Identification of Potential Core Genes and Promising Compounds in STEMI Using Bioinformatics Analysis

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Abstract

Purpose

The objective of this research was to reveal the fundamental molecular processes and determine the critical pathways and genes for ST-segment elevation myocardial infarction by performing bioinformatics analysis.

Methods

The Gene Expression Omnibus Gene (GEO) database was utilized to acquire the microarray data for GSE60993 and GSE61144. The R package limma was employed for the purpose of identifying differentially expressed genes (DEGs). The DAVID database was retrieved to conduct enrichment analyses for both gene ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway. STRING was employed to construct a DEG-related protein-protein interaction (PPI) network, which was then visualized in Cytoscape. The modules belonging to the PPI network were analyzed using MCODE. With the aid of Connectivity Map (CMap), we determined potential medications according to the genes that had previously been identified.

Results

A total of 201 downmodulated and 43 upmodulated genes were discovered. The findings from GO and KEGG pathway enrichment analyses demonstrated a significant correlation between the DEGs and immunological responses, inflammatory responses, and pathways such as cytokine-cytokine receptor interface and Hematopoietic cell lineage. MMP9, PGLYRP1, CAMP, FOLR3, ORM1, QPCT, LRG1, ARG1, CDA and S100A12 were determined as the hub genes in the PPI network according to their extent of connectivity. The hub genes that were identified together with their corresponding transcriptional factors included ELF-1, PAX, PEA3, Pu.1, ZF5, EGR-3, Dp-1, FOXP3, etc.

Conclusions

The microarray data and bioinformatics analyses conducted in the present research offer a viable option for identifying critical pathways and genes correlated with STEMI.

Introduction

ST-segment elevation myocardial infarction (STEMI) is a deadly type of coronary heart disease and has been identified to be a leading cause of morbidity and death on a global scale[1]. In spite of the significant advances in medical and revascularization therapies, STEMI still results in an unfavorable prognosis. STEMI survivors often experience multiple problems that dramatically shorten their expected lifespan and deteriorate the overall quality of life. It has been and continues to be crucial to make the diagnosis of septic STEMI according to distinctive clinical manifestations and Electrocardiographic alterations, which are then supported by elevated cardiac enzymes [2]. In most cases, the clinical signs of

early STEMI are emergent, fatal, and likely to be ignored. The molecular mechanism of STEMI is not completely understood. Given the significant morbidity and mortality among patients with STEMI, we explored the underlying mechanism responsible for molecular mechanisms. The comprehension of early STEMI molecular diagnosis might assist patients and physicians in recognizing the problem and initiating treatment procedures as soon as possible.

With the development of high-throughput and microarray technology, the bioinformatics analysis method has been increasingly recognized as an approach with significant clinical value in areas such as screening biomarkers and predicting intermolecular interactions of disease[3]. The practicality of applying this technique to screen for essential genes and dysregulated pathways associated with the occurrence and progression of STEMI, on the other hand, remains to be determined. In the present research, microarray datasets GSE60993 and GSE61144 were obtained from GEO (<http://www.ncbi.nlm.nih.gov>) and examined for the purpose of identifying the DEGs between STEMI patients and control[4]. David, KEGG, and STRING databases were used to analyze the molecular function, biological process, and signal pathway of the main enrichment of the target gene. Meanwhile, by using the bioinformatics analysis method, we might provide effective biomarker candidates for clinical trials and clinical practice of STEMI.

Methods

Microarray data

In this paper, the two gene expression profiles, GSE60993 and GSE61144, were identified following retrieval of the GEO (<https://www.ncbi.nlm.nih.gov/geo/>). Subsequently, the data sets were detected using the GPL6106 Sentrix Human-6 v2 Expression BeadChip and the GPL6884Illumina HumanWG-6 v3.0 expression bead chip. Data of gene chips were extracted, and all samples were grouped into STEMI and normal. The characteristics of these microarray expression profiles are shown in Table 1.

Table 1
Detailed data of GSE6099and GSE61144.

Sequence number of Chip	GSE6099	GSE61144
Platform	GPL6884	GPL6106
Annotation of platform	Illumina HumanWG-6 v3.0 expression BeadChip	Sentrix Human-6 v2 Expression BeadChip
Research object	Human	Human
Sample type	Peripheral blood	Peripheral blood
Number of chip samples (Case/ Control)	7/7	7/10

Screening Genes Of Differential Expression

The ggplot2 function in R (<http://ggplot2.org>) was employed to plot a volcano map, which was used to probe into the overall differential expression of genes [5]. The standardized microarray data were processed with the limma package[6], and the differential genes were calculated. The criteria used to screen differential genes were: $|\log_2(\text{fold change})| > 1$, and $p\text{-value} < 0.05$. Subsequently, the heatmap was also plotted using the package ggplot2 in R[7]. Then, a Venn diagram was employed for the purpose of identifying the final co-expression DEGs[8].

