


RESEARCH

Open Access



# Potential molecular mechanism of ACE gene at different time points in STEMI patients based on genome-wide microarray dataset

Yao-Zong Guan<sup>1</sup>, Rui-Xing Yin<sup>1,2,3\*</sup> , Peng-Fei Zheng<sup>1</sup>, Guo-Xiong Deng<sup>1</sup>, Chun-Xiao Liu<sup>1</sup> and Bi-Liu Wei<sup>1</sup>

## Abstract

**Background:** This study aimed to investigate the angiotensin converting enzyme (ACE) co-expression genes and their pathways involved in ST-segment elevation myocardial infarction (STEMI) at different time points.

**Methods:** The array data set of GSE59867 was examined for the ACE co-expression genes in peripheral blood samples from 111 patients with STEMI at four time points (admission, discharge, and 1 and 6 months after MI). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment, Gene Ontology (GO) annotation and protein-protein interaction (PPI) of the co-expression genes were determined using online analytical tools. The Cytoscape software was used to create modules and hub genes.

**Results:** The number of biological processes (BP), cellular components (CC) and molecular functions (MF) was 43, 22 and 24 at admission; 18, 19 and 11 at discharge; 30, 37 and 21 at 1 month after MI; and 12, 19 and 14 at 6 months after MI; respectively. There were 6 BP, 8 CC and 4 MF enriched at every time point. The co-expression genes were substantially enriched in 12, 5, 6 and 14 KEGG pathways at the four time points, respectively, but no KEGG pathway was found to be common in all time points. We identified 132 intersectional co-expression genes (90 positive and 42 negative) from the four time points and 17 BP, 13 CC, 11 MF and 7 KEGG pathways were enriched. In addition, the PPI network contained 129 nodes and 570 edges, and only 1 module was identified to be significantly enriched in just 1 BP (chromatin-mediated maintenance of transcription).

**Conclusions:** The results of the present study showed that the ACE co-expression genes and their pathways involved in STEMI were significantly different at four different time points. These findings may be helpful for further understanding the functions and roles of ACE in different stages of STEMI, and providing reference for the treatment of STEMI.

**Keywords:** Co-expression genes, ACE, Gene ontology annotation, Kyoto encyclopedia of genes and genomes (KEGG) pathway, ST-segment elevation myocardial infarction

\* Correspondence: [yinruixing@163.com](mailto:yinruixing@163.com)

<sup>1</sup>Department of Cardiology, Institute of Cardiovascular Diseases, the First Affiliated Hospital, Guangxi Medical University, 22 Shuangyong Road, Nanning 530021, Guangxi, People's Republic of China

<sup>2</sup>Guangxi Key Laboratory Base of Precision Medicine in Cardio-cerebrovascular Disease Control and Prevention, Nanning 530021, Guangxi, People's Republic of China

Full list of author information is available at the end of the article



## Introduction

Coronary artery disease (CAD) is one of the leading causes of mortality among cardiovascular and cerebrovascular diseases, responsible for approximately 700,000 deaths in China [1, 2]. ST-segment elevation myocardial infarction (STEMI) is the most common cause of mortality in patients with CAD. Although with the establishment of coronary care units, improvements in medical therapy, and widespread use of early reperfusion therapy by primary percutaneous coronary intervention (PCI), the in-hospital mortality after STEMI has dramatically decreased to  $\approx 5\%$ , cardiac deaths after discharge cannot be ignored [3].

Widely accepted risk factors for CAD include age, gender, hypertension, diabetes, smoking, dyslipidemia, family history, and genetic variation [4–6]. Current indicators of diagnosis and prognosis of myocardial infarction (MI) include electrocardiogram, troponin, myocardial enzyme, and left ventricular ejection fraction [7–9]. But the molecular mechanisms responsible for the development and progression of STEMI remain unclear. The angiotensin converting enzyme (ACE) is associated with vasoconstriction, inflammation, vascular remodeling, thrombosis, apoptosis, and eventual plaque rupture [10]. The present study aimed to utilize bioinformatics to identify genes co-expressed with ACE genes and pathways associated with STEMI at different time points and to provide stage specific therapy for patients.

In the present study, the GSE59867 microarray expression dataset was extracted from the Gene Expression Omnibus (GEO) database, a global free-access repository of next-generation sequence functional genomic data sets and high-throughput microarray [11]. A genome-wide co-expression screening was performed by *cor* function in the R platform. All intersectional co-expression genes at the four time points were determined and depicted with Venn Diagrams. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were used to define biological functions of the intersectional co-expression genes and the co-expressing genes at different time points. The GO and KEGG pathways were compared to separate the common genes as well as unique genes throughout the whole STEMI process and at specific time points. Finally, the Search Tool for the Retrieval of Interacting Genes (STRING) [12] was used to construct protein-protein interaction (PPI) network and to detect the hub genes.

## Materials and methods

### Affymetrix microarray data

The GSE59867 gene expression dataset was retrieved from GPL6244 Affymetrix Human Gene 1.0 ST Array platform from the GEO database (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE59867>).

The GSE59867 dataset contained 436 samples, out of which 390 samples from patients ( $n = 111$ ) with STEMI at four time points (admission, discharge, 1 month after MI, and 6 months after MI) and 46 samples from patients ( $n = 46$ ) with stable CAD and without a history of MI were included in the study [13]. The data extracted was normalized by *limma* package (<http://www.bioconductor.org/packages/release/bioc/html/limma.html>) in the R platform, which is a software package providing powerful facilities for reading, normalizing and exploring microarray data [14, 15].

### Identification of ACE co-expression genes

A genome-wide co-expression gene screening for ACE in patients with STEMI was performed by *cor* function in the R platform. The screening criteria were as follows:  $P < 0.05$ , and  $|\text{Pearson correlation coefficient}| \geq 0.2$ . Then the online analytical tool Draw Venn Diagram (<http://bioinformatics.psb.ugent.be/webtools/Venn/>) was used to determine the intersectional co-expression genes at each time point.

### GO and KEGG pathway enrichment analyses

GO and KEGG enrichment analyses of the co-expression genes were conducted separately on the Database for Annotation, Visualization and Integrated Discovery (DAVID) (version 6.8). Statistical significance was set at  $P$ -value  $< 0.05$ . The results were visualized by the *R-ggplot2* package (version 3.5.3).

