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Bioinformatics analysis of time series gene expression in left ventricle (LV) with acute myocardial infarction (AMI)

Tong Zhang [a], Li-Li Zhao [b], Xue Cao [a], Li-Chun Qi [a], Guo-Qian Wei [a], Jun-Yan Liu [a], Shu-Jun Yan [a], Jin-Gang Liu [c], Xue-Qi Li [a,*]

[a] Department of Cardiology, The Fourth Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang Province, China
[b] Department of Gastroenterology, The Fourth Affiliated Hospital of Harbin Medical University, Harbin 150001, Heilongjiang Province, China
[c] The Central Hospital of the Heilongjiang Prison Administrative Bureau, Harbin 150001, Heilongjiang Province, China

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ABSTRACT

This study is to investigate the key genes and their possible function in acute myocardial infarction (AMI). The data of GSE4648 downloaded from the Gene Expression Omnibus (GEO) database include 6 time points (15 min, 60 min, 4 h, 12 h, 24 h and 48 h) of 12 left ventricle (LV) samples, 12 surviving LV free wall (FW) samples, 12 inter-ventricular septum (IVS) samples after AMI operation and corresponding sham-operated samples. The data of each sample were analyzed with Affy and Bioconductor packages, and differentially expressed genes (DEGs) were screened out using BETR package with false discovery rate (FDR) < 0.01. Then, functional enrichment analysis for DEGs was conducted with Database for Annotation, Visualization and Integrated Discovery (DAVID). Totally 194 DEGs were identified in LV, and only the gene tubulin beta 2a (Tubb2a) and natriuretic peptide B (Nppb) were respectively up-regulated in surviving FW tissue and IVS tissue. The biological process response to wounding and inflammatory response were significantly enriched, as well as leukocyte transendothelial migration pathway. Besides, the expression pattern analysis showed the DEGs mostly up-regulated at 4 h after AMI, and these genes were mainly associated with immunity. Additionally, in transcriptional regulatory network, early growth response 1 (Egr1), activating transcription factor 3 (Atf3), Atf4, Myc and Fos were considered as the key transcription factors related to immune response. The key transcription factors and potential target genes might provide new information for the development of AMI, and leukocyte transendothelial migration pathway might play a vital role in AMI.

1. Introduction

Acute myocardial infarction (AMI) was identified in the mid-1970s (Keeley et al., 2003), one of the leading factors in mortality, morbidity, and cost to the society (Boersma et al., 2003; Lloyd-Jones et al., 2009). It can be identified from a number of different perspectives related to clinical, electrocardiographic (ECG), biochemical and pathologic characteristics (Antman et al., 2000). Infarcts are usually classified by size: microscopic (focal necrosis), small (10% of the left ventricle, LV), medium (10% to 30% of the left ventricle) or large (30% of the left ventricle) (Antman et al., 2000). Left ventricular coronary arterial occlusion can also result in AMI characterized by the short-term development of stable scar formation in the ischemic zone (Harpster et al., 2006). The left ventricle remodeling may be considered to be pathological in AMI, cardiomyopathy, hypertension, or valvular heart disease (Sutton and Sharpe, 2000).

In recent years, genome-wide DNA microarray analysis is used as an effective method for exploring the pathology-associated changes in the transcriptome level. In animal models, microarray analysis was widely used in mice cardiac remodeling (Mirotsou et al., 2003), murine model of compensated pressure overload hypertrophy (Zhao et al., 2004), canine hearts with myocardium ischemic preconditioning (Zubakov et al., 2003), swine ischemia/reperfusion model (Depre et al., 2001) and rat hearts with ischemic preconditioning (Ónody et al., 2003),