Functional And Pathway Enrichment Analysis

With the aid of the cluster Profiler function package of the R software, we performed gene ontology (GO) analysis (encompassing molecular function [MF], cellular component [CC], and biological process [BP]) [9, 10] and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway[11] enrichment analysis. Moreover, the threshold to screen significantly enriched GO terms and KEGG pathways was defined by $P < 0.05$.

Construction Of Ppi Network And Validation Of Hub Genes

Prediction and analysis of the functional connections and interactions among proteins were carried out with the aid of the STRING database[12, 13] (<https://string-db.org/>, version 11.0). PPI networks were created with the assistance of Cytoscape (version 3.8.2)[14]. For the purpose of filtering the PPI networks modules present in Cytoscape, we performed a plug-in called molecular complex detection (MCODE) [15]. The hub genes were identified by using the plug-in cytoHub[16].

Transcriptional Factors Analysis

The STEMI transcriptional factors were predicted utilizing PASTAA[17]. P-values that were derived from hypergeometric distributions were employed to determine whether STEMI and transcription factors are correlated. Prediction of potential correlation was conducted by TRAP [18]. Co-expression DEGs were imported into the database, with the DNA binding domain being predicted using JASPAR[19] (version 2016).

Cmap Analysis

CMap [20] is regarded as the links below which are online references for new drugs in the field of diseases, genes, and therapeutic drugs. Co-expression DEGs were used as queries on the CMap website (<https://portals.broadinstitute.org/cmap/>). The relationship present between a perturbagen and a query signature in any particular cell line is investigated by a connectivity score (τ), within the ranges of + 100 and - 100. This τ provides a quantification of the signature proportions within the reference database

with a stronger similarity to the perturbagen as opposed to the existing query signature. The median tau score is a quantitative statistic, which summarizes the connection score between a perturbagen and a query signature throughout all cell lines. In the case where two signatures receive an elevated positive connectivity score, they are considered as exhibiting a negative connection whereas those having a greater negative score are considered as exhibiting a negative connection. High connectivity is determined to have been achieved when the tau scores between the two signatures are above 90 or below - 90.

Results

Identification of DEGs

The limma package was employed to normalize quartile data and conduct background correction on two expression microarray datasets, GSE60993 and GSE61144. The volcano plot demonstrates a summary of all DEGs in the GSE60993 dataset (Figure. 1A) and GSE61144 dataset (in Figure. 1C), with the cutoff criteria in the volcano plot established at $p\text{-value} < 0.05$ and $|\log_2(\text{fold change})| > 1$; the downmodulated genes are represented by the green plots whereas the upmodulated genes are represented by the red plots. Subsequently, in the case of setting the cutoff criteria at adjusted $P < 0.05$ and $|\log_2 Fc| > 1$, a total of 244 DEGs were screened in the GSE60993 dataset, in which 201 were upmodulated and 43 were downmodulated. Using the same methodology, 214 DEGs were obtained from the GSE61144 dataset, including 56 down- and 158 upregulated genes. Heat maps (Figure. 1B and Figure. 1D) illustrate the expression of these DEGs in each sample. Venn diagrams (Figure. 1E) illustrate the number of upregulated and downregulated genes in healthy controls and patients with STEMI. The intersection represents the DEGs shared between the two groups.

Analysis Of Functional And Pathway Enrichment

On the basis of DAVID, GO functional and KEGG pathway analyses were conducted to determine the biological classification of co-expression DEGs. The findings recorded from the GO analysis illustrated a significant enrichment of biological process (BP) annotations in innate immune responses, negative modulation of MAP kinase activity, immunological responses, inflammatory responses, cellular responses to lipopolysaccharide, negative modulation of interleukin-6 production, and defensive responses against bacterium (Figure. 2A). Changes evidently enriched in CC of DEGs were predominantly enriched in extracellular regions, plasma membranes, anchored components of membrane, extracellular exosome, extracellular space, and membrane (Figure. 2B). Changes in MF were shown to have a remarkable enrichment in RAGE receptor binding, receptor activity, carbohydrate-binding, serine-type endopeptidase activity, pantetheine hydrolase activity, and interleukin-1 receptor activity (Figure. 2C). The analytical findings obtained from the KEGG pathway demonstrated a remarkable enrichment of DEGs that were enriched in pathways correlated with the Cytokines-cytokine receptors interface and

hematopoietic cell lineage. (Figure. 2D). Table 2 contains further detailed findings from the GO and KEGG analyses.

