Identification of lncRNA competitively regulated subpathways in myocardial infarction

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Abstract. The functions of long non-coding RNAs (lncRNAs) in myocardial infarction (MI) remain largely unknown. Thus, we used the subp athway-LINCE method to characterize the potential roles of lncRNAs in MI. Candidate lncRNA-mRNA interactions were obtained from miRNA-mRNA interactions and lncRNA-miRNA interactions. Then the lncRNA and mRNA co-expression relationship pairs (LncGenePairs) were screened from the lncRNAs and mRNA intersections, which were extracted through candidate lncRNA-mRNA interactions and sample gene expression profiles. The lncRNAs in LncGenePairs were embedded into pathway graphs as nodes through linking to their regulated mRNAs, which resulted in obtaining condition-specific lncRNA competitively regulated signal pathways (csLncRPs). Finally, the csLncRPs were calculated using lenient distance similarity to obtain the lncRNA competitively regulated subpathways. Based on the statistical significance of signal subpathways, lncRNA-mRNA networks were constructed, in which hub lncRNAs were selected. A total of 65 lncRNAs competitively regulated subpathways and 13 hub lncRNAs were obtained, which associated with a risk of MI. Identifying lncRNAs competitively regulated subpathways not only provides potential lncRNA biomarkers for MI, but also helps the understanding of pathogenesis of MI.

Introduction

Myocardial infarction (MI), a common presentation for ischemic heart disease/coronary artery disease, is a major contributor to mortality rates worldwide (1). The major trigger of MI is generally owing to thrombus formation in a coronary artery. Accordingly, the current treatments mainly include medical therapy (e.g. anticoagulant medications, antiplatelets) and elective catheterization. However, some disadvantages can not be ignored, such as high risk of bleeding in medical therapy and high cost of treatment in elective catheterization (2). In order to effectively prevent and treat MI, seeking the exact pathogenesis of MI at various aspects is necessary. Currently research directions mainly include improvement of coronary blood flow, inhibition of apoptosis, reduction of oxygen consumption, and revascularization procedures (3). However, few studies have been conducted in the pathogenesis of MI at the non-coding RNA (ncRNA) level.

ncRNAs, RNA molecules, are not translated into proteins, which mainly include ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), short non-coding RNAs such as microRNAs (miRNAs) and the long non-coding RNAs (lncRNAs). lncRNAs are a set of RNAs longer than 200 nucleotides, and participate in many fundamental biological processes mainly including genomic imprinting and chromatin modification (4). Although the effects of lncRNAs on various cancers (5) and neuronal diseases (6,7) have been widely investigated, the study number of lncRNA function in cardiovascular diseases is very limited. Currently, some transcripts have been investigated for their potential role as biomarkers of cardiovascular diseases. The mitochondrial lncRNA LIPCAR, as a novel biomarker, can predict future death in heart failure patients (8). lncRNA CoroMarker is a diagnostic biomarker for coronary artery disease (9). In addition, lncRNA MIAT might regulate MI via functioning as a competing endogenous RNA for various targets (10,11).

miRNAs are short non-coding RNAs (approximately 20 nucleotides) and negatively regulate target genes. Different from lncRNAs, miRNAs have been largely investigated in the context of MI (12). The relationship between miRNAs and lncRNAs has been extensively demonstrated, among which lncRNAs can indirectly compete with mRNAs through binding to miRNAs (13,14). For instance, lncRNA CHRF could regulate cardiac hypertrophy by targeting miR-489 (15). Recognizing lncRNA competitively regulated subpathway can reveal the pathogenesis of disease and the molecular mechanism of lncRNAs in the disease context. However, the relevant regulated mechanism of lncRNAs in MI remains unclear. Subpathway-LNCE, as a novel method, can effectively integrate lncRNA-mRNA expression profile and identify lncRNA competitively regulated subpathway (16). Moreover,

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subpathway-LNCE method is more accurate, advanced and its calculation results are more relevant to disease. Accordingly, we used the subpathway-LNCE method to investigate pathogenesis of MI at genetic level.

Materials and methods

Recruitment and pretreatment of gene expression data. Gene expression profiles with accession number (GSE34198) for MI were recruited from the Gene Expression Omnibus (GEO) (http://www.ncbi.nlm.nih.gov/geo/) database. GEO is a public functional genomics data repository that freely distributes high throughput gene expression profiles and other functional genomics data sets. GSE34198 consists of 48 healthy controls and 49 patients with MI, and is deposited on GPL6102 data platform.