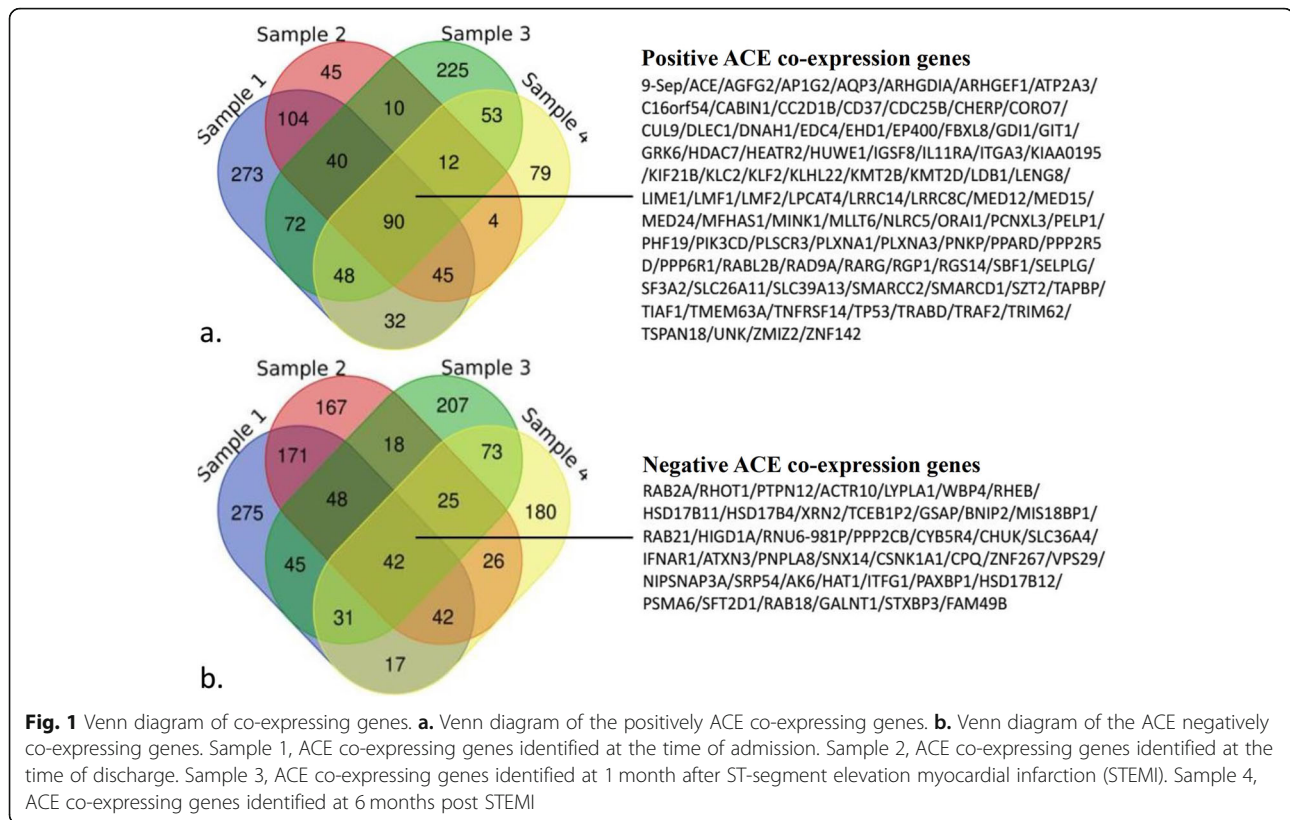
### Integration of the PPI network

Interactions among the co-expression genes were evaluated using the STRING (version 10.5) database; a combined score of  $> 0.15$  was considered statistically significant interaction. In addition, the Cytoscape plugin cytoHubba (version 0.1), a package common used to identified the hub objects and sub-networks from complex interaction [14, 16], with the ranking methods of maximal clique centrality (MCC) was used to identify the top 10 hub genes.

## Results

### Identification of ACE co-expression genes

A total of 704 positively and 671 negatively co-expressed genes at admission, 350 positively and 489 negatively co-expressed genes at discharge, 550 positively and 539 negatively co-expressed genes at 1 month after MI, and 363 positively and 436 negatively co-expressed genes 6 months after MI were identified in this study. Figure 1 depicts a Venn diagram showing the 90 positively and 42 negatively co-expressed genes common across the time points.



### Functional analysis of GO and KEGG pathways enrichment of co-expression genes

GO function clustering revealed 43 biological processes (BP), 22 cellular components (CC), and 24 molecular functions (MF) at the time of admission; 18 BP, 19 CC, and 11 MF were identified at the time of discharge; 30 BP, 37 CC, and 21 MF were identified at the time of 1 month after MI; and 12 BP, 19 CC, and 14 MF were identified at the time of 6 month after MI (Additional file 1: Tables S1-S4). We selected the top seven BP, CC, and MF in descending order of count with  $P < 0.01$  at different time points for visualization (Fig. 2). Six BP (intracellular protein transport, positive regulation of transcription/DNA-templated, proteasome-mediated ubiquitin-dependent protein catabolic process, protein transport, small GTPase mediated signal transduction, Wnt signaling pathway), 4 MF (chromatin binding, GTPase activator activity, GDP binding, protein binding) and 8 CC (cytoplasm, cytosol, intracellular, nucleus, catalytic step 2 spliceosome, Golgi apparatus, membrane, nucleoplasm) were shared at all the time points. The analysis further identified 17 BP, 13 CC and 11 MF as intersectional co-expression genes (Table 1 and Fig. 3).

The KEGG pathway analysis showed that genes co-expressing with ACE genes were substantially enriched in 12, 5, 6 and 14 pathways at each time points, respectively (Additional file 1: Tables S5-S8) The intersectional

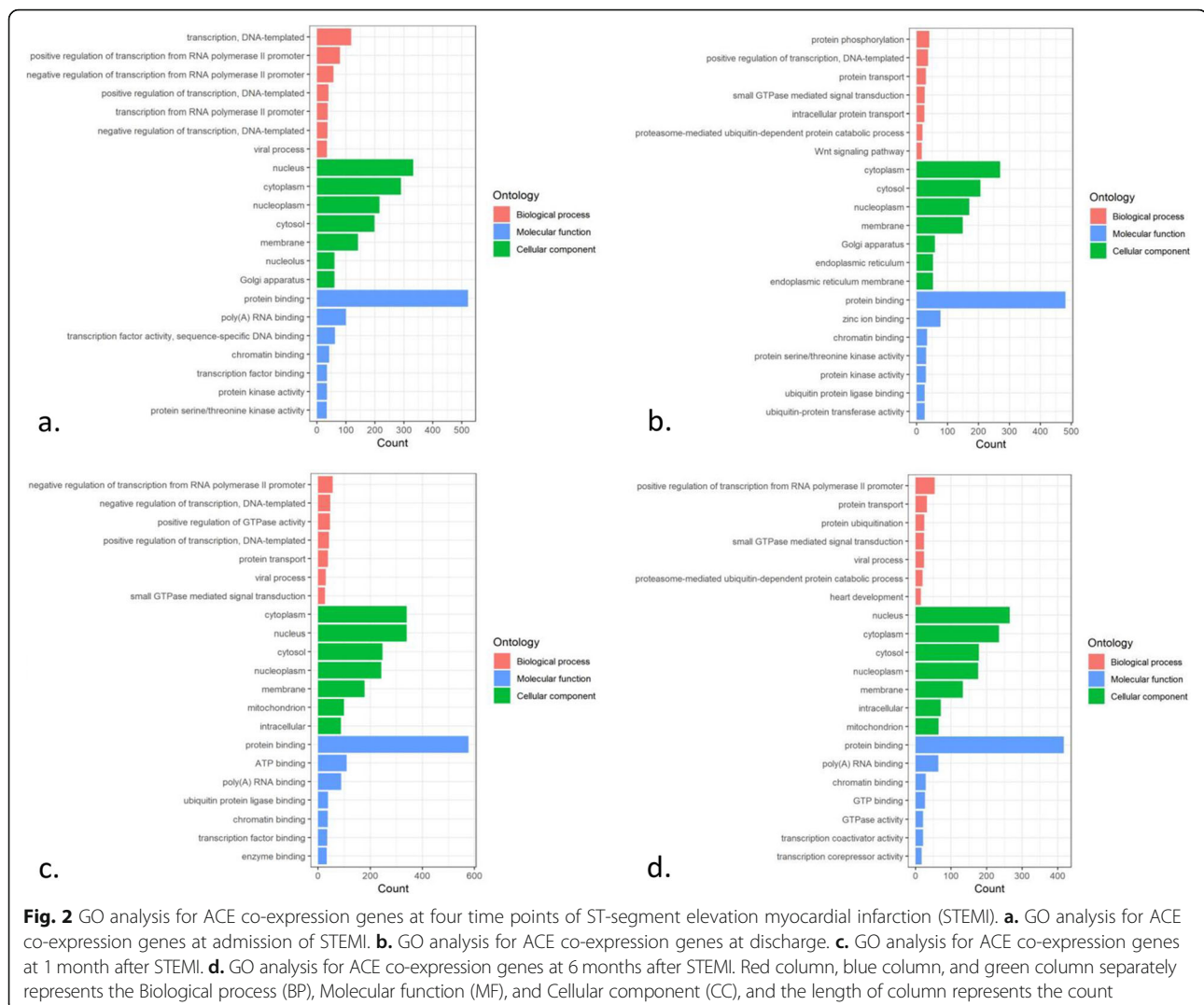
co-expression genes mainly clustered into 7 pathways, including hepatitis C, small cell lung cancer, apoptosis, thyroid hormone signaling pathway, sphingolipid signaling pathway, AMPK signaling pathway, and PI3K-Akt signaling. However, no KEGG pathway was found to be common across the four time points (Fig. 4).