Table 2
The functional enrichment analyses of co-expression DEGs ranked by *P*-value

Category	Pathway ID	Pathway description	Genes	Count	<i>P</i> -value
GO_BP	GO:0045087	innate immune response	CLEC4D, HMGB2, S100A12, PADI4, PGLYRP1, BMX, CLEC4E, TREM1, TLR4, CAMP, CD55, KLRG1	12	1.33E-05
GO_BP	GO:0006955	immune response	IL18RAP, NFIL3, CD8A, GZMA, IL1R2, NCF4, AQP9, PGLYRP1, TLR4, IL18R1, GZMH	11	6.31E-05
GO_BP	GO:0042742	defense response to bacterium	CLEC4D, GNLY, S100A12, CLEC4E, TLR4, CAMP	6	9.38E-04
GO_BP	GO:0071222	cellular response to lipopolysaccharide	ARG1, HMGB2, TLR4, CAMP, CXCL16	5	0.00281774
GO_BP	GO:0006954	inflammatory response	TPST1, ORM1, IL18RAP, FPR1, PROK2, S100A12, TLR4, KLRG1	8	0.003510251
GO_BP	GO:0032715	negative regulation of interleukin-6 production	ORM1, IRAK3, TLR4	3	0.009190494
GO_BP	GO:0043407	negative regulation of MAP kinase activity	RGS2, DUSP1, IRAK3	3	0.014913344
GO_BP	GO:0002292	T cell differentiation involved in immune response	CLEC4D, CLEC4E	2	0.015463642
GO_BP	GO:0032720	negative regulation of tumor necrosis factor production	ORM1, IRAK3, TLR4	3	0.016530744
GO_BP	GO:0030890	positive regulation of B cell proliferation	IRS2, TLR4, ADA	3	0.017366306

GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; BP, biological process; CC, cellular component; MF, molecular function.

Category	Pathway ID	Pathway description	Genes	Count	P-value
GO_BP	GO:0038094	Fc-gamma receptor signaling pathway	CLEC4D, CLEC4E	2	0.020565474
GO_BP	GO:0006935	chemotaxis	FPR1, PROK2, CMTM2, CXCL16	4	0.025500206
GO_BP	GO:0019221~	cytokine-mediated signaling pathway	CSF3R, IL1R2, IL2RB, IRAK3	4	0.030600263
GO_BP	GO:0050829	defense response to Gram-negative bacterium	HMGB2, TLR4, CAMP	3	0.033001142
GO_BP	GO:0032609	interferon-gamma production	EOMES, TLR4	2	0.035714688
GO_BP	GO:0015939	pantothenate metabolic process	VNN2, VNN3	2	0.040712771
GO_BP	GO:0030593	neutrophil chemotaxis	CSF3R, S100A12, TREM1	3	0.045966815
GO_BP	GO:0001938	positive regulation of endothelial cell proliferation	LRG1, ARG1, HMGB2	3	0.049779713
GO_CC	GO:0005886	plasma membrane	CSF3R, KLRB1, AQP9, DYSF, FPR1, IRS2, PYGL, TREM1, CXCL16, PANX2, RGS2, IL18RAP, CA4, S100A12, CD55, KLRG1, MGAM, MME, ACSL1, IL1R2, KCNJ15, GAB2, CKAP4, F5, CLEC4D, VNN2, CD8A, VNN3, CPD, IL2RB, ALPL, CLEC4E, TLR4, ADA, IL18R1, CDK5R1	36	2.86E-04
GO_CC	GO:0005576	extracellular region	CDA, ORM1, CSF3R, IL1R2, GZMA, TREM1, MMP9, F5, CXCL16, GZMK, LRG1, CRISPLD2, CD8A, PROK2, S100A12, FOLR3, PGLYRP1, CD55, CAMP	19	6.82E-04

GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; BP, biological process; CC, cellular component; MF, molecular function.