For purpose of controlling the quality of GSE34198, GSE34198 was pretreated as follows: Background correction was performed by Robust Multi-array Average (RMA) algorithm (17), the normalization was evaluated by quantiles algorithm (18), perfect match and mismatch was revised by Micro Array Suite (MAS) algorithm (19), and all expression values were summarized by medianpolish method (17). After removing invalid or duplicated probes, we converted them into gene symbols by the annotate package (20). Thus, 19,027 genes were obtained in the pretreated GSE34198 of MI for further application.

Constructing the candidate lncRNA-mRNA interactions. As far as we known, small non-coding RNAs target Base version 2.0 (starBase v2.0, http://starbase.sysu.edu.cn/) has been used to identify the RNA-RNA and protein-RNA interaction networks. Hence, miRNA-lncRNA interactions and miRNA-mRNA interactions were collected using StarBase v2.0. The miRNA-mRNA interactions were acquired based on miRecords (21), mir2Disease (22), mirTarBase (23) and TarBase (24). Then candidate lncRNA-mRNA competitively regulated relationships were constructed using their shared miRNAs between miRNA-mRNA and miRNA-lncRNA interactions. To ensure the data reliability, we used two criteria to identify the candidate competing miRNA of each lncRNA as follows: i) hypergeometric test of shared miRNAs under a threshold of P=0.05 and ii) Jaccard Coefficient of shared miRNAs rank at top 20%.

To make the candidate lncRNA-mRNA interactions involved in MI, all the genes in GSE34198 were mapped on them and the intersections were selected for further analysis.

Obtaining the lncRNA and mRNA co-expression relationship pairs. To screen the candidate lncRNA-mRNA interactions, we evaluated co-expression for any pair of relations in the candidate lncRNA-mRNA network using Pearson's correlation coefficient. Subsequently, the significance of Pearson's correlation coefficient was evaluated by Fisher's Z-transform, which converts the values into the normally distributed variable Z. Then the Z-transform test utilizes the one-to-one mapping of the standard normal curve to the P-value of a one tailed test. When the calculation value exceeded a significant positive threshold ($P<0.05$), the lncRNA-mRNA co-expression relationship pairs (LncGenePairs) were retained.

Reconstructing condition-specific lncRNA competitively regulated signal pathways. We used Fisher's test to identify the gene enrichment pathways in the mRNA-gene expression profiles, and the pathways were obtained from KEGG database. The gene enrichment pathways were collected when the P-value of gene enrichment pathway was no longer than 0.01, and considered as the candidate difference pathways. We put lncRNAs in the LncGenePairs into the candidate difference pathway graphs as nodes, then we acquired condition-specific lncRNA regulated signal pathways (csLncRPs). The lncRNA nodes were considered as signature nodes.

Located subpathways within pathways according to signature nodes. Signature nodes represent information on the competing regulation and genes of interest, which can help to efficiently locate subpathways through further considering their topologies within pathways. Moreover, distances are usually similar between certain nodes in a subpathway. We utilized 'lenient distance' similarity of signature nodes to locate subpathways competing for regulation by lncRNAs. We computed the shortest path between any two signature nodes as follows: If the molecule number between two signature nodes was less than n, they were combined into a single node. Finally, the node number in the molecule sets within pathway was longer than s, and defined as subpathway regions. The n parameter conducts the intensity of regulated signals, and the s parameter regulates the size of candidate subpathways. Thus, n=1 and s=8 were used as default parameters.

Statistical significance of candidate subpathways. Wallenius approximation methods were applied to evaluate the statistical significance of each subpathway. The needed values were shown as follows: i) the number of interesting mRNAs (x) submitted for analysis; ii) background mRNAs (n) number; iii) the number of background mRNAs (m1) annotated to each subpathway; iv) the number of interesting mRNAs (m2) annotated to each subpathway and v) the weight of each subpathway (w), which indicated the intensity of competitively regulated lncRNAs involved in this subpathway. The formula of the subpathway weight is as follows:

$$W = 1 + \beta\left(-\log_2\left(\frac{G_L}{P_G}\right)\right)$$

According to the formula above, P_G represents the number of mRNAs in the subpathways. G_L represents the number of mRNAs competing regulation by lncRNAs in this subpathway. Moreover, β is the control parameter ($\beta = 1$). The Wallenius approximation methods were carried out by R package BiasedUrn (25).

Identifying hub lncRNAs. According to the values of the subpathways, the subpathways competing for regulation by lncRNAs were obtained and constructed, that is,

Table I. The diagram of the top 6 LncGenePairs.