### PPI network construction and hub gene identification

A PPI network with 129 nodes and 570 edges was constructed to detect the interactions among the co-expressing genes with a combined score  $> 0.15$ . With a cutoff criterion of MCODE score  $> 4$ , only 1 module was identified, which was significantly enriched in just 1 biological process chromatin-mediated maintenance of transcription with co-expressing genes *KMT2D*, *KMT2B* and *SMARCD1* (Fig. 5).

### Discussion

Over 80 million people have cardiovascular disease (CVD) in the United States, resulting in over 7 million revascularization procedures each year. Among them, STEMI accounts for a large proportion [17]. Not only the risk of death at the time of admission, but also the complications like dysfunction or rupture of papillary muscle, rupture of the heart, coronary stent thrombosis, malignant arrhythmia, post-infarction syndrome and heart failure give rise to the mortality [10, 18–20]. The



biological and regulatory mechanisms in the early or post-myocardial infarction stages remain understudied. The rapid development of microarray expression data and bioinformatics has offered improved methods and the tools to better understand complex diseases, like CVD, diabetes, and cancer. It is widely accepted that renin-angiotensin-aldosterone system (RAAS) is activated in myocardial ischemia and heart failure [21]. The ACE localized mainly in the endothelium and smooth muscle, promotes the conversion of angiotensin II (Ang II, a potent vasoconstrictor and growth factor) from angiotensin I in the renin-angiotensin system (RAS), and degrades bradykinin. Ang II activates its receptor AT1, which in turn activates fibroblasts, promoting myocardial fibrosis and scar formation. Furthermore, Ang II destabilizes Kv4.3 messenger RNA, resulting in decrease of outward potassium and prolongation of action potential duration, finally induces arrhythmias and heart failure [22, 23]. Interestingly, previous studies suggested

that ACE can regulate the immune-related cytokines, IL-12, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and nitric oxide (NO), but finally proved the effect was due to the activation of AT1 by Ang II [24, 25]. A previous report by Tham et al showed that Ang II could regulate inflammation by down-regulated the PPAR receptors [25]. Thus, ACE involves in many mechanisms of physiology and pathophysiology with its central role in production of Ang II, chronic over-expression of tissue ACE causes over-production of Ang II. At the same time, decrease in bradykinin reduces the vasodilatory, profibrinolytic, antioxidant and antiapoptotic effects [26]. In the past decades, ACE inhibitors have been well received clinically with remarkable success based on their powerful effect on decreasing the production of Ang II [27]. In the present study, we identified genes co-expressed with ACE, and their GO enrichments and KEGG pathways at four time points of the STEMI. The analysis also identified the intersectional co-expression genes in all the time



**Table 1** GO analysis for intersectoral ACE co-expression genes

Category	ID	Description	Count	P-Value	Gene ID
BP	GO:0007264	small GTPase mediated signal transduction	8/200	1.77E-03	RAB2A/GDI1/RAB18/MFHAS1/RHOT1/RHEB/RAB21/RABL2B
BP	GO:0050771	negative regulation of axonogenesis	3/200	7.74E-03	GDI1/ARHGEF1/ARHGDI1
BP	GO:0030334	regulation of cell migration	4/200	1.53E-02	PLXNA3/PLXNA1/LDB1/MINK1
BP	GO:0046677	response to antibiotic	3/200	2.12E-02	CYB5R4/PPP2CB/TP53
BP	GO:0015031	protein transport	8/200	2.15E-02	SFT2D1/RAB2A/VPS29/GDI1/RAB18/SNX14/CORO7/RAB21
BP	GO:0006367	transcription initiation from RNA polymerase II promoter	5/200	2.24E-02	PPARD/RARG/MED15/MED12/MED24
BP	GO:0008277	regulation of G-protein coupled receptor protein signaling pathway	3/200	3.06E-02	GIT1/GRK6/RGS14
BP	GO:0043549	regulation of kinase activity	2/200	3.46E-02	NLRC5/LDB1
BP	GO:0014910	regulation of smooth muscle cell migration	2/200	3.46E-02	ACE/PLXNA1
BP	GO:0014842	regulation of skeletal muscle satellite cell proliferation	2/200	4.14E-02	PPARD/PAXBP1
BP	GO:0046939	nucleotide phosphorylation	2/200	4.14E-02	PNKP/AK6
BP	GO:2000288	positive regulation of myoblast proliferation	2/200	4.14E-02	PPARD/PAXBP1
BP	GO:0016569	covalent chromatin modification	4/200	4.54E-02	PHF19/SMARCC2/SMARCD1/CABIN1
BP	GO:0043547	positive regulation of GTPase activity	9/200	4.58E-02	GIT1/GDI1/ARHGEF1/SBF1/BNIP2/AGFG2/RGP1/ARHGDI1/RGS14
BP	GO:0048841	regulation of axon extension involved in axon guidance	2/200	4.82E-02	PLXNA3/PLXNA1
BP	GO:0019827	stem cell population maintenance	3/200	4.82E-02	PHF19/MED12/MED24
BP	GO:0007266	Rho protein signal	3/200	4.82E-02	ARHGEF1/ARHGDI1/CHUK

**Table 1** GO analysis for intersectoral ACE co-expression genes (Continued)

Category	ID	Description	Count	P-Value	Gene ID
		transduction			
CC	GO:0016020	membrane	36/200	6.08E-07	ORAI1/PLXNA3/GALNT1/CHERP/AP1G2/AGFG2/LRRC8C/LMF2/EDC4/RGP1/KLC2/TAPBP/SFT2D1/ACE/FAM49B/PELP1/HSD17B4/EHD1/SELPLG/CSNK1A1/GIT1/MED12/CORO7/AK6/IL11RA/LPCAT4/PNKP/PNPLA8/IGSF8/CD37/MED15/HUWE1/GRK6/RHOT1/RHEB/XRN2
CC	GO:0005789	endoplasmic reticulum membrane	15/200	1.88E-03	RAB2A/CYB5R4/GALNT1/LMF2/LRRC8C/HSD17B12/LMF1/LPCAT4/TAPBP/PNPLA8/ATXN3/RAB18/ATP2A3/RHEB/RAB21
CC	GO:0005654	nucleoplasm	32/200	2.42E-03	KMT2D/PPARD/PPP2R5D/KMT2B/HAT1/MED24/EDC4/WBP4/SLC26A11/PELP1/CC2D1B/CHUK/RARG/TP53/MED12/RAD9A/SF3A2/AK6/CDC25B/PNKP/ATXN3/PHF19/PSMA6/MED15/HUWE1/ZMIZ2/SMARCC2/CABIN1/MIS18BP1/EP400/XRN2/HDAC7
CC	GO:0005829	cytosol	36/200	2.94E-03	VPS29/HSD17B11/TRAF2/PPP2R5D/PPP6R1/NIPSNAP3A/EDC4/RGP1/KLC2/PAXBP1/NLRC5/PPP2CB/CHUK/ARHGDI1/CSNK1A1/GIT1/GDI1/SRP54/ARHGEF1/PIK3CD/TP53/MINK1/CORO7/STXB3/LYPLA1/TRIM62/PTPN12/CDC25B/ATXN3/RAB18/PSMA6/HUWE1/BNIP2