Category	Pathway ID	Pathway description	Genes	Count	P-value
GO_CC	GO:0031225	anchored component of membrane	VNN2, VNN3, CA4, ALPL, CD55	5	0.002282272
GO_CC	GO:0005615	extracellular space	ORM1, ARG1, HMGB2, MMP9, F5, CXCL16, LRG1, GNLY, VNN3, CPD, ALPL, CMTM2, ADA, CAMP	14	0.013520571
GO_CC	GO:0070062	extracellular exosome	MGAM, ORM1, MME, ARG1, DYSF, PYGL, MMP9, CKAP4, LRG1, CRISPLD2, QPCT, CPD, BOLA2, CA4, ALPL, S100P, PGLYRP1, CD55, TGM3, CAMP, FKBP5, CREB5, B4GALT5	23	0.01479944
GO_CC	GO:0016020	membrane	ACSL1, NCF4, KCNJ15, CKAP4, F5, CXCL16, GZMH, TPST1, LRG1, CPD, IL2RB, ALOX5AP, CA4, ALPL, FOLR3, ADA, FKBP5, CDK5R1	18	0.036187003
GO_MF	GO:0050786	RAGE receptor binding	FPR1, HMGB2, S100A12, S100P	4	1.97E-05
GO_MF	GO:0004872	receptor activity	CSF3R, IL18RAP, CLEC4E, TREM1, TLR4, IL18R1, KLRG1	7	7.91E-04
GO_MF	GO:0030246	carbohydrate binding	MGAM, CLEC4D, KLRB1, CLC, CLEC4E, KLRG1	6	0.003104335
GOMF	GO:0017159	pantetheine hydrolase activity	VNN2, VNN3	2	0.015030693
GO_MF	GO:0004908	interleukin-1 receptor activity	IL1R2, IL18R1	2	0.034724823
GO_MF	GO:0004252	serine-type endopeptidase activity	GZMK, GZMA, MMP9, GZMH, F5	5	0.039819959
KEGG_PATHWAY	hsa04640	Hematopoietic cell lineage	CSF3R, MME, CD8A, IL1R2, CD55	5	0.002395496

GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; BP, biological process; CC, cellular component; MF, molecular function.

Category	Pathway ID	Pathway description	Genes	Count	P-value
KEGG_ PATHWAY	hsa04060	Cytokine-cytokine receptor interaction	CSF3R, IL18RAP, IL1R2, IL2RB, IL18R1, CXCL16	6	0.020392791
GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; BP, biological process; CC, cellular component; MF, molecular function.					

Key Genes In Ppi Networks

Co-expression DEGs were used as queries in the STRING database (Figure.3A). The STRING analysis identified the interaction among the encoded proteins. Cytoscape analyzes and predicts 10 hub genes: MMP9, PGLYRP1, CAMP, FOLR3, ORM1, QPCT, LRG1, ARG1, CDA and S100A12 (Figure.3B). The expression of 10 hub genes in the STEMI group and normal group is shown in Fig. 4. It can be seen from the figure that the expression levels of all hub genes in the STEMI group are remarkably elevated as opposed to those in the normal group. Further, the main functions of each hub gene are obtained by querying the gene cards database (Table 3).

Table 3
Summary of the function of 10 hub genes

Symbol	Full name	Function
MMP9	matrix metalloproteinase 9	play a role in bone osteoclastic resorption (By similarity), cleaves KiSS1 at a Gly-I-Leu bond, cleaves NINJ1 to generate the Secreted ninjurin-1 form, cleaves type IV and type V collagen into large C-terminal three quarter fragments and shorter N-terminal one quarter fragments and degrades fibronectin but not laminin or Pz-peptide
PGLYRP1	peptidoglycan recognition protein 1	Forms an equimolar complex with heat shock protein HSPA1A and induces programmed cell death through apoptosis and necroptosis in tumor cell lines by activating the TNFR1 receptor on the target cell membrane, acts in complex with the Ca(2+)-binding protein S100A4 as a chemoattractant able to induce lymphocyte movement, acts as a ligand of the chemotactic receptors CCR5 and CXCR3 which are present on the cells of the immune system, promotes also the activation of lymphocytes that become able to kill virus-infected cells as well as tumor cells by modulating the spectrum of their target-cell specificity and induction of cytotoxicity on monocyte surface requires interaction with TREM1 receptor
CAMP	cathelicidin antimicrobial peptide	In addition to its antibacterial, antifungal, and antiviral activities, the encoded protein functions in cell chemotaxis, immune mediator induction, and inflammatory response regulation
FOLR3	folate receptor gamma	Binds to folate and reduced folic acid derivatives and mediates delivery of 5-methyltetrahydrofolate to the interior of cells.
ORM1	orosomucoid 1	Functions as transport protein in the blood stream. Binds various ligands in the interior of its beta-barrel domain, binds synthetic drugs and influences their distribution and availability in the body. Appears to function in modulating the activity of the immune system during the acute-phase reaction.
QPCT	glutaminyl-peptide cyclotransferase	Responsible for the biosynthesis of pyroglutamyl peptides. Also catalyzes N-terminal pyroglutamate formation. In vitro, catalyzes pyroglutamate formation of N-terminally truncated form of APP amyloid-beta peptides [Glu-3]-amyloid-beta. May be involved in the N-terminal pyroglutamate formation of several amyloid-related plaque-forming peptides.
LRG1	leucine rich alpha-2-glycoprotein 1	involves in protein-protein interaction, signal transduction, and cell adhesion and development and express during granulocyte differentiation
ARG1	arginase 1	Key element of the urea cycle converting L-arginine to urea and L-ornithine, which is further metabolized into metabolites proline and polyamides that drive collagen synthesis and bioenergetic pathways critical for cell proliferation
CDA	cytidine deaminase	involves in pyrimidine salvaging. It is one of several deaminases responsible for maintaining the cellular pyrimidine pool.

