CREB1, BNIP3L, AKAP12, ARID1A, PIAS1, FOXO3, PIK3R1
31326	0.00352	Cellular biosynthetic process	EGFR, ZBTB20, ERBB4, YY1, CREB1, AKAP12, ARID1A, PIAS1, FOXO3
51171	0.00352	Nitrogen compound metabolic process	EGFR, ZBTB20, ERBB4, YY1, CREB1, AKAP12, ARID1A, PIAS1, FOXO3
9889	0.00352	Biosynthetic process	EGFR, ZBTB20, ERBB4, YY1, CREB1, AKAP12, ARID1A, PIAS1, FOXO3
60255	0.00179	Macromolecule metabolic process	EGFR, ZBTB20, ERBB4, YY1, CREB1, BNIP3L, ARID1A, PIAS1, FOXO3, TIMP3
80090	0.00254	Primary metabolic process	EGFR, ZBTB20, ERBB4, YY1, CREB1, AKAP12, ARID1A, PIAS1, FOXO3, TIMP3
31323	0.00292	Cellular metabolic process	EGFR, ZBTB20, ERBB4, YY1, CREB1, AKAP12, ARID1A, PIAS1, FOXO3, TIMP3
19222	0.00115	Metabolic process	EGFR, ZBTB20, ERBB4, YY1, CREB1, BNIP3L, AKAP12, ARID1A, PIAS1, FOXO3, TIMP3
50794	0.00292	Regulation of cellular process	EGFR, ZBTB20, ERBB4, YY1, CREB1, BNIP3L, AKAP12, ARID1A, PIAS1, FOXO3, TIMP3, PIK3R1
50789	0.00351	Regulation of biological process	EGFR, ZBTB20, ERBB4, YY1, CREB1, BNIP3L, AKAP12, ARID1A, PIAS1, FOXO3, TIMP3, PIK3R1
65007	0.00463	Biological regulation	EGFR, ZBTB20, ERBB4, YY1, CREB1, BNIP3L, AKAP12, ARID1A, PIAS1, FOXO3, TIMP3, PIK3R1

FDR, false discovery rate; GO, gene ontology.

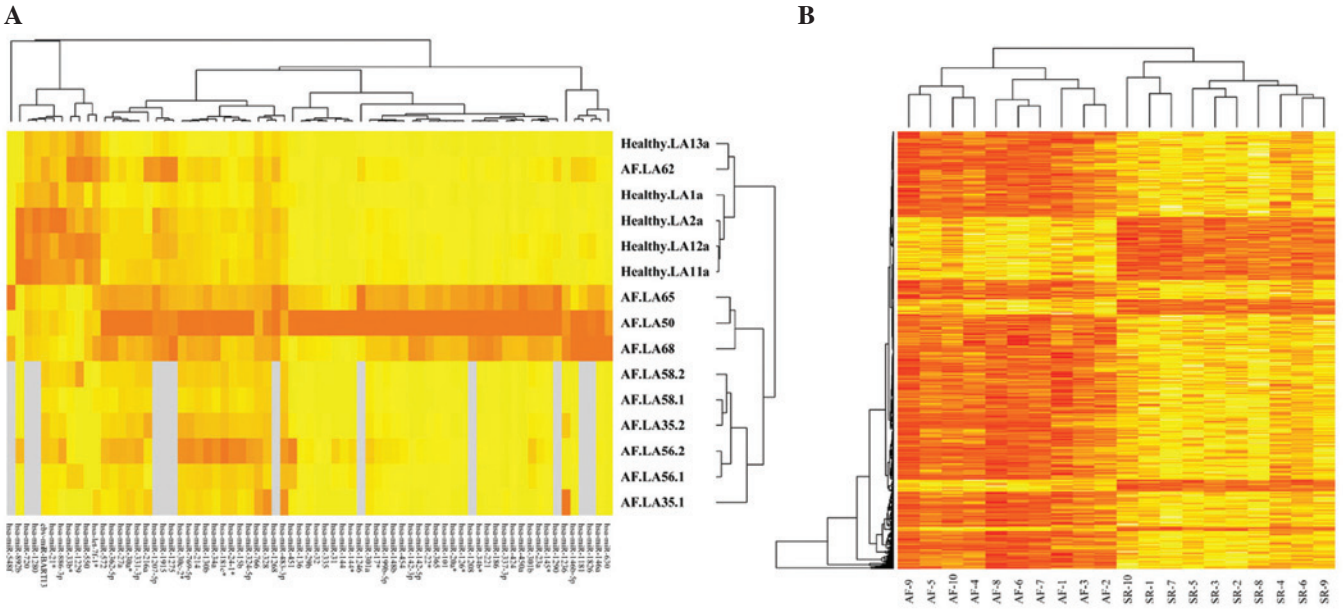

Figure 1. (A) Heat-map of selected microRNA expression and (B) mRNA expression in the atrial fibrillation (AF) and normal control samples. Red indicates high expression, yellow indicates low expression and gray indicates missing values. SR, sinus rhythm.