**Table 1** GO analysis for intersectional ACE co-expression genes (Continued)

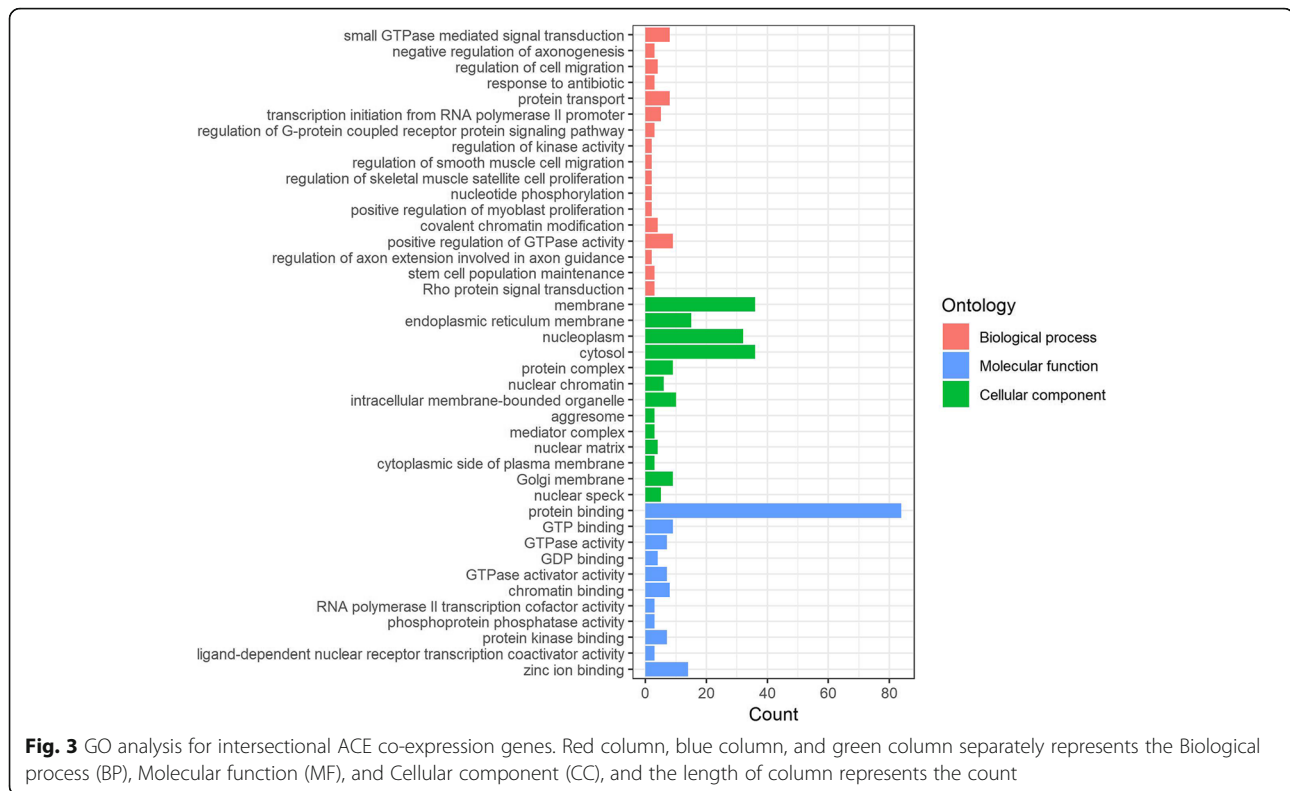
Category	ID	Description	Count	P-Value	Gene ID
CC	GO: 0043234	protein complex	9/200	6.55E-03	FBXL8/RHOT1/RHEB GDI1/ORAI1/LDB1/SMARCC2/TP53/HAT1/RGP1/KLC2/HIGD1A
CC	GO: 0000790	nuclear chromatin	6/200	9.67E-03	PPARD/RARG/LDB1/SMARCC2/TP53/HAT1
CC	GO: 0043231	intracellular membrane-bounded organelle	10/200	1.27E-02	HSD17B11/VPS29/PLXNA3/BNIP2/HAT1/EDC4/CC2D1B/HSD17B4/SLC26A11/CHUK
CC	GO: 0016235	aggresome	3/200	2.05E-02	GIT1/CABIN1/XRN2
CC	GO: 0016592	mediator complex	3/200	2.29E-02	MED15/MED12/MED24
CC	GO: 0016363	nuclear matrix	4/200	2.74E-02	ATXN3/PSMA6/TP53/HAT1
CC	GO: 0009898	cytoplasmic side of plasma membrane	3/200	3.22E-02	TRAF2/RAB21/CHUK
CC	GO: 0000139	Golgi membrane	9/200	4.51E-02	RAB2A/PNPLA8/GALNT1/AP1G2/PPP6R1/RHEB/CORO7/RGP1/TAPBP
CC	GO: 0016607	nuclear speck	5/200	4.62E-02	CSNK1A1/SRP54/SF3A2/WBP4/EP400
MF	GO: 0005515	protein binding	84/200	2.44E-06	PPARD/PLXNA3/CHERP/AP1G2/PPP2R5D/LRRC8C/NIPSNAP3A/EDC4/MED24/RGP1/WBP4/TAPBP/NLRC5/FAM49B/MFHAS1/CUL9/SMARCD1/KLHL22/CHUK/RAB21/RARG/ARHGEF1/LDB1/PIK3CD/TP53/MED12/MINK1/CORO7/TNFRSF14/STXBP3/RAD9A/LENG8/IFNAR1/PNKP/CD37/IGSF8/PSMA6/HUWE1/MED15/RAB18/FBXL8/BNIP2/ZMIZ2/EP400/XRN2/VPS29/TRAF2/

**Table 1** GO analysis for intersectional ACE co-expression genes (Continued)

Category	ID	Description	Count	P-Value	Gene ID
					KMT2D/ORAI1/SLC39A13/LMF2/KMT2B/HSD17B12/PPP6R1/HAT1/KLC2/PELP1/PPP2CB/CC2D1B/MLLT6/EHD1/SELPLG/ARHGDI/ARHGDI/CSNK1A1/GIT1/RAB2A/GDI1/SRP54/ITGA3/SF3A2/AK6/PTPN12/RGS14/CDC25B/ATXN3/PHF19/SMARCC2/PLSCR3/RHOT1/GRK6/MIS18BP1/KLF2/HDAC7/ACTR10
MF	GO: 0005525	GTP binding	9/200	4.29E-03	RAB2A/SRP54/RAB18/MFHAS1/RHOT1/RHEB/EHD1/RAB21/RABL2B
MF	GO: 0003924	GTPase activity	7/200	4.91E-03	RAB2A/SRP54/RAB18/RHOT1/RHEB/RAB21/RABL2B
MF	GO: 0019003	GDP binding	4/200	5.65E-03	RAB2A/SRP54/RAB18/RAB21
MF	GO: 0005096	GTPase activator activity	7/200	1.12E-02	GIT1/GDI1/ARHGEF1/BNIP2/AGFG2/ARHGDI/RGS14
MF	GO: 0003682	chromatin binding	8/200	1.61E-02	PELP1/LDB1/SMARCC2/SMARCD1/TP53/MED12/EP400/HDAC7
MF	GO: 0001104	RNA polymerase II transcription cofactor activity,	3/200	2.41E-02	MED15/MED12/MED24
MF	GO: 0004721	phosphoprotein phosphatase activity	3/200	3.65E-02	PPP2CB/PTPN12/CDC25B
MF	GO: 0019901	protein kinase binding	7/200	4.07E-02	TRAF2/TP53/RHEB/RAD9A/RGS14/HDAC7/CDC25B

points to determine the GO enrichments and KEGG pathways throughout the stages of MI and the recovery process, and the unique GO enrichments and KEGG pathways at different time points of STEMI.