Symbol	Full name	Function
S100A12	S100 calcium binding protein A12	plays a prominent role in the regulation of inflammatory processes and immune response. Its proinflammatory activity involves recruitment of leukocytes, promotion of cytokine and chemokine production, and regulation of leukocyte adhesion and migration. Acts as an alarmin or a danger associated molecular pattern (DAMP) molecule and stimulates innate immune cells via binding to receptor for advanced glycation endproducts (AGER). Binding to AGER activates the MAP-kinase and NF-kappa-B signaling pathways leading to production of proinflammatory cytokines and up-regulation of cell adhesion molecules ICAM1 and VCAM1. Acts as a monocyte and mast cell chemoattractant. Can stimulate mast cell degranulation and activation which generates chemokines, histamine and cytokines inducing further leukocyte recruitment to the sites of inflammation. Can inhibit the activity of matrix metalloproteinases

Transcriptional Factor Analysis

Table 4 displays the transcriptional factors anticipated by PASTAA involved in the regulation of gene expression in STEMI. EIF-1, PEA3 and PU.1transcription factor families make a valuable contribution to the upregulation of the expression of genes. In contrast, E2F-1, Dp-1and EGR-3 families are considered to perform an instrumental function in down-modulating the expression levels of genes. The JASPAR-predicted transcriptional factor-binding domain is depicted in Fig. 5.

Table 4
Results of PASTAA analysis

Rank	Matrix	Transcription Factor	Association Score	P-Value
a. TFs predicted to regulate up-regulated genes				
1	ETS_Q6	Elf-1, Elfr	5.452	9.80E-05
2	PAX_Q6	Pax-1, Pax-2	4.794	4.12E-04
3	LFA1_Q6	N/A	4.606	6.36E-04
4	PEA3_Q6	Pea3	4.522	7.39E-04
5	PU1_Q6	Pu.1	4.522	7.39E-04
6	ETS_Q4	Erf, Elf-1	3.833	3.06E-03
7	HLF_01	Hlf	3.766	3.43E-03
8	GC_01	N/A	3.328	8.00E-03
9	ZF5_01	Zf5	3.325	8.01E-03
10	ELF1_Q6	Elf-1, Elf-1	3.317	8.06E-03
b. TFs predicted to regulate down-regulated genes				
1	EGR3_01	Egr-3	3.353	2.92E-03
2	E2F_01	E2f-1	3.123	4.87E-03
3	E2F_Q4	N/A	3.123	4.87E-03
4	E2F_Q6	N/A	3.123	4.87E-03
5	KAISO_01	N/A	3.122	4.87E-03
6	E2F1_Q4	E2f-1	2.822	9.32E-03
7	E2F_Q6_01	Dp-1, E2f-1	2.822	9.32E-03
8	FOXP3_Q4	Foxp3	2.658	1.34E-02
9	E2F1_Q6_01	E2f-1	2.646	1.34E-02
10	E2F_Q4_01	Dp-1, E2f-1	2.646	1.34E-02

The CMap Analysis Identified Significant Connections Between compounds and genes in STEMI

Co-expression DEGs were used as queries in the CMap website. According to the findings, the CMap investigation revealed connectivity between compounds and genes in STEMI across 9 different cell lines. For the purpose of focusing on the compounds with the greatest connectivity, we only included those

whose median tau score was > 90 or ≤ -90 . There were no compounds that demonstrated remarkable negative connectivity. However, 17 compounds demonstrated a strong positive connectivity (Fig. 6).

