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The Role of Competing Endogenous RNA (ceRNA) Network in Ischemic Cardiomyopathy by Bioinformatic Analysis

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Abstract: ***Background:*** *Ischemic cardiomyopathy (ISCM) following myocardial infarction is closely related with a poor prognosis in patients with coronary heart disease. Several researches have showed that noncoding RNAs, including long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) are involved in the progression of ISCM. The aim of the present study was to explore the potential biomarkers and competing endogenous RNA (ceRNA) machenism in ISCM.* ***Methods:*** *Based on the open-source database, we identified differentially expressed genes (DEGs) and differentially expressed lncRNAs (DELs) between samples from ISCM patients and controls using affy and limma package in R (absolute log2 fold change ≥1 and p<0.05). We prediced target miRNAs of DELs and DEGs by TargetScanHuman, miRDB and miRTarBase with at least two validations in three databases. Gene ontology (GO) analysis of DEGs was performed by clusterProfiler package in R. Taken the nodes together, we tried to build a net according to ceRNA theory.* ***Results:*** *We integrated the crosstalk of DEGs, DELs and miRNAs and constructed a ceRNA network. There are 21 lncRNAs, 39 miRNAs, and 41 mRNAs involved in the network. Functional analysis showed that DEGs were most prominently associated with molecular functions in extracellular matrix.* ***Conclusion:*** *By constructing ceRNA net in ISCM, we found that several important lncRNAs and genes were included. More nodes need to be verified both* in vivo *and* in vitro.

Keywords: *Ischemic cardiomyopathy (ISCM), Long nongcoding RNA (lncRNA), Bioinformatics, Competing endogenous RNA (ceRNA), Cardiovascular disease*

1. Introduction

Ischemic cardiomyopathy (ISCM) following myocardial infarction is caused by complex and dynamics changes of the myocardium and ultimately can give rise to heart failure. Ischemia results in neurohormonal activation and intracellular signaling processes in the infarct border zone and the non-infarcted myocardium, and triggers processes such as ventricular remodeling[1, 2]. A fraction of ISCM patients often display no obvious symptoms after silent ischemia, however, a strong relationship between ischemic heart failure and mortality has been demonstrated. Therefore, it is critical to explore the molecular mechanisms of myocardial injury and identify novel biomarkers of ISCM.

There is increasing evidence that noncoding RNAs, including long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) play a key role in ISCM progression, where these RNAs can exert both protective and harmful effects on ventricular remodeling[3, 4]. A traditional mode of action of lncRNAs is to compete with mRNAs and thereby "block" miRNAs, which can downregulate the corresponding mRNA. Despite several predictions were made on dysregulated ceRNA interaction in heart failure arising from different etiologies or dilated cardiomyopathy, little literature is available on the ceRNA network between ISCM and normal status[5, 6]. Using bioinformatic tools, we aimed to elucidate the role of noncoding RNAs in ISCM based on this competing endogenous RNA (ceRNA) hypothesis in order to improve diagnosis and prognosis of ISCM.

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2. Methods

2.1. Data collection

Datasets containing expression data of mRNAs and lncRNAs in ISCM patients were obtained from NCBI's Gene Expression Omnibus (GEO)[7]. A total of 39 myocardial mRNA array samples were collected, including ISCM and control samples. GSE1145 and GSE76701[8] contained 20 and 4 ISCM samples, as well as 11 and 4 control samples, respectively, obtained using the GPL570 platforms. The myocardial lncRNA expression data in GSE77399[9] consisted of data from 13 ISCM patients and 12 control patients.

2.2. Data processing

Based on raw data annotation, data normalization of GSE1145 and GSE76701 was performed using the robust multiarrary average (RMA) expression measure and data filtering using the Wilcoxon signed rank-based gene expression presence/absence detection algorithm by the affy package in R[10]. Probes were then converted to gene symbols. After merging of the two datasets and performing batch normalization, the limma package was used to identify the differentially expressed genes (DEGs)[11]. The same method was applied to obtain differentially expressed lncRNAs (DELs) in GSE77399. All thresholds of mRNAs and lncRNAs were FDR(false discovery rate) corrected ($p < 0.05$) and filtered by an absolute $\log_2$ fold change ≥1 ($|\log_2(\text{fold-change})| \geq 1$).