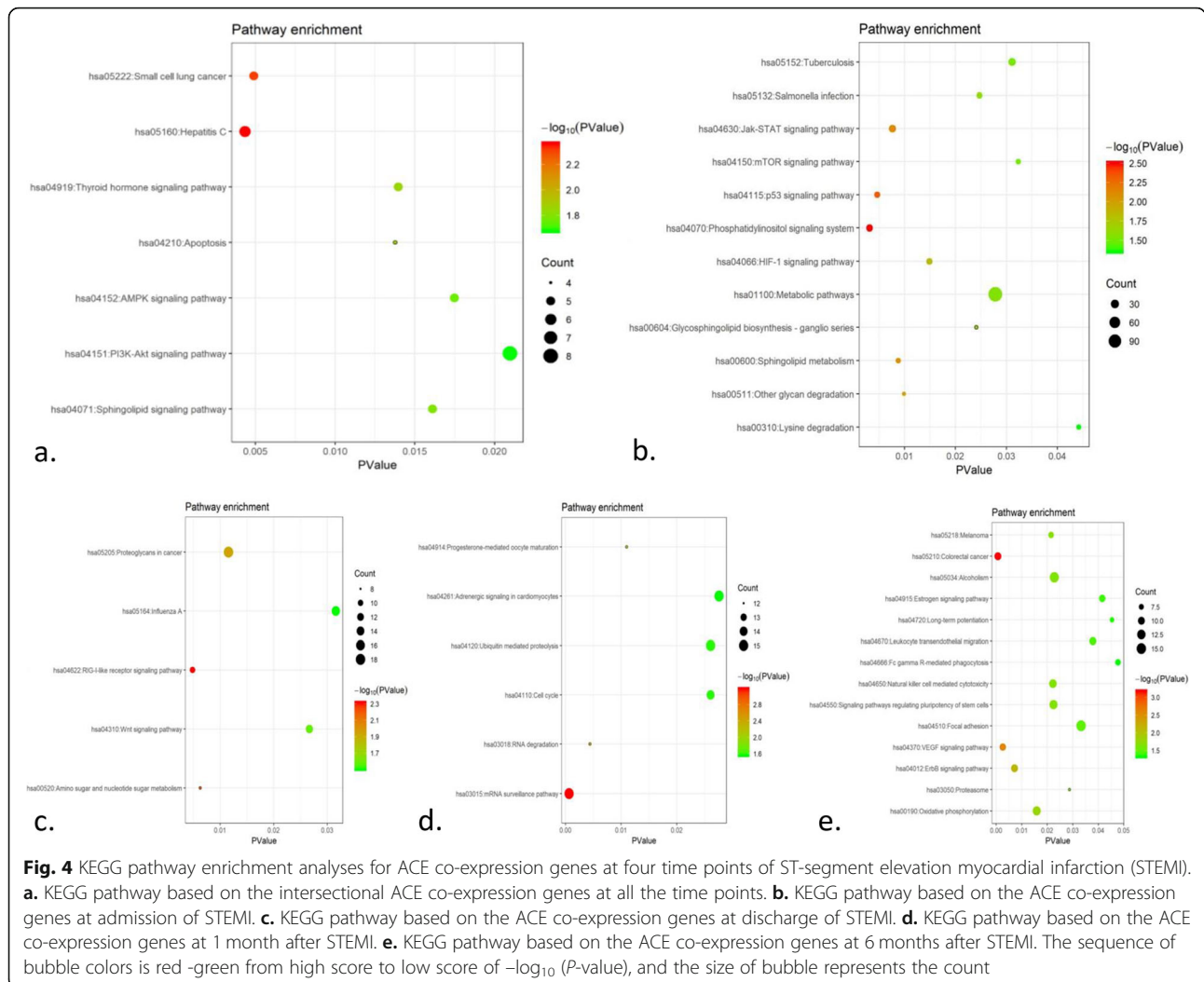
Identification of co-expressed genes is the cornerstone of BP, CC, MF and enrichment pathway analysis. Using



the Venn diagram, we identified 90 positively and 42 negatively co-expressing genes of the intersection of the four time points. The gene *SELPLG*, also called *PSGL-1* was reported to be expressed at a high level in CD4+ T-Cells from patients with plaque rupture or intracoronary thrombus. It was also implicated in plaque instability in acute coronary syndrome (ACS) [28–30]. The *KLF2* gene is a vascular homeostasis-associated molecular marker, which regulates the expression of a wide range of anti-inflammatory, antioxidant, and antithrombotic genes in endothelial cells. Compared with patients with stable angina pectoris or normal controls, *KLF2* expression in dendritic cells in patients with ACS was found to be reduced [31, 32]. Some previous study reported that FBW7 tumor suppressor induces endothelial differentiation by modulating the NF1/RAS axis. The SCF<sup>FBW7-RBX2/SAG</sup> (an ubiquitin ligase) activates RAS by promoting the degradation of NF1, and *KLF2* acts as physiological substrate of FBW7. These results suggest that expression of *KLF2* may indirectly affect the activity of ACE [33]. *P53*, the known tumor suppressor with characteristic of promoting apoptosis, was also reported to be associated with CAD [34–36]. What's more, the TNF signals can activate both renin and p53 by inhibiting phosphoinositide 3-kinases (PI3Ks) via JNK pathway [37, 38]. This may be one of the reasons for the positive correlation between the expression of *ACE* and *P53*. In our study, *PSGL-1*, *KLF2* and *P53* were among the positively co-expression genes of *ACE* at

every time points of STEMI, that is to say, high-expressed *ACE* is accompanied by high-expressed *PSGL-1*, *KLF2* and *P53*. *ACE* mainly mediates the production of Ang II, promoting the activation of inflammation and apoptosis, co-expressed of it, *PSGL-1* and *p53* may promote the inflammation and apoptosis, while *KLF2* plays the opposite role involved in the progression of STEMI. Whether *ACE* positively regulates these genes directly or through a feedback way is still the direction of our next step would focus on.

On the other hand, the *PNPLA1-PNPLA9* are members of the *PNPLA* family, playing different biological functions. Among them, *PNPLA2* is a key enzyme in the hydrolysis of stored triglycerides (TG), while *PNPLA8* is a myocardial phospholipase, maintaining mitochondrial integrity [39]. The *GALNT* family with lipase and transacylase properties appeared to play major roles in the regulation of lipid metabolism [40]. In addition, data from Pulido et al [41] supported that *RAB18* is a common mediator of lipolysis and lipogenesis, and suggested that the endoplasmic reticulum is the link that connected *RAB18* action on these two processes. In the current study, we showed that the *PNPLA*, *RAB18* and *GALNT1* were the negatively co-expressed genes of *ACE* at all the time points, in other words, increased *ACE* expression was accompanied by decreased expression of these genes. In the development of STEMI, decreased expression of *PNPLA2* may decrease hydrolysis of stored