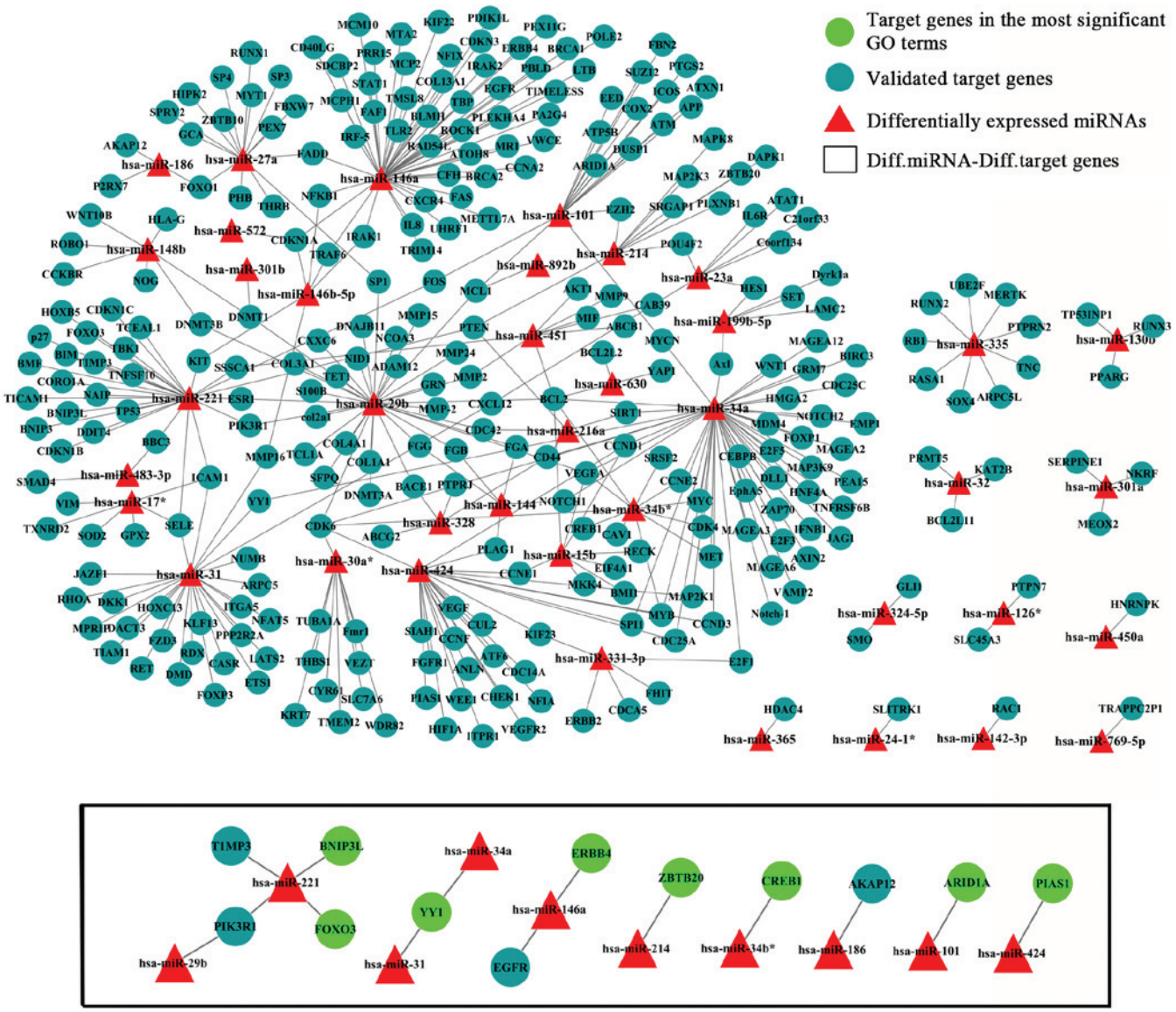

Figure 2. Candidate microRNA (miRNA)-mRNA target network was constructed using Cytoscape. Red triangles represent differentially expressed miRNAs; blue circles represent miRNA-targeted genes; the black box refers to the 14 interactive pairs of selected miRNAs and their targets that were predicted by miRecords and TarBase; and the green circles represent target genes involved in the most significantly enriched Gene Ontology terms. Diff., differentially expressed.