Discussion

The mortality of STEMI has remained high over the past few years[21]. Early diagnosis, proper categorization, as well as prompt treatment of STEMI in the early stages are critical in lowering fatality [22]. By performing bioinformatic analyses, we successfully revealed the fundamental molecular processes involved in the occurrence and progression of STEMI, providing a new and more efficacious approach of identifying feasible diagnostic markers and targeted therapies, contributing to the prevention and treatment of STEMI. Overall, 201 upmodulated DEGs and 43 downmodulated DEGs were discovered among patients suffering from STEMI in contrast with those who did not develop this disease in the present research. The identified genes predominantly played a role in biological processes, including inflammatory responses, immunological responses, and pathways such as cytokine-cytokine receptor interface and Hematopoietic cell lineage. Within the PPI network, MMP9, PGLYRP1, CAMP, FOLR3, ORM1, QPCT, LRG1, ARG1, CDA, and S100A12 were determined to be the hub genes according to the extent of their connectivity. All of the hub genes were expressed at elevated levels among STEMI patients in contrast with healthy controls.

The DEGs were closely related to inflammatory and immune responses, according to functional pathway enrichment analysis. STEMI has been associated with innate immunity[23], acquired immunity, and inflammatory pathways[24, 25]. Immediately after a coronary atherothrombosis, a markedly inflammatory response is stimulated with the activation of several immune cells and inflammatory molecules, which altogether contributes to the thrombus formation that is rapidly followed by myocardial ischemia[26]. The innate immunological response induced by the Toll-like receptor (TLR)2 and TLR4 activation on circulating blood cells during AMI has been shown in animal models, which negatively influences the progression of disease in experimental models, i.e., worsening ventricular remodeling and increasing infarct size. In myocardial infarction models, TLR4 deficiency, as well as pharmacologic suppression of TLR4 or TLR2, lowers monocyte influx and granulocyte influx into the infarcted region, thus minimizing the infarct size and improving cardiac remodeling [27]. Inflammatory dysregulation may result in greater ultimate infarct size as well as maladaptive remodeling inside the myocardium, both of which would lead to heart failure [28]. Treatment of patients with STEMI that targets the inflammatory pathways that are triggered in the process of reperfusion may be an effective approach for lowering the ultimate infarct size and improving prognosis status following STEMI[26, 29].

We created a PPI network for the purpose of screening for the hub genes as well as a co-expression network comprising the top ten hub genes. It is postulated that atherosclerotic plaque is the fundamental cause of acute MI [22, 30]. In the case of atherosclerosis, the plaque is composed of a diverse population of biological components, all of which are embedded by an extracellular matrix (ECM)[1, 31]. A growing number of reports suggest that the matrix metalloproteinases (MMPs) perform a fundamental function in the degradation of the extracellular matrix (ECM) by means of preferentially hydrolyzing specific

elements of the ECM[32]. Nevertheless, these apparently typically functional processes of MMPs also accelerate remodeling and deterioration of the fibrous cap encapsulating atherosclerosis plaque, resulting in a plaque that is more susceptible to rupture and consequent atherothrombosis [33]. It is the bursting of an atherosclerotic plaque that is the most often observed culprit of an acute MI, which subsequently leads to an unregulated thrombotic reaction, culminating in an acute atherothrombotic MI [34].