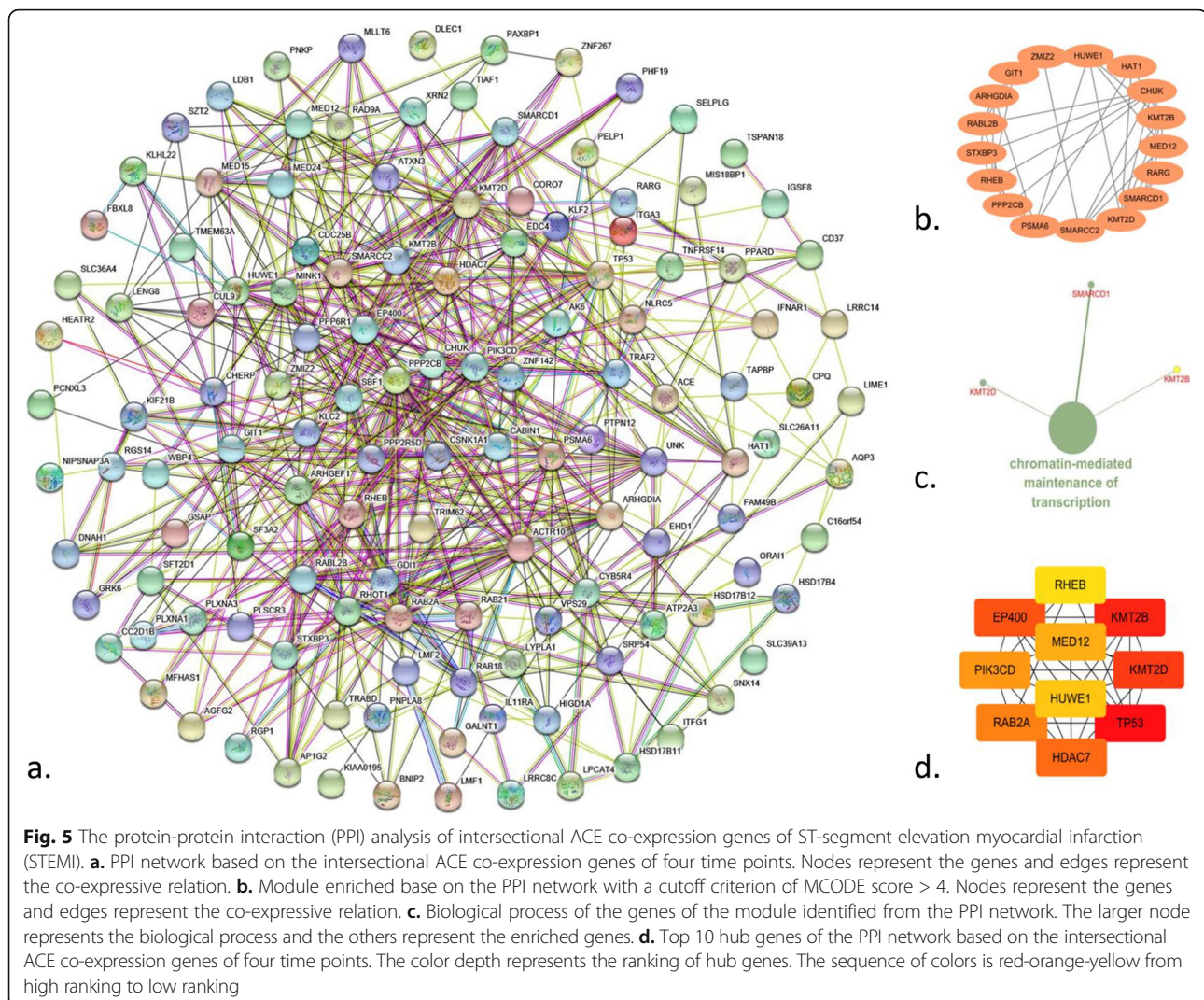
TG to reduce the serum TG levels, while decreased expression of *PNPLA8* may weaken mitochondrial integrity and reduce energy supply. In context of *RAB18*, its decrease expression may be partly responsible for the changes in serum lipid levels. Passos-Silva et al showed that Ang (1–7) regulated the metabolism by increasing glucose uptake and lipolysis, and decreasing insulin resistance and dyslipidemia [42]. The expression of ACE may affect the expression of Ang (1–7), in turn affects the metabolism. Therefore, the expression of these genes may be negatively regulated by ACE or negative feedback from ACE, but it needs further researches to confirm.

GO and KEGG pathways enrichment analysis revealed several shared pathways across the time points. The Wnt signaling plays dominant roles in the pathology of CVDs including inflammation, fibrosis, intracellular cholesterol accumulation and heart failure following MI, mobilization and proliferation of cells in the endothelium and epicardium in an infarcted heart [43–46]. The

endothelium is directly involved in heart disease, peripheral vascular disease, diabetes, insulin resistance, stroke, venous thrombosis, chronic kidney failure, metastasis, tumor growth, and severe viral infectious diseases directly [47]. After injury, migration, proliferation of endothelial cells, and reendothelialization of the vessel is essential in the restoring of blood vessel health. Many of these processes are regulated, and are dependent on small GTPases [17, 48]. Thus, regulation of the Wnt signaling pathway or promotion of endothelialization might attenuate cardiovascular events after STEMI and that studying the regulation of the small GTPase could be an interesting starting point.

Using the MCODE, we identified only 1 module enriched and just 1 biological process- chromatin-mediated maintenance of transcription from the PPI network. In addition, 10 hub genes were identified using CytoHubba with a high level of connectivity - *TP53* (*p53*), *KMT2B* (*MLL4*), *KMT2D*, *EP400* (*p400*), *HDAC7*, *RAB2A*, *PIK3CD* (*PI3K*), *MED12* (*OPA1*), *HUWE1*, and





**Fig. 5** The protein-protein interaction (PPI) analysis of intersectional ACE co-expression genes of ST-segment elevation myocardial infarction (STEMI). **a.** PPI network based on the intersectional ACE co-expression genes of four time points. Nodes represent the genes and edges represent the co-expressive relation. **b.** Module enriched based on the PPI network with a cutoff criterion of MCODE score > 4. Nodes represent the genes and edges represent the co-expressive relation. **c.** Biological process of the genes of the module identified from the PPI network. The larger node represents the biological process and the others represent the enriched genes. **d.** Top 10 hub genes of the PPI network based on the intersectional ACE co-expression genes of four time points. The color depth represents the ranking of hub genes. The sequence of colors is red-orange-yellow from high ranking to low ranking

*RHEB* (*mTORC1*). In the context of cellular immunity and apoptosis, Rahnamour et al. [49] reported a novel mechanism in which the mutant *TP53* and *KMT2B* cooperated to regulate aberrant enhancer activity and tumor-promoting gene expression in response to chronic immune signaling. The EP400 E1A-associated protein, which mediates H2A.Z incorporation at specific promoters, plays a major role in cell fate decisions; it promotes cell cycle progression and inhibits apoptosis or senescence [50]. Decrease in *MED12*, which is important for maintaining normal cristae structure and function, resulted in increased apoptosis and mitochondrial fragmentation, and thereby reduction in energy supplement [51]. Li et al. [52] reported that, compared to non-CAD controls, *HDAC7* mRNA expression level was markedly lower in monocytes of CAD patients. That means these genes either participate in or regulate immune response and apoptosis. In our study, *p53*, *KMT2B*, *KMT2D*, *EP400*, and *HDAC7* were positively co-expressed with *ACE*, and increase in their

expression may inhibit apoptosis and decrease mitochondrial energy metabolism. As both immune cells and apoptosis play important roles in the development of CAD, these genes could be promising targets for intervention for the treatment of CAD.

For blood glucose and lipid metabolism, previous studies give us the point that *RAB2A* knockdown inhibited glucose-stimulated insulin secretion, what's more, it also regulated both initiation and termination of autophagy in mammalian cells [53, 54]. Silencing the ligases, *HUWE1* and *NEDD4-1*, increased the cholesterol export from cells [55]. In the context of thrombosis and endothelial injury, the p110 $\delta$  plays a partial role in aggregation and spreading of platelet, and PI3K-Akt is cardio-protective in ischemic pre-conditioning [56, 57]. The mechanistic target of rapamycin complex 1 (*mTORC1*), one of the major pathways associated with cellular energy sensing, mediates vascular endothelial function through modulation of ROS signaling [58]. These findings indicated that the hub genes

*RAB2A*, *PI3K*, *HUWE1* and *mTORC1* are the regulators of glucose metabolism, lipid metabolism, platelet and endothelial function. Our results suggested that these genes were negatively co-expressed with ACE, and decrease in their expression may reduce insulin secretion, increases serum cholesterol levels or result in vascular endothelial dysfunction and are closely related to the occurrence and development of CAD. Although to date clear evidence that ACE directly or indirectly regulates their expression is still lack, in depth understanding of the regulation of these genes may provide effective strategies for the recovery of patients with STEMI.

Our study aims to explore the mechanism of STEMI at different times from the perspective of positively or negatively co-expressed genes with ACE, which is different from the previous approach of analysis based on up-regulation and down-regulation of genes. However, there are some limitations of our research. Firstly, the results of our study cannot definitively confirm whether ACE could directly or indirectly regulates these genes. Secondly, the data from GSE59867 does not provide the factors associated with CAD like age, gender and blood lipid levels for correction. Finally, some potential factors that we have not clear may interfere with the end results.