2.3. Functional enrichment analysis of DEGs in ISCM

Gene ontology (GO) analysis of DEGs was performed in R using the clusterProfiler package[12]. $P < 0.05$ was considered statistically significant.

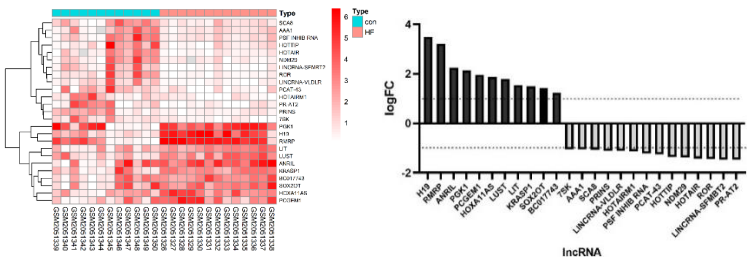
2.4. Construction of lncRNA-miRNA-mRNA network

MiRNA targets were predicted using miRcode[13], which identifies the miRNA family and lncRNA interactions and provides a "whole transcriptome" human microRNA target prediction based on the comprehensive GENCODE gene annotation[14]. We then evaluated connections between miRNAs and DEGs, with at least two validations in three databases, TargetScanHuman[15], miRDB[16] and miRTarBase[17]. Cytoscape v3.7.1[18] was used to construct and visualize the lncRNA-miRNA-mRNA competing endogenous RNA (ceRNA) network.

3. Results

3.1. Cluster analysis of differentially expressed mRNAs and lncRNAs

DEGs were identified comparing samples from ISCM patients and control. We detected a total of 80 DEGs in our merged datasets (based on GSE1145 and GSE76701), of which 31 genes were upregulated and 49 were downregulated. In GSE77399, there were 14 downregulated lncRNAs and 11 upregulated lncRNA in ISCM patients compared to controls (Fig. 1). The top 5 DEGs and DELs are listed in Table 1 and Table 2, and the heatmap and volcano plot of DEGs are shown in Fig. 2a and Fig. 2b.



(a) *(b)*

Figure 1: Expression signature of lncRNAs. (a)heatmap. (b) Relative expression of DELs. DELs with absolute $\log_2$(fold-change)≥1. logFC: $\log_2$(fold-change).

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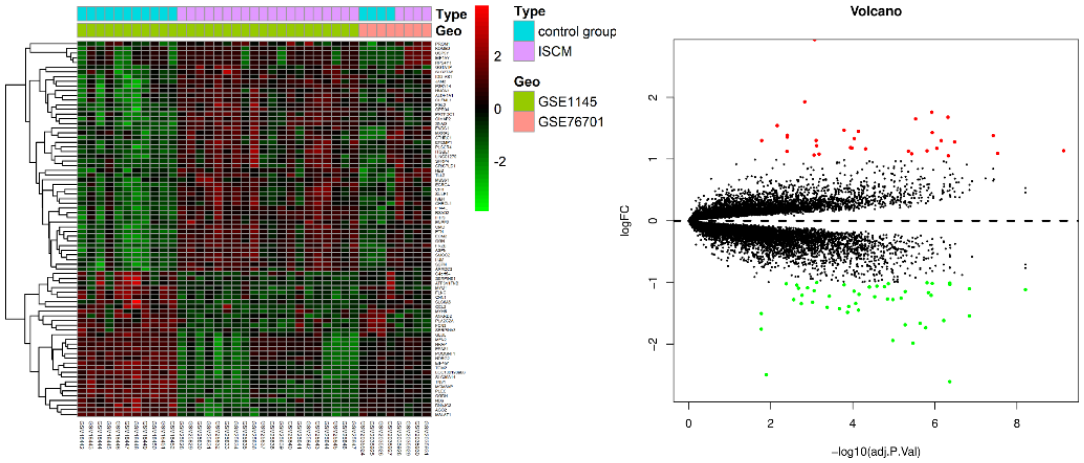

(a) *(b)*

Figure 2: Expression signature of mRNAs. (a)heatmap. (b)volcano plot.

Table 1: Top ten DEGs ranked by fold change in up-regulated and down-regulated genes of the ISCM samples compared to the control group.