Results

Differentially expressed miRNAs and DEGs, and cluster analysis. Following normalization using the RMA algorithm and SAM analysis of raw data, 71 significantly differentially expressed miRNAs and 390 DEGs were identified between the AF and normal tissues. In addition, the expression levels of these miRNAs and mRNAs were analyzed via heat-maps (Fig. 1).

Construction of the miRNA-target network. Using the criteria: Score ≥50 and energy ≤-20, 3,506 miRNA-mRNA pairs were predicted. A total of 372 validated miRNA-mRNA relationship pairs were simultaneously predicted by the miRecords database and TarBase, and were therefore used to construct the miRNA-mRNA regulatory network (Fig. 2, upper panel). Furthermore, 10 miRNAs and 12 targeted mRNAs were identified, which formed 14 interactive pairs (Fig. 2, lower panel). The selected miRNAs were upregulated in AF tissues, whereas the mRNAs were downregulated in the AF tissues. The expression levels of the 14 miRNA-mRNA pairs are presented in Table I, which indicated that the selected miRNAs were upregulated in AF tissues, whereas the mRNAs were downregulated.

Functional analysis of miRNA-targeted genes. The miRNA-targeted genes were significantly enriched into 14 Gene Ontology (GO) categories (Table II). The GO term gene expression (GO10468) was the most significantly enriched, and was associated with 8 miRNAs (miR-146a, miR-31, miR-34a, miR-221, miR-424, miR34b*, miR-214, miR-101) and 8 target genes [zinc finger and BTB domain

containing 20 (ZBTB20), Erb-B2 receptor tyrosine kinase 4 (ERBB4), YY1 transcription factor (YY1), cAMP response element-binding protein (CREB1), BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like (BNIP3L), AT rich interactive domain 1A (ARID1A), protein inhibitor of activated STAT, 1 (PIAS1), forkhead box O3 (FOXO3)]. No significantly enriched Kyoto Encyclopedia of Genes and Genomes pathway was detected.

Discussion

miRNAs are negative regulators of gene expression, which regulate various biological processes via inhibition of their target gene expression. It is important to identify miRNA targets and elucidate their complex regulatory networks, in order to contribute to a systematic understanding of pathological changes in medical and clinical studies. AF is associated with alterations to several proteins, molecules and pathways. As a result, these changes result in disease progression, which may develop into heart failure. In the present study, a very strict criteria was adopted to identify miRNA targets. Briefly, the target genes had to be significantly differentially expressed, and predicted by both miRecords and TarBase. Consequently, 14 miRNA-mRNA pairs were identified to have a high probability of association with AF.

Compared with previous studies, the miRNAs selected in the present study included genes that have been reported to be involved in heart disease, including miR-221 (7,24) and miR-101 (25,26). In the present study, ARID1A gene expression was shown to be predominantly regulated by miR-101, which binds with the 3'-UTR of ARID1A, thus inducing ARID1A instability or translational inhibition. miR-101 and its target gene ARID1A participated in the most significant GO term (GO: 10468, regulation of gene expression) and therefore may be considered a specific biosignature of AF. In addition, several other miRNAs, including miR-146a, miR-31, miR-34a, miR-221, miR-424, miR34b* and miR-214, were identified to be strongly associated with AF. The regulation of miRNA-mRNA pairs differs in various diseases, resulting in disease-specific expression profiles that interact via a complex regulatory network. Although numerous methods have been used to identify regulatory miRNA-mRNA pairs in disease, no method is perfect or able to determine all miRNA-mRNA pairs.

The present study identified 8 target genes: ZBTB20, ERBB4, YY1, CREB1, BNIP3L, ARID1A, PIAS1 and FOXO3. It has previously been demonstrated that ErbB receptors (ErbB2, ErbB3, ErbB4) are overexpressed in the atrium, compared with the ventricle, and are downregulated in AF (27). It has therefore been hypothesized that downregulation of ErbB may contribute to the propensity for structural remodeling in AF and congestive heart failure. Furthermore, ZBTB20 (28), YY1 (29), BNIP3L (30), PIAS1 (31) and FOXO3 (32) have been suggested to be associated with AF. Notably, no previous study has reported a relationship between CREB1 expression and AF.

There are several limitations to the present study. Firstly, the miRNA and mRNA data of AF and normal tissues were obtained from different studies, which may affect the results. Furthermore, the results are based on pure public data and further experimental validation is required, such as target miRNA and mRNA knockdown experiments.

In conclusion, the miRNA-mRNA interactions identified in the present study may act as biosignatures for AF, and may provide evidence for the identification of a novel agent for the diagnosis and gene-targeted therapy of AF.

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