## Conclusions

In this study, genome-wide co-expressing genes based on the GSE59867 dataset were used to identify the functions and mechanism of ACE gene at different time points of STEMI. We found that the ACE co-expression genes and their pathways involved in STEMI were significantly different at four different time points. These findings may help to better understand the functions and roles of ACE and co-expression genes in STEMI, and provide reference for future treatment strategies. However, further studies are required to validate the role of these co-expressing genes and pathways involved in different stages of STEMI.

## Supplementary information

**Supplementary information** accompanies this paper at <https://doi.org/10.1186/s12944-019-1131-3>.

**Additional file 1: Table S1.** GO enrichment at admission of STEMI. **Table S2.** GO enrichment at discharge of STEMI. **Table S3.** GO enrichment at 1 month after STEMI. **Table S4.** GO enrichment at 6 months after STEMI. **Table S5.** KEGG pathway at admission of STEMI. **Table S6.** KEGG pathway at discharge of STEMI. **Table S7.** KEGG pathway at 1 month after STEMI. **Table S8.** KEGG pathway at 6 months after STEMI.

## Abbreviations

ACE: Angiotensin converting enzyme; BP: Biological processes; CAD: Coronary artery disease; CC: Cellular components; CVD: Cardiovascular disease; ER: Endoplasmic reticulum; GEO: Gene Expression Omnibus; GO: Gene Ontology annotation; KEGG: Kyoto Encyclopedia of Genes and

Genomes pathway enrichment analyses; MCODE: Molecular Complex Detection; MF: Molecular functions; PCI: percutaneous coronary intervention; PPI: Protein-protein interaction; RAS: Renin-angiotensin system; STEMI: ST-segment elevation myocardial infarction; TG: triglycerides

## Acknowledgements

Not applicable.

## Authors' contributions

YZG conceived the study, participated in the design, performed the statistical analyses, and drafted the manuscript. RXY conceived the study, participated in the design and helped to draft the manuscript. PFZ and GXD contributed in formal analysis. CXL and BLW helped to draft the manuscript. All authors read and approved the final manuscript.

## Funding

This study was supported by the National Natural Science Foundation of China (No. 81460169). The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the Gene Expression Omnibus repository (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE59867>).

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## Author details

<sup>1</sup>Department of Cardiology, Institute of Cardiovascular Diseases, the First Affiliated Hospital, Guangxi Medical University, 22 Shuangyong Road, Nanning 530021, Guangxi, People's Republic of China. <sup>2</sup>Guangxi Key Laboratory Base of Precision Medicine in Cardio-cerebrovascular Disease Control and Prevention, Nanning 530021, Guangxi, People's Republic of China. <sup>3</sup>Guangxi Clinical Research Center for Cardio-cerebrovascular Diseases, Nanning 530021, Guangxi, People's Republic of China.

Received: 17 July 2019 Accepted: 3 October 2019

Published online: 23 October 2019

## References

- Wang F, Xu CQ, He Q, Cai JP, Li XC, Wang D, et al. Genome-wide association identifies a susceptibility locus for coronary artery disease in the Chinese Han population. *Nat Genet.* 2011;43(4):345–9.
- Smith SC, Jackson R, Pearson TA, Fuster V, Yusuf S, Faergeman O, et al. Principles for national and regional guidelines on cardiovascular disease prevention. *Circulation.* 2004;109(25):3112–21.
- Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003;361(9351):13–20.
- Banerjee A, Lim CC, Silver LE, Welch SJ, Banning AP, Rothwell PM. Familial history of stroke is associated with acute coronary syndromes in women. *Circ Cardiovasc Genet.* 2011;4(1):9–15.
- Yamada Y, Matsui K, Takeuchi I, Fujimaki T. Association of genetic variants with coronary artery disease and ischemic stroke in a longitudinal population-based genetic epidemiological study. *Biomed Rep.* 2015;3(3):413–9.
- Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet.* 2012;45(1):25–33.
- Eyuboglu M, Akdeniz B. Left ventricular ejection fraction in the prognosis of acute coronary syndromes. *Int J Cardiol.* 2017;234:137.