ID	logFC	AveExpr	*t*	*p*	*adj.p*	*B*	Regulation
C4orf54	2.94	7.43	4.45	<0.01	<0.01	1.49	Upregulation
NRAP	1.93	10.27	4.21	<0.01	<0.01	0.78	Upregulation
TGM2	1.76	9.11	7.37	<0.01	<0.01	10.55	Upregulation
OGDH	1.68	8.43	7.82	<0.01	<0.01	11.91	Upregulation
SERPINA3	1.65	9.28	6.94	<0.01	<0.01	9.2	Upregulation
RPS4Y1	-1.75	10.17	-3.09	<0.01	<0.01	-2.25	Downregulation
HBB	-1.94	11.01	-6.33	<0.01	<0.01	7.29	Downregulation
ASPN	-1.98	9.79	-6.88	<0.01	<0.01	9.01	Downregulation
EIF1AY	-2.49	8.59	-3.23	<0.01	0.01	-1.91	Downregulation
OGN	-2.6	9.23	-7.88	<0.01	<0.01	12.09	Downregulation

FC: fold change; AveExpr: average expression; *adj.p*: adjusted *p* value.

Table 2: Top ten DELs ranked by fold change in up-regulated and down-regulated lncRNAs of the ISCM samples compared to the control group.

ID	logFC	AveExpr	*t*	*p*	*adj.p*	*B*	Regulation
H19	3.49	3.21	7.19	0.01	0.04	7.70	Upregulation
RMRP	3.22	3.82	5.01	<0.01	<0.01	2.10	Upregulation
ANRIL	2.24	3.35	3.69	<0.01	<0.01	-1.31	Upregulation
PGK1	2.14	3.56	2.95	<0.01	0.02	-3.09	Upregulation
PCGEM1	1.96	2.59	3.53	<0.01	<0.01	-1.71	Upregulation
PR-AT2	-1.47	1.13	-3.25	<0.01	<0.01	-2.37	Downregulation
LINCRNA-SFMBT2	-1.47	0.99	-3.82	<0.01	<0.01	-0.99	Downregulation
ROR	-1.44	1.06	-3.38	<0.01	0.03	-2.07	Downregulation
HOTAIR	-1.43	1.12	-4.01	<0.01	<0.01	-0.53	Downregulation
NDM29	-1.38	1.28	-3.10	<0.01	<0.01	-2.73	Downregulation

FC: fold change; AveExpr: average expression; *adj.p*: adjusted *p* value.

3.2. Functional analysis of DEGs in ISCM

To elucidate the biological function of the DEGs identified above, we carried out GO analysis (Fig. 3). This revealed that the DEGs were most prominently associated with the molecular functions of "extracellular matrix structural component", "actin binding" and "sulfur compound binding".

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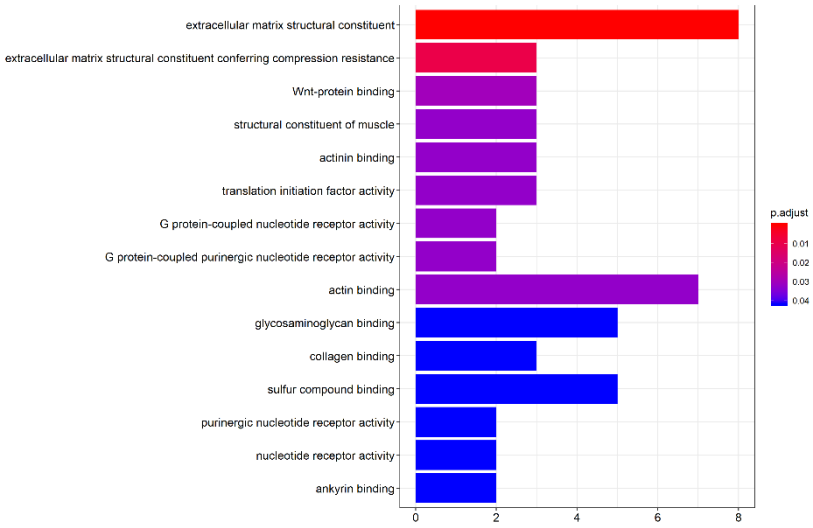

Figure 3: GO analysis of DEGs.