Lnc	Gene	corValue	P-value
TDRG1	*HENMT1*	0.220560501443871	0.0299373311676897
LIMD1-AS1	*LRRC56*	0.246484637523062	0.0149413386406672
LEF1-AS1	*MAGEH1*	0.454787669314928	$2.8722154063221 1x10^{-6}$
SNHG11	*MRPL53*	0.680510717664986	$1.75464015432401x10^{-14}$
LINC00485	*NME7*	0.249365243302853	0.0137715015048636
LEF1-AS1	*SLC27A5*	0.424727193889112	0.0000145102562949063

Table II. The diagram of the top 6 candidate different pathways.

Index	Pathway_id	Pathway_pvalue	p.adjust (FDR)
05215	hsa05215: Prostate cancer	$9.99732401124532x10^{-12}$	$9.99732401124532x10^{-12}$
05200	hsa05200: Pathways in cancer	$8.45066918278111x10^{-14}$	$8.45066918278111x10^{-14}$
05220	hsa05220: Chronic myeloid leukemia	$7.81664671803157x10^{-17}$	$7.81664671803157x10^{-17}$
04910	hsa04910: Insulin signaling pathway	0.0000771758111031205	0.0000771758111031205
04510	hsa04510: Focal adhesion	$6.65828057822821x10^{-06}$	$6.65828057822821x10^{-06}$
05166	hsa05166: HTLV-I infection	$6.59501272205171x10^{-07}$	$6.59501272205171x10^{-07}$

lncRNA-mRNA networks were constructed. Then, we collected the hub lncRNAs when the lncRNA degree was longer than the average lncRNA degree in the lncRNA-mRNA networks.

Results

Identifying the relationship between lncRNAs and mRNAs for MI. In this study, 19,027 genes were selected from GSE34198 of MI after standard corrections and normalizations. To understand the relationship between lncRNA and mRNA, we extracted lncRNA-mRNA interactions by their shared miRNAs based on mRNA-miRNA interactions and lncRNA-miRNA interactions. All genes in GSE34198 were mapped on these lncRNA-mRNA interactions and the intersections were selected. We then collected these intersections which satisfied P<0.05. The results revealed that 7,693 lncRNA-mRNA interactions were obtained, which included 835 lncRNAs and 1,749 mRNAs. Next, 1,681 mRNAs and 112 lncRNAs were indentified for MI after taking intersections with 19,027 genes in gene expression data. Subsequently, Pearson's correlation coefficient was performed to evaluate co-expression for any pair of relations in the intersections. We obtained 300 lncRNA-mRNA co-expression relationship pairs (LncGenePairs), among which include 58 lncRNAs, and 243 mRNAs. The top 6 LncGenePairs are illustrated in Table I.

Reconstruction of condition-specific lncRNA competitively regulated signal pathways. In order to obtain the lncRNA competitively regulated signal pathways (csLncRPs), we firstly annotated the mRNAs in the mRNAs-gene expression profiles into KEGG pathways. A total of 62 candidate difference pathways were obtained, among which the top 6 pathways were selected as shown in Table II. We then put lncRNAs based on the LncGenePairs in the candidate difference pathways as nodes through linking to their regulated mRNAs. Hence, a total of 1,241 csLncRPs were acquired, among which the top 14 pathways were selected as shown in Table III.

Table III. The diagram of the top 14 csLncRPs.

path_name	matched_lnc	matched_gene
3008	*DLEU2*	*BMS1*
3008	C14orf169	*BMS1*
3008	*ERVK13-1*	*RCL1*
3008	*PCBP1-AS1*	*POP1*
3008	*ERVK13-1*	*MDN1*
3008	*ERVK13-1*	*WDR75*
3008	*ERVK13-1*	*UTP15*
3008	*PDXDC2P*	*HEATR1*
3008	*ERVK13-1*	*WDR43*
3008	ERVK13-1	*LSG1*
3010	*ERVK13-1*	*RPS6*
3010	*ERVK13-1*	*RPS27*
3010	*ERVK13-1*	RPS25
3010	*ERVK13-1*	RPS3A

Identifying the signal subpathways competitively regulated by lncRNA for MI. The csLncRPs were calculated using lenient distance similarity to obtain the lncRNA competitively regulated subpathways. Then the Wallenius approximation methods were performed to evaluate the significance of signal subpathways. A total of 65 lncRNA competitively regulated subpathways were obtained, among which the top rank 6 subpathways are listed in Table IV. We illustrated the schematic diagram of

Table IV. The diagram of the top six of the lncRNA competitively regulated subpathways.