Peptidoglycan recognition protein 1 (PGLYRP1), an essential constituent of the innate immune function and inflammatory system, was shown to be one of the most significant variables in controlling endothelial dysfunction throughout the pathologic course of atherosclerosis [35]. PGLYRP1 has the capacity of forming a stable complex with the Ca^{2+} -binding protein Mts1. The resultant PGLYRP1-Mts1 complex has the ability to induce chemotaxis migration of lymphocytes, thus impacting the pathogenesis of atherosclerosis progression in its early stages [36]. Most probably, PGLYRP1 influences atherosclerosis by inhibiting the production of adhesion molecules, including ICAM-1, VCAM-1, and E-selectin, eventually decreasing the adherence of monocytes to the endothelium [36]. As shown in the present research, endothelial cells create adhesion molecules that draw monocytes, allowing them to adhere to the endothelium [37]. Upon maturation into macrophages, these monocytes internalize ox-LDL, contributing to the development of foam cells, which contributed to the initial stages of atherosclerosis[38]. It has been demonstrated that the human antimicrobial peptide LL-37, the only recognized human cathelicidin whose encoding is achieved by the human cathelicidin antimicrobial peptide (CAMP) gene, is found in human atherosclerosis plaques and is related to the induction of thrombosis and activation of platelets, with elevated levels of serum in the coronary circulation as opposed to the systemic levels in patients with STEMI [38, 39]. FOLR3 is known to have the ability to encode folate receptor gamma, which belongs to the family of folate receptor proteins[40]. Orosomucoid 1(ORM1) produced by endothelial cells has been associated with anti-inflammatory, immunomodulating, and antiapoptotic effects that could be of importance for the pathogenesis of cardiovascular diseases [41]. ORM1 levels were higher in patients with MI[42]. As the development of atherosclerosis and ischemia progresses, inflammation plays a critical role[43]. Glutaminyl-peptide cyclotransferase (QPCT) gene encodes glutaminyl cyclase (QC)[44]. Monocyte chemotactic protein-1 (MCP-1) (also recognized as chemokine (C-C motif) ligand 2 (CCL2)) is affiliated with the family of the CC chemokine [45]. The chemotactic activity of CCL2 is controlled by a modified N-terminus of the polypeptide, especially the formation of a pyroglutamate (pE)-residue protecting against proteolytic degradation *in vivo* [46]. QC has the ability to posttranslationally modify the N-terminal pE of CCL2 [47]. Acute local increases in MCP-1 in the infarct-associated vessel have been observed in individuals suffering from STEMI [48]. Alpha-2-glycoprotein 1(LRG1) functions as an acute-phase protein and inflammatory marker, whose concentrations increase in inflammatory diseases and contribute to atherosclerosis progression through inflammation[49]. A clinical investigation demonstrated that the expression level of arginase (ARG1) is elevated in individuals with STEMI and that it serves as an indicator of plaque susceptibility and has a correlation with infarction size in the clinical progression of this disease [50]. The underlying mechanism is that ARG1 lowers NO bioavailability and leads to atherosclerosis by depleting its common substrate (L-arginine)[51]. In acute MI, reduced NO bioavailability leads to endothelial impairment, plaque destabilization, and greater vulnerability to ischemia-reperfusion damage[52]. As S100A12 is mostly produced in the cytoplasm of myeloid cells with

a significant elevation in expression level when the cells are exposed to inflammatory stimuli, it has been shown to be a crucial protein throughout inflammation, especially in the occurrence and progression of atherosclerosis [53]. A 1.4-times growth in the size of atherosclerotic plaques as well as calcified plaque region was observed in ApoE-deficient S100A12 transgenic mice [54]. Recent studies have shown that S100A12, the ligand of endogenous TLR2 and TLR4, is produced in ischemic tissues and secreted in the circulation, resulting in an enhanced TLR activation and elevated expression levels of circulating cells. The inhibition of S100A12 could also be a good target to enhance cardiac functionality among patients with atherosclerosis via the mechanism of inhibiting the further release of TLR-4[53]. Moreover, because of the possible role of S100/calgranulins in the occurrence and progression of atherosclerosis, plaque susceptibility, ischemia-related myocardial inflammation, and heart failure, these proteins could be crucial treatment targets for STEMI [55]. The role of FOLR3, ORM1, and CDA in the occurrence and progression of STEMI, on the other hand, remains controversial. Thus, identifying the association between these genes and STEMI will necessitate additional research. These observations are consistent with the underlying mechanism and provide new therapeutic targets in patients with STEMI.

The differential expression of genes in STEMI might be regulated by transcription factors. Our study found that EIF-1, PEA3, and PU.1 transcription factor families make a valuable contribution to the up-regulation of gene expression in the STEMI group. By contrast, E2F-1, Dp-1 and EGR-3 families are considered to perform a fundamental function in down-modulating gene expression in the STEMI group. The study proved that PU.1 was involved in immune regulation[56]. At the same time, PU.1 is a transcription factor that has the ability to modulate the human gene CAMP, which encodes the antimicrobial peptide LL-37 [57]. PEA3 can directly bind to VEGF and MMP-9 promoters[58]. PEA3 siRNA down-modulated hypoxia-triggered Pref-1 expression[59]. Early growth response 3 (Egr-3) contributes to the stimulation of VEGF in endothelial cells [60], which is associated with microvascular obstruction in patients with STEMI. These findings were potentially important clinical implications in STEMI.