3.3. Prediction of target miRNAs

MiRNAs targeting the DELs (differentially expressed lncRNAs) identified above were searched using miRcode datase. Then, we predicted targets of miRNAs by TargetScanHuman, miRTarBase, and miRDB. A total of 21,605 miRNA-target interactions are presented in at least two of the three databases. After collecting all these targets in the interactions, we defined 8,605 genes as target set of miRNAs (Fig. 4).

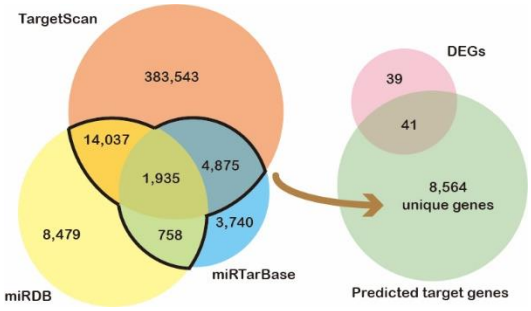

Figure 4: Collection of miRNAs and miRNA targets. We searched target miRNA of DELs by miRcode database. Then 21,605 interactions of miRNAs and target genes were predicted in at least two of the three databases (TargetScanHuman, miRTarBase, and miRDB). All these interactions have 8,605 unique genes.

3.4. Construction of lncRNA-miRNA-mRNA competing endogenous RNA (ceRNA) network

According to our work above, we found 41 DEGs are among target set of miRNAs (Fig. 4). Therefore, we built a ceRNA network to show potential interactions between lncRNAs, miRNAs, and mRNAs. The network is shown in Fig. 5, where we included 11 lncRNAs, 39 miRNAs, and 41 mRNAs.

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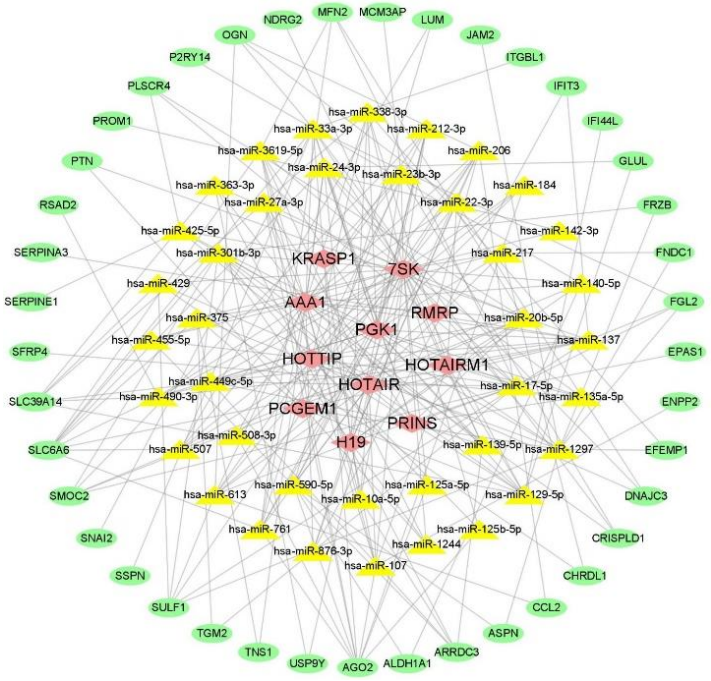

Figure 5: lncRNA-miRNA-mRNA competing endogenous RNA network. The red rhombuses represent lncRNAs, the green circles represent mRNAs, and the yellow triangles represent miRNAs.

4. Discussion

In our analysis, we identified 80 DEGs and 25 DELs between ISCM and control samples. GO analysis revealed that the DEGs are predominantly components of the extracellular matrix structure. Based on DEGs, DELs and predictions from miRNA databases, we found a total of 39 miRNAs to potentially link the function of lncRNAs and mRNAs in ISCM. Using this information, we constructed a ceRNA network. Among the knots in the network, a number of them were revealed in experiments or clinical trials connected with cardiovascular disorders. Fewer researches displayed the crosstalk between them.