Pathway Id	Pathway name	Molecule ratio (m2/x)	Bg ratio (m1/n)	Weight	P-value	FDR
03010_1	Ribosome	13/264	13/26232	1.000000	<0.001	0.0000E+0000
03013_1	RNA transport	11/264	13/26232	1.241008	<0.001	0.0000E+0000
04010_1	MAPK signaling pathway	17/264	25/26232	1.556393	<0.001	0.0000E+0000
04012_1	ErbB signaling pathway	10/264	15/26232	1.736966	<0.001	0.0000E+0000
04062_1	Chemokine signaling pathway	14/264	20/26232	1.514573	<0.001	0.0000E+0000
04066_1	HIF-1 signaling pathway	11/264	16/26232	1.540568	<0.001	0.0000E+0000

lncRNAs, long non-coding RNA; MAPK, mitogen activated protein kinase.

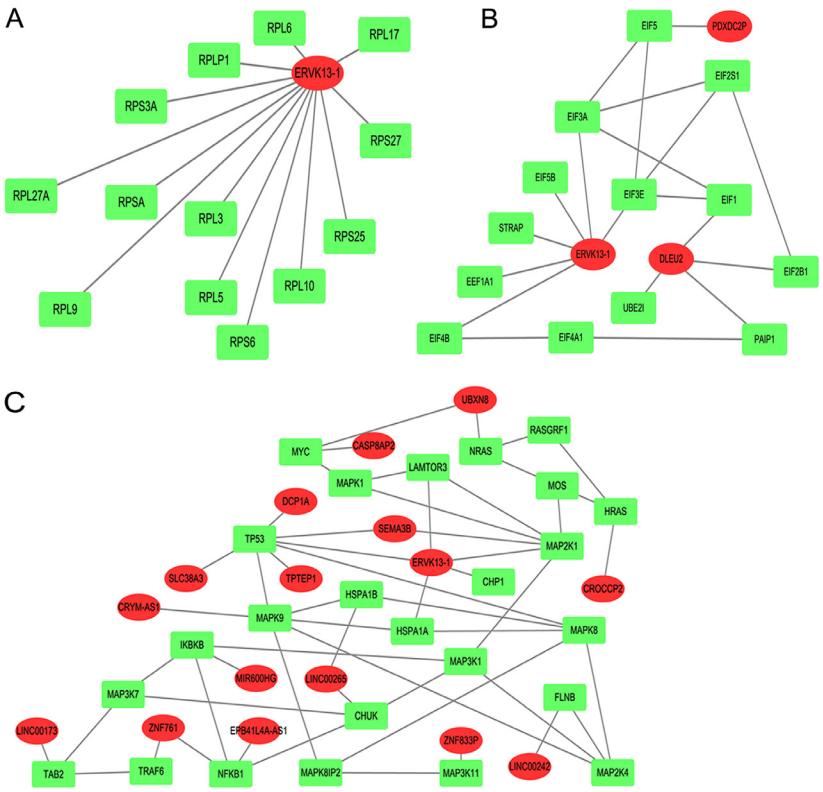

Figure 1. The diagram of the top three subpathways: (A) the ribosome subpathways; (B) the MAPK signaling subpathways; (C) the RNA transport subpathways. Green, mRNA; red, lncRNA. MAPK, mitogen activated protein kinase; lncRNA, long non-coding RNA.

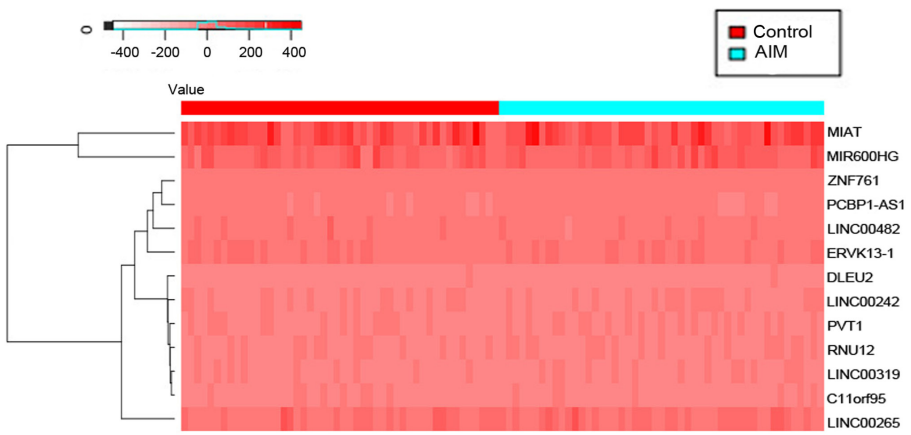

Figure 2. The heatmap indicates the expression quantity of hub lncRNAs (rows) for two groups of patients (colums). The degree of expression is indicated by different colors, with expression increasing between white and red. White, low expression; red, high expression. lncRNA, long noncoding RNA.