8. Lim WY, Thevarajah TM, Goh BT, Khor SM. Paper microfluidic device for early diagnosis and prognosis of acute myocardial infarction via quantitative multiplex cardiac biomarker detection. *Biosens Bioelectron.* 2019;128:176–85.
9. Tung R, Zimetbaum P. Chapter 11 - use of the electrocardiogram in acute myocardial infarction. In: Jeremias A, Brown DL, editors. *Cardiac intensive care* (Second Edition). Philadelphia: W.B. Saunders; 2010. p. 106–9.
10. Cubedo J, Blasco A, Padro T, Ramaola I, Juan-Babot O, Goicolea J, et al. Molecular signature of coronary stent thrombosis: oxidative stress and innate immunity cells. *Thromb Haemost.* 2017;117(9):1816–27.
11. Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, et al. NCBI GEO: archive for functional genomics data sets—update. *Nucleic Acids Res.* 2012;41(D1):D991–D5.
12. Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, et al. STRING v10: protein–protein interaction networks, integrated over the tree of life. *Nucleic Acids Res.* 2015;43(D1):D447–D52.
13. Maciejak A, Kiliszek M, Michalak M, Tulacz D, Opolski G, Matlak K, et al. Gene expression profiling reveals potential prognostic biomarkers associated with the progression of heart failure. *Genome Med.* 2015;7(1):26.
14. Ritchie ME, Diyagama D, Neilson J, van Laar R, Dobrovic A, Holloway A, et al. Empirical array quality weights in the analysis of microarray data. *BMC Bioinformatics.* 2006;7:261.
15. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. Limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Res.* 2015;43(7):e47.
16. Shannon P. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res.* 2003;13(11):2498–504.
17. Flentje A, Kalsi R, Monahan TS. Small GTPases and their role in vascular disease. *Int J Mol Sci.* 2019;20(4):E917.
18. López-Sendón J, Gurfinkel EP, Lopez de Sa E, Agnelli G, Gore JM, Steg PG, et al. Factors related to heart rupture in acute coronary syndromes in the global registry of acute coronary events. *Eur Heart J.* 2010;31(12):1449–56.
19. Eitel I, Gehmlich D, Amer O, Wohrle J, Kerber S, Lauer B, et al. Prognostic relevance of papillary muscle infarction in reperfused infarction as visualized by cardiovascular magnetic resonance. *Circ Cardiovasc Imaging.* 2013;6(6):890–8.
20. Doimo S, Fabris E, Chiapolino S, Barbati G, Priolo L, Korcova R, et al. Prognostic role of left ventricular dysfunction in patients with coronary artery disease after an ambulatory cardiac rehabilitation program. *Am J Cardiol.* 2019;124(3):355–61.
21. Al Chekatie MO. Traditional heart failure medications and sudden cardiac death prevention: a review. *J Cardiovasc Pharmacol Ther.* 2013;18(5):412–26.
22. Zhang TT, Takimoto K, Stewart AF, Zhu C, Levitan ES. Independent regulation of cardiac Kv4.3 potassium channel expression by angiotensin II and phenylephrine. *Circ Res.* 2001;88(5):476–82.
23. McIntosh MA, Cobbe SM, Kane KA, Rankin AC. Action potential prolongation and potassium currents in left-ventricular myocytes isolated from hypertrophied rabbit hearts. *J Mol Cell Cardiol.* 1998;30(1):43–53.
24. Gonzalez-Villalobos RA, Shen XZ, Bernstein EA, Janjulia T, Taylor B, Giani JF, et al. Rediscovering ACE: novel insights into the many roles of the angiotensin-converting enzyme. *J Mol Med (Berl).* 2013;91(10):1143–54.
25. Tham DM, Martin-McNulty B, Wang YX, Wilson DW, Vergona R, Sullivan ME, et al. Angiotensin II is associated with activation of NF-kappaB-mediated genes and downregulation of PPARs. *Physiol Genomics.* 2002;11(1):21–30.
26. Dzau VJ, Bernstein K, Celermajer D, Cohen J, Dahlöf B, Deanfield J, et al. The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and endpoint data. *Am J Cardiol.* 2001;88(9A):1L–20L.
27. Manfredini O, Morrell C, Das R, Barth JH, Hall AS, Gale CP, et al. Effects of angiotensin-converting enzyme inhibitors and beta blockers on clinical outcomes in patients with and without coronary artery obstructions at angiography (from a register-based cohort study on acute coronary syndromes). *Am J Cardiol.* 2014;113(10):1628–33.
28. Ozaki Y, Imanishi T, Teraguchi I, Nishiguchi T, Orii M, Shiono Y, et al. Association between P-selectin glycoprotein ligand-1 and pathogenesis in acute coronary syndrome assessed by optical coherence tomography. *Atherosclerosis.* 2014;233(2):697–703.
29. Kappelmayer J, Nagy B Jr. The interaction of selectins and PSGL-1 as a key component in thrombus formation and cancer progression. *Biomed Res Int.* 2017;2017:6138145.
30. Kitamura K, Sato K, Sawabe M, Yoshida M, Hagiwara N. P-selectin glycoprotein ligand-1 (PSGL-1) expressing CD4 T cells contribute plaque instability in acute coronary syndrome. *Circ J.* 2018;82(8):2128–35.
31. Fang H, Lin J, Wang L, Xie P, Wang X, Fu J, et al. Kruppel-like factor 2 regulates dendritic cell activation in patients with acute coronary syndrome. *Cell Physiol Biochem.* 2013;32(4):931–41.
32. Niu N, Xu S, Xu Y, Little PJ, Jin ZG. Targeting mechanosensitive transcription factors in atherosclerosis. *Trends Pharmacol Sci.* 2019;40(4):253–66.
33. Zhao Y, Sun Y. The FBW7-KLF2 axis regulates endothelial functions. *Cell Res.* 2013;23(6):741–3.
34. Khan S, Phulukdaree A, Ramkaran P, Moodley D, Chuturgoon AA. The Arg72 variant of the p53 functional polymorphism (rs1042522) is associated with coronary artery disease in young south Africans of Indian ancestry. *Gene.* 2016;593(2):261–4.
35. Saccucci P, Banci M, Amante A, Bottini E, Gloria-Bottini F. Coronary artery disease: evidence of interaction between PTPN22 and p53 genetic polymorphisms. *Cardiology.* 2011;120(3):166–8.
36. Kolovou V, Tsipis A, Mihas C, Katsiki N, Vartela V, Koutelou M, et al. Tumor protein p53 (TP53) gene and left main coronary artery disease. *Angiology.* 2018;69(8):730–5.
37. Li JH, Pober JS. The cathepsin B death pathway contributes to TNF plus IFN-gamma-mediated human endothelial injury. *J Immunol.* 2005;175(3):1858–66.
38. Fuchs SY, Adler V, Pincus MR, Ronai Z. MEK1/JNK signaling stabilizes and activates p53. *P Natl Acad Sci USA.* 1998;95(18):10541–6.
39. Kienesberger PC, Oberer M, Lass A, Zechner R. Mammalian patatin domain containing proteins: a family with diverse lipolytic activities involved in multiple biological functions. *J Lipid Res.* 2009;50(Supplement):S63–S58.
40. Baulande S, Langlois C. Proteins sharing NPPLA domain, a new family of enzymes regulating lipid metabolism. *Med Sci (Paris).* 2010;26(2):177–84.
41. Pulido MR, Diaz-Ruiz A, Jimenez-Gomez Y, Garcia-Navarro S, Gracia-Navarro F, Tinahones F, et al. Rab18 dynamics in adipocytes in relation to lipogenesis, lipolysis and obesity. *PLoS One.* 2011;6(7):e22931.
42. Passos-Silva DG, Verano-Braga T, Santos RA. Angiotensin-(1-7): beyond the cardio-renal actions. *Clin Sci (Lond).* 2013;124(7):443–56.
43. Gay A, Towler DA. Wnt signaling in cardiovascular disease. *Curr Opin Lipidol.* 2017;28(5):387–96.
44. Fu WB, Wang WE, Zeng CY. Wnt signaling pathways in myocardial infarction and the therapeutic effects of Wnt pathway inhibitors. *Acta Pharmacol Sin.* 2018;40(1):9–12.
45. Stylianidis V, Hermans KCM, Blankesteyn WM. Wnt signaling in cardiac remodeling and heart failure. *Handb Exp Pharmacol.* 2017;243:371–93.
46. Haybar H, Khodadi E, Shahabi S. Wnt/β-catenin in ischemic myocardium: interactions and signaling pathways as a therapeutic target. *Heart Fail Rev.* 2019;24(3):411–9.
47. Rajendran P, Rengarajan T, Thangavel J, Nishigaki Y, Sakthisekaran D, Sethi G, et al. The vascular endothelium and human diseases. *Int J Biol Sci.* 2013; 9(10):1057–69.
48. Tzima E. Role of small GTPases in endothelial cytoskeletal dynamics and the shear stress response. *Circ Res.* 2006;98(2):176–85.
49. Rahnamoun H, Hong J, Sun Z, Lee J, Lu H, Laubert SM. Mutant p53 regulates enhancer-associated H3K4 monomethylation through interactions with the methyltransferase MLL4. *J Biol Chem.* 2018;293(34):13234–46.
50. Matterna L, Courilleau C, Legube G, Ueda T, Fukunaga R, Chevillard-Briet M, et al. The E1A-associated p400 protein modulates cell fate decisions by the regulation of ROS homeostasis. *PLoS Genet.* 2010;6(6):e1000983.
51. Bao Y, Lin C, Ren J, Liu J. MicroRNA-384-5p regulates ischemia-induced cardioprotection by targeting phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit delta (PI3K p110delta). *Apoptosis.* 2013;18(3):260–70.
52. Xiao LI, Cao Y, Wang Y, Lai X, Gao KQ, Du P, et al. Aberrant histone modifications of global histone and MCP-1 promoter in CD14(+) monocytes from patients with coronary artery disease. *Pharmacazie.* 2018;73(4):202–6.
53. Sugawara T, Kano F, Murata M. Rab2A is a pivotal switch protein that promotes either secretion or ER-associated degradation of (pro) insulin in insulin-secreting cells. *Sci Rep.* 2014;4:6952.
54. Ding X, Jiang X, Tian R, Zhao P, Li L, Wang X, et al. RAB2 regulates the formation of autophagosome and autolysosome in mammalian cells. *Autophagy.* 2019:1–13.
55. Aleidi SM, Howe V, Sharpe LJ, Yang A, Rao G, Brown AJ, et al. The E3 ubiquitin ligases, HUWE1 and NEDD4-1, are involved in the post-translational regulation of the ABCG1 and ABCG4 lipid transporters. *J Biol Chem.* 2015;290(40):24604–13.
56. Senis YA, Atkinson BT, Pearce AC, Wonerow P, Auger JM, Okkenhaug K, et al. Role of the p110δ PI 3-kinase in integrin and ITAM receptor signalling in platelets. *Platelets.* 2009;16(3–4):191–202.

57. Rossello X, Riquelme JA, Davidson SM, Yellon DM. Role of PI3K in myocardial ischaemic preconditioning: mapping pro-survival cascades at the trigger phase and at reperfusion. *J Cell Mol Med.* 2018;22(2):926–35.
58. Reho JJ, Guo DF, Rahmouni K. Mechanistic target of rapamycin complex 1 signaling modulates vascular endothelial function through reactive oxygen species. *J Am Heart Assoc.* 2019;8(9):e010662.

### **Publisher's Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Ready to submit your research? Choose BMC and benefit from:**

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

**At BMC, research is always in progress.**

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