Asporin (ASPN) has previously been reported to regulate chondrogenesis by inhibition of transforming growth factor-beta-1-induced gene expression in cartilage. This protein also binds collagen and calcium and may induce collagen mineralization. Li et al. found that ASPN can subsequently increase cardiomyocyte apoptosis, which can be however reversed by GSPB2[19]. Osteoglycin (OGN) is a member of the small leucine-rich proteoglycan (SLRP) family of proteins which regulates osteoblast differentiation. It is a basic component of the vascular extracellular matrix (ECM) and is involved in biological processes such as inflammation, fibrosis, and cell proliferation[20]. OGN has previously been linked to an elevated left ventricular mass in cardiomyopathy and increased serum OGN is associated with poor angiographic coronary collateralization in patients with coronary total occlusion[21, 22]. OGN might participate in cardiac remodeling after myocardial infarction (MI) by promoting maturation of cells and infarct healing, as well as suppressing cardiac myofibroblast proliferation and migration[23]. In a study involving 462 patients, plasma levels of OGN were high in the coronary artery disease (CAD) group, however, it was not an independent risk factor for CAD[22]. Another study involving 383 patients with stage 3 and 4 chronic kidney disease (CKD) stage showed that higher OGN levels came along with increased mortality and composite outcome (i.e., the occurrence of major adverse cardiovascular and cerebrovascular events or all-cause mortality), in particular in patients without diabetes[24].

SERPINA3 encodes the alpha-1-antichymotrypsin precursor protein, which has previously been shown to participate in inflammation. Yang et al. found that heart failure patients exhibit higher SerpinA3 levels than that controls, both in epicardial adipose tissue and plasma samples[25]. Nonetheless, the prognostic value of SerpinA3 is unclear[26]. Transglutaminase2, encoded by the TGM2 gene, participates in the differentiation of human monocytes into macrophages *in vivo*, and is furthermore involved in macrophage phagocytosis which can help to maintain the stability of atherosclerotic plaques[27, 28]. Sulf1 has been found to regulate vascular smooth muscle cell proliferation, migration and apoptosis, and to promote the anti-hypertensive actions of CCL5 via the AT2R pathway in hypertensive rats[29, 30]. Wollert et al. demonstrated that both Sulf1 and Sulf2 attenuate adverse left ventricle remodeling after MI and

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promoted angiogenesis in the infarct zone[31].

Among the DELs, the dysregulations of CDKN2B-AS (ANRIL), HOTAIR and LOC285194 (TUSC7) have previously been validated in heart tissue and peripheral blood of post-ischemic end-stage heart failure patients. It has little reported whether they interact with other knots in our network. As a ceRNA competing inhibiting miRNAs, H19 plays a protective role after ischemic reperfusion injury. Experiments *in vivo* and *in vitro* have shown that H19-derived miR-675 targets PPARα to damage cardiac structure and function following myocardial ischemia and reperfusion (I/R) injury[32]. H19 has been found to alleviate injury of heart cells by competing with B cell leukemia/lymphoma 2 (Bcl-2) to sponge miR-887-3p in myocardial I/R model and the cellular inhibitor of apoptosis protein 1 (cIAP1) to sponge miR-29b-3p in hypoxia/postconditioning model[33, 34]. Furthermore, H19 has been shown to directly bind to miR-103/107 and positively influence the expression of (FADD) which inhibit H2O2-induced necrosis[35]. HOX transcription antisense RNA (HOTAIR), is one of the most prominently studied lncRNAs with reported involvements in cancer and cardiovascular diseases, amongst others. HOTAIR has been demonstrated to act as a "miRNA sponge" for miR-519d-3p and miR-1 in myocardial infarction animal models, resulting in a protective effect following acute myocardial infarction (AMI)[36, 37]. Zhang et al. studied 50 AMI patients and 50 age- and sex-matched control patients and found that plasma HOTAIR levels at 24 h following AMI were lower than in the control group, indicating a negative correlation with the cardiac troponin I (cTnI) concentration[37]. In addition, HOTAIR participates in the progression of diabetic cardiomyopathy where it competes with SIRT1 to block miR-34a *in vivo* and *in vitro*[38].

Nevertheless, there were some limitations in our work. First, the miRNAs were predicted by bioinformatic tools, not by microarray or sequencing. Second, we collect online data from different group of people, and the sample size was small. Last but not the least, we need further research into confirming our prediction. Meanwhile, ex vitro experiments were necessary to explore the crosstalk.

Our analyses based on GEO datasets GSE1145, GSE76701 and GSE77399 helped to develop a ceRNA network for ISCM. Several components of this network have previously been shown to be involved in ISCM by fundamental experiments or clinical trials. To a certain extent, this suggested the network is worth going into more verification.

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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.

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