With the aid of CMap, we proved that a data-driven analytic strategy was a viable option for identifying novel therapeutic targets for STEMI treatment from multiple potential candidates. Heart failure and chronic remodeling following myocardial ischemia are suppressed by IKK inhibitors, which play a role via the mechanism of altering MMP [61]. The expression of the epidermal growth factor receptor (EGFR) along with its corresponding ligands are elevated in the vascular lesions of humans with atherosclerosis[62]. JAK3 inhibitor VI is a specific inhibitor for EGFR[63]. Linifanib is a VEGF inhibitor and the levels of VEGF are correlated with microvascular obstruction among STEMI patients[62]. The expression levels of both PDGFR-a and PDGFR-b are significantly up-modulated within the vessel wall of patients with atherosclerosis, which are produced by macrophages as well as vascular SMCs. In addition, PDGFR-b signaling may serve as a key player in the process of atherogenic onset. In an atherosclerotic murine model, treatment with a PDGFR blocking kinase inhibitor slowed the progression of atherosclerosis [64]. Following a myocardial infarction, hypoxia-inducible factor 1 and carbonic anhydrase IX function in a combined manner to reduce heart dysfunction. In CMap prediction, adenosine receptor agonists, as well as opioid receptor agonists, are identified as the most crucial targets, suggesting that integrating various medications might result in more effective therapies.

Conclusions

In conclusion, by performing multiple bioinformatics analyses comparing DEGs between STEMI samples and healthy controls, we discovered several novel and crucial pathways and genes that are strongly related to the occurrence and progression of STEMI. The genes and pathways that have been discovered could deliver a more complete comprehension of the molecular processes involved in the occurrence and progression of STEMI. Moreover, they may also offer new opportunities as prospective biological markers and treatment targets. More detailed research, nonetheless, will be necessary to corroborate the findings in the present research.

Abbreviations

GEO	Expression Omnibus Gene
DEGs	Differentially expressed genes
GO	Gene ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
PPI	protein–protein interaction
BP	Biological processes
CC	Cellular component
MF	Molecular function
CMap	Connectivity Map
STEMI	ST-segment elevation myocardial infarction
MCODE	molecular complex detection

Declarations

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Authors’ contributions

Hong Ding, Shu Liu, Zi-Wei Zhu and Xiao-Wei Zhang contributed to the design, analysis, and interpretation of data; drafting of the manuscript; and critical revision of the manuscript. Hong Ding and Shu Liu contributed to the statistical analysis. Hong Ding, Shu Liu, Zi-Wei Zhu, Yu-Qin Wang, Dan Li and Xiao-Wei Zhang contributed to the methodology. Zi-Wei Zhu, Yu-Qin Wang, Dan Li and Xiao-Wei Zhang contributed to the project administration. Hong Ding and Shu Liu wrote the manuscript. All authors read and approved the final manuscript.

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Data Availability

All raw and processed data are freely available from GEO database (<https://www.ncbi.nlm.nih.gov/geo/>).

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

Figure 1

Identification of DEGs. (A) Volcano plot of DEGs between STEMI patients and healthy controls from the GSE60993 dataset. The horizontal axis shows $\log_2FC$ and the vertical axis shows $-\log_{10}(FDR)$. Red points represent up-regulated genes, green points represent down-regulated genes, and black points indicate no significant difference. (B) Heatmap of DEGs between STEMI patients and healthy controls from the GSE60993 dataset. The horizontal axis shows genes and the vertical axis shows samples. Red indicates high expression and blue indicates low expression. (C) Volcano plot of DEGs between STEMI patients and healthy controls from the GSE61144 data set. The horizontal axis shows $\log_2FC$ and the vertical axis shows $-\log_{10}(FDR)$. Red points represent up-regulated genes and blue points represent down-regulated genes. (D) Heatmap of DEGs between STEMI patients and healthy controls from the

GSE61144 dataset. The horizontal axis shows genes and the vertical axis shows samples. Red indicates high expression and green indicates low expression. (e) Venn diagram of DEGs.

DEGs, differentially expressed genes; STEMI, acute ST segment elevation

Figure 2

GO terms and KEGG pathway enrichment.

A

B

Visual Legend for default

Node Fill Color Mapping

Edge Width Mapping

Edge Label Color Mapping

Edge Transparency Mapping

Edge Label Font Size Mapping

Figure 3

Construction of the PPI network. (A) PPI network of shared genes. Each dot represents a node. Importance of the gene in the network is reflected by the degree of the node which is represented by the number of lines connected to the dot (node). A thicker line reflects a stronger interaction between two nodes. Red points represent up-regulated genes and blue points represent down-regulated genes. (B) The network of key genes selected using the Maximal Clique Centrality algorithm. Important genes are shown in redder colors. PPI, protein–protein interaction.

Figure 4

Hub gene expression map.

Figure 5

Transcription factors binding site predicted by JASPAR.

Figure 6

Connectivity Map (CMap) results displaying significant connections between compounds and genes in STEMI.