Abbreviations: AMI, acute myocardial infarction; LV, left ventricle; FW, free wall; IVS, inter-ventricular septum; DEGs, differentially expressed genes; FDR, false discovery rate; DAVID, Database for Annotation, Visualization and Integrated Discovery; Tubb2a, tubulin beta 2a; Nppb, natriuretic peptide B; Egr1, early growth response 1; Atf3, activating transcription factor 3; ECG, electrocardiographic; miRNAs, microRNAs; GEO, Gene Expression Omnibus; GO, Gene Ontology; KEGG, Kyoto Encyclopaedia of Genes and Genomes; TFdb, transcription factor database; TRED, Transcriptional Regulatory Element Database; Actg1, actin, gamma 1; Icam1, intercellular adhesion molecule 1; Cyba, cytochrome b-245 alpha polypeptide; Rassf5, domain family 5; Ncf2, neutrophil cytosol factors; Actn4, actinin alpha 4; Mmp9, matrix metallopeptidase 9; Itgb2, integrin beta 2; Vasp, vasodilator-stimulated phosphoprotein; Itga, integrin alpha; CHF, chronic heart failure; TGF, transforming growth factor; I/R, ischemia/reperfusion.

* Corresponding author at: Department of Cardiology, The Fourth Affiliated Hospital of Harbin Medical University, No. 37 Yiyuan Street, Nangang District, Harbin 150001, Heilongjiang Province, China.
E-mail address: xueqili89856@hotmail.com (X.-Q. Li).

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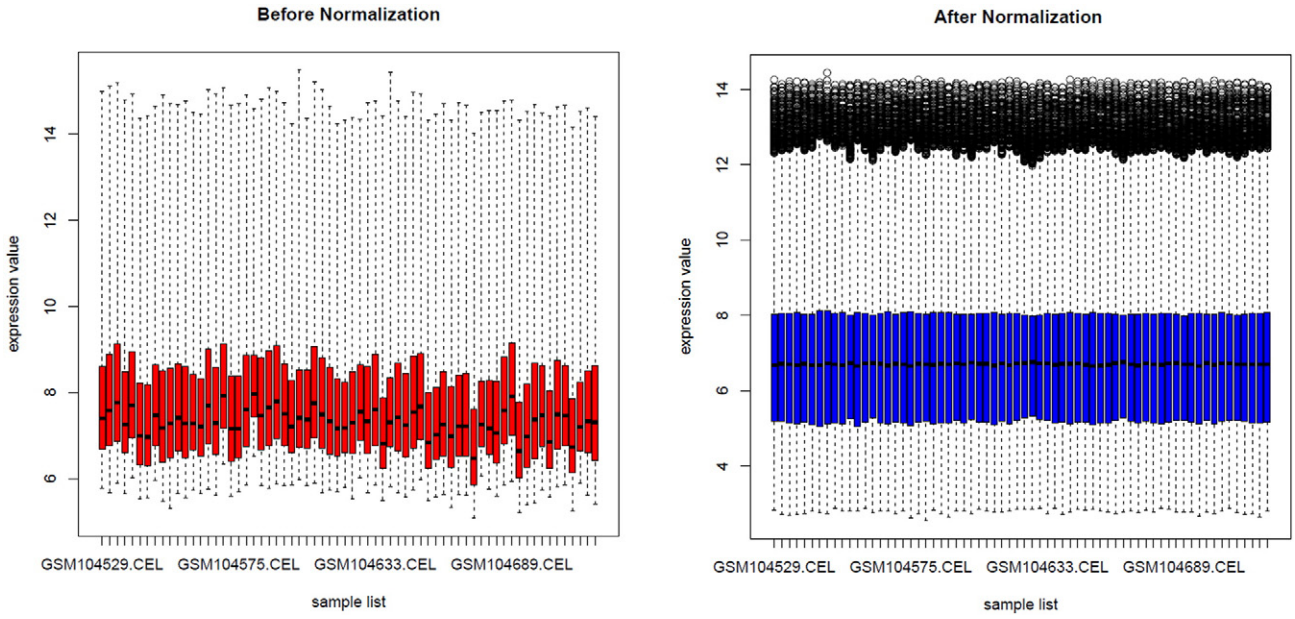

Fig. 1. The box diagram of expression profile before and after normalization. Horizontal axis represents the samples, vertical axis represents the expression value. The left diagram is the expression profile before normalization, and the right is after normalization. The black lines in the box diagram represent the median of all probes in each sample, their distribution can estimate the degree of the normalization, when the black lines tend to one straight line that indicate a good normalization.

characterizing the gene expressions involved in these heart diseases. In humans, microarray analysis has mainly focused on identifying differentially regulated genes in dilated cardiomyopathy (Barrans et al., 2002), hypertrophic cardiomyopathy (Hwang et al., 2002) and heart failure (Yang et al., 2000) for exploring the potential targets for targeted therapy.