top rank 3 lncRNA competitively regulated subpathways, that is Ribosome, RNA transport and mitogen activated protein kinase (MAPK) subpathways (Fig. 1). According to the value, the signal subpathways were constructed into lncRNA-mRNA networks. Then 13 hub lncRNAs were collected from the lncRNA-mRNA networks (Fig. 2).

Discussion

In our study, the subpathway-LNCE method was first used to identify the lncRNAs competitively regulated subpathways for MI. Then the lncRNA-mRNA network was constructed according to these signal subpathways, in which the hub lncRNAs were detected.

Plenty of literature has reported that lncRNAs regulate many fundamental biological processes and play a key role in various diseases (4,5). Besides, lncRNAs competitively regulate mRNA expression levels through binding to miRNAs, so that lncRNAs can maintain normal biological functions (13,14). Hence, identifying the functional relationships between lncRNA and disease relevant subpathways may help understand the pathogenesis of diseases. However, the relevant regulated mechanism of lncRNAs in MI remains unclear. Thus, it is very important to search for a suitable method to examine the functions of lncRNAs in MI.

Therefore, we applied subpathway-LINCE with GEO data set of MI and identified a total of 65 lncRNA competitively regulated subpathways under the condition of $P<0.01$. Of which, P-values of 36 subpathways were nearly zero, which showed the significant difference between MI group and control group, such as Ribosome, RNA transport and MAPK subpathways. Ribosome subpathways are critical to ribosome assembly and protein synthesis. When using some methods to regulate the ribosome biogenesis, the cell growth will be extensively affected. For example, mTOR signaling can regulate multiple steps in ribosome biogenesis, thus influencing the cell proliferation and survival (26,27). Moreover, mTOR is activated in MI and mTOR inhibition could reduce cardiac dilation and infract size and improve cardiac function (28). Hence, clarifying the effect of ribosome subpathways on MI may offer opportunities for new therapies. RNA transport is the process where specific RNA molecules are transported from one cellular region to another via different sorting and transport mechanisms (29). In the present study, RNA transport subpathway in MI was associated with lncRNAs, which might assist in better understanding of the pathogenesis of MI. In particular, MAPK influences mitochondria mediated cell functions, mainly including proliferation, apoptosis and gene expression, because mitochondria are great power providers and gate-keepers of cell life and death. Moreover, MAPK can significantly affect cellular signaling underlying cardiac compensation and decompensation via interacting with the mitochondria (30). Our study showed that MAPK signaling subpathways participate in the pathological process of MI and are involved in lncRNAs. This could help to clarify the pathogenesis of MI.

In order to explore hub lncRNAs in the signal subpathways, the lncRNA-mRNA network was constructed through selecting the high degree of the subpathways. Then, a total of 13 hub lncRNAs were collected from the lncRNA-mRNA networks. Among these hub lncRNAs, MI associated transcript (MIAT), as an lncRNA, has been associated with a risk of MI (10,31). It has been reported that MIAT expression levels are found to change in peripheral blood cells in patients who have suffered from MI, and smoking as a cardiovascular risk factor is found to be positively associated with MIAT (32). Apart from MIAT, other new hub lncRNAs for MI were found using subpathway-LINCE in this study. These hub lncRNAs could become potential diagnostic and therapeutic targets for MI.

In conclusion, using subpathway-LINCE to study MI lncRNA competitively regulated subpathways were gained, and the hub lncRNAs for MI in lncRNA-mRNA network were also obtained. Identifying the lncRNAs competitively regulated subpathways could help us to understand the pathogenesis of MI. The hub lncRNAs might represent novel regulators of MI and become new diagnostic and therapeutic targets for MI. Although the results in this study still need to be verified by experiments, these findings can help understand the roles of lncRNAs in MI.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

XW and LS conceived the study and drafted the manuscript. XW acquired the data. LS and ZW analyzed the data and revised the manuscript. All authors read and approved the final study.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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