Recently, the microRNA (miRNA) expression has been identified in rats at 6 h after AMI, including 38 miRNAs differentially expressed in infarcted areas and 33 miRNAs in the border areas (Dong et al., 2009). Harpster et al. reported the left ventricular transcriptome after AMI and identified the AMI-responsive genes in different tissues (Harpster et al., 2006). In human, blood samples for RNA and protein analysis were conducted in patients with AMI, and three possibly specific biomarkers were identified containing vascular endothelial growth factor B, thrombospondin-1 and placental growth factor (Devaux et al., 2010).

However, few studies explored the key genes and potential transcriptional regulatory relationship in AMI. In this research, various bioinformatics analysis methods were applied to further explore the important genes in LV, surviving LV free wall (FW) and inter-ventricular septum (IVS) after AMI, basing on the gene expression profile downloaded from GEO database. The potential functions and pathways of the DEGs in LV were enriched. Besides, the expression patterns of the DEGs in LV were clustered and the core transcription factors in the

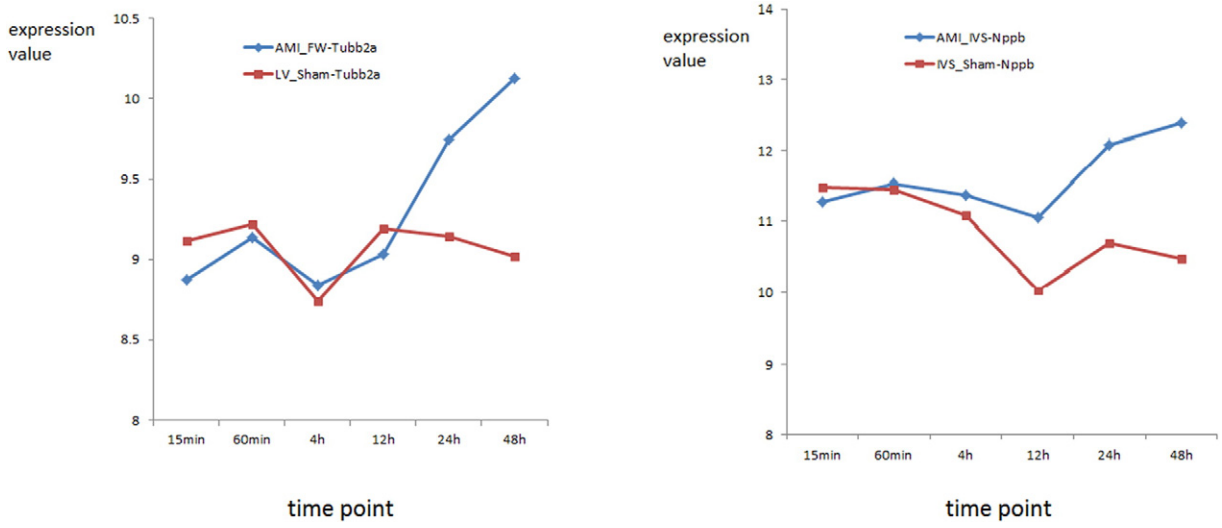

Fig. 2. The expression changes of the genes Tubb2a and Nppb in acute myocardial infarction group and in sham operation group. The left is the expression pattern of Tubb2a in surviving LV free wall after acute myocardial infarction operation and sham operation, the right is the expression pattern of Nppb in inter-ventricular septum after acute myocardial infarction operation and sham operation. Horizontal axis represents the time points, including 15 min, 60 min, 4 h, 12 h, 24 h and 48 h, vertical axis represents the expression value.