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ORIGINAL RESEARCH

SULF1 and EPB41L3: Potential Biomarkers of Acute Myocardial Infarction and the Vascular Inflammatory Milieu

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Background and Objective: Coronary endothelial dysfunction is considered one of the key pathological components in acute myocardial infarction (AMI). This study aimed to explore the expression patterns and potential significance of the differentially expressed genes SULF1 and EPB41L3 in AMI by integrating bioinformatics analysis and clinical validation.

Methods: Differentially expressed genes (DEGs) were screened from two public microarray datasets (GSE66360 and GSE132651). Their functional profiles were summarized via Gene Ontology and pathway analysis. In parallel, whole-blood samples from 29 patients with coronary artery disease were collected, and gene expression was measured using quantitative real-time PCR (qPCR). Multivariate logistic regression was adjusted, and bootstrap resampling was applied to assess robustness. Exploratory single-cell expression analysis and drug–gene interaction prediction were also performed.

Results: Bioinformatics analysis identified SULF1 and EPB41L3 as consistently upregulated in AMI. In clinical samples, both genes showed significantly higher expression in AMI patients compared with non-obstructive coronary artery disease controls (P=0.036 and 0.021), and this association remained significant after multivariate adjustment (P=0.039 and 0.034). Single-cell data indicated expression in endothelial cells and fibroblasts. Drug prediction suggested metoprolol and paclitaxel as potential modulators of SULF1.

Conclusion: This study, through integrated analysis, first validated the upregulated expression of candidate biomarkers SULF1 and EPB41L3 in the peripheral blood of AMI patients within a clinical cohort. Combined with their baseline expression profiles in cell types associated with vascular inflammation such as endothelial cells, these findings suggest that these two genes may be involved in the pathological process of AMI. This research provides new candidate targets and clues for exploring the molecular mechanisms of AMI.

Keywords: acute myocardial infarction, endothelial dysfunction, SULF1, EPB41L3, inflammation

Introduction

Acute myocardial infarction (AMI) is one of the leading causes of mortality worldwide. Although the death rate has declined in recent years due to the advent of coronary artery intervention surgery and coronary artery bypass grafting techniques, the risk of subsequent cardiovascular adverse events and the economic burden they impose remain a significant concern for these patients.[1–4] Therefore, delving deeper into the etiology of AMI holds crucial clinical strategic value for preventing the disease and the subsequent adverse reactions it may cause.

Coronary endothelial dysfunction is a critical event in the pathogenesis of myocardial infarction (MI). Beyond impairing vasomotor balance, dysfunctional endothelium actively promotes platelet activation and triggers localized

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inflammatory responses. This dual pro-thrombotic and pro-inflammatory milieu significantly contributes to coronary thrombosis and subsequent ischemic injury.[5–7] However, the underlying molecular mechanisms remain inconclusive.

Bioinformatics analysis has become a key tool for understanding complex diseases such as AMI by leveraging gene sequencing data to reveal disease-associated genes and their potential mechanisms of action. In this study, we employed bioinformatics methods to preliminarily explore the potential association between coronary endothelial dysfunction and AMI. Specifically, we obtained two microarray datasets (GSE66360, sourced from whole blood circulating endothelial cells; GSE132651, sourced from blood-derived outgrowth endothelial cells) from the Gene Expression Omnibus (GEO) database and performed differential expression analysis. The results indicated that the SULF1 and EPB41L3 genes were identified as candidate genes differentially expressed under the relevant conditions. Notably, this study adopted a translational strategy progressing "from mechanism-oriented discovery to clinically feasible validation." We first performed bioinformatic screening using endothelial cell-specific transcriptomic data, aiming to directly identify molecular clues from the core pathological component of the disease—endothelial dysfunction. Subsequently, we conducted validation in patient peripheral whole-blood samples. Although whole blood is a mixed sample containing various cell types, it represents a routinely available, easily accessible clinical material that is crucial for assessing the practical application value of potential biomarkers. We hypothesized that if genes differentially expressed in endothelial cells produce a signal strong enough or are also expressed in relevant immune/inflammatory cells, they might be detectable in accessible peripheral blood, thereby offering potential for subsequent non-invasive or minimally invasive testing.

SULF1 (Sulfatase 1) encodes a sulfatase that finely regulates the signaling of various growth factors such as FGF and VEGF by modifying heparan sulfate proteoglycans on the cell surface and in the extracellular matrix, thereby influencing cell proliferation, migration, and angiogenesis. Previous studies have suggested its roles in tumor biology, organ fibrosis, and vascular dysfunction.[8–10] EPB41L3 (Erythrocyte Membrane Protein Band 4.1 Like 3) is a member of the protein 4.1 superfamily. As a cytoskeletal linker protein, it participates in maintaining cell morphology, adhesion, and junctions. Its functional abnormalities are closely associated with tumorigenesis and progression,[11–14] but its role in cardiovascular diseases remains unclear. Currently, there is a lack of systematic research on the specific roles of both genes in AMI, particularly in pathological processes related to coronary endothelial dysfunction.

Building on the candidate genes identified through the aforementioned screening and the translational research strategy, to further investigate the potential roles of SULF1 and EPB41L3 in AMI, this study conducted preliminary validation using a small clinical cohort and relevant datasets, and performed exploratory analyses including single-cell analysis and drug prediction. This exploratory work aims to provide new clues for understanding the molecular mechanisms of AMI. The overall workflow of this study is outlined in Figure 1.

Methods

Bioinformatics Analysis and Candidate Gene Screening

Data Discovery

We searched the GEO database for datasets related to endothelial dysfunction and acute myocardial infarction. The GSE66360 dataset was identified as a target dataset. This dataset includes expression profile data from 99 patients (50 controls and 49 AMI patients), derived from circulating endothelial cells obtained from whole blood. The GSE132651 dataset was also identified as a target dataset. It includes expression profile data from 19 patients (6 controls and 13 patients with coronary endothelial dysfunction), sourced from blood-derived outgrowth endothelial cells.

Differential Expression Analysis

GEO2R was used to perform differential expression analysis on GSE66360 and GSE132651 separately. Genes with a P-value < 0.05 and an absolute value of Log Fold Change (LogFc) > 1 were considered significantly differentially expressed. The intersection of the datasets was used to identify differentially expressed genes (DEGs) common to both datasets.

Functional Analysis

To characterize the biological functions of the identified candidate genes SULF1 and EPB41L3, we performed gene ontology (GO) and pathway analyses using WebGestalt (https://www.webgestalt.org/option.php). The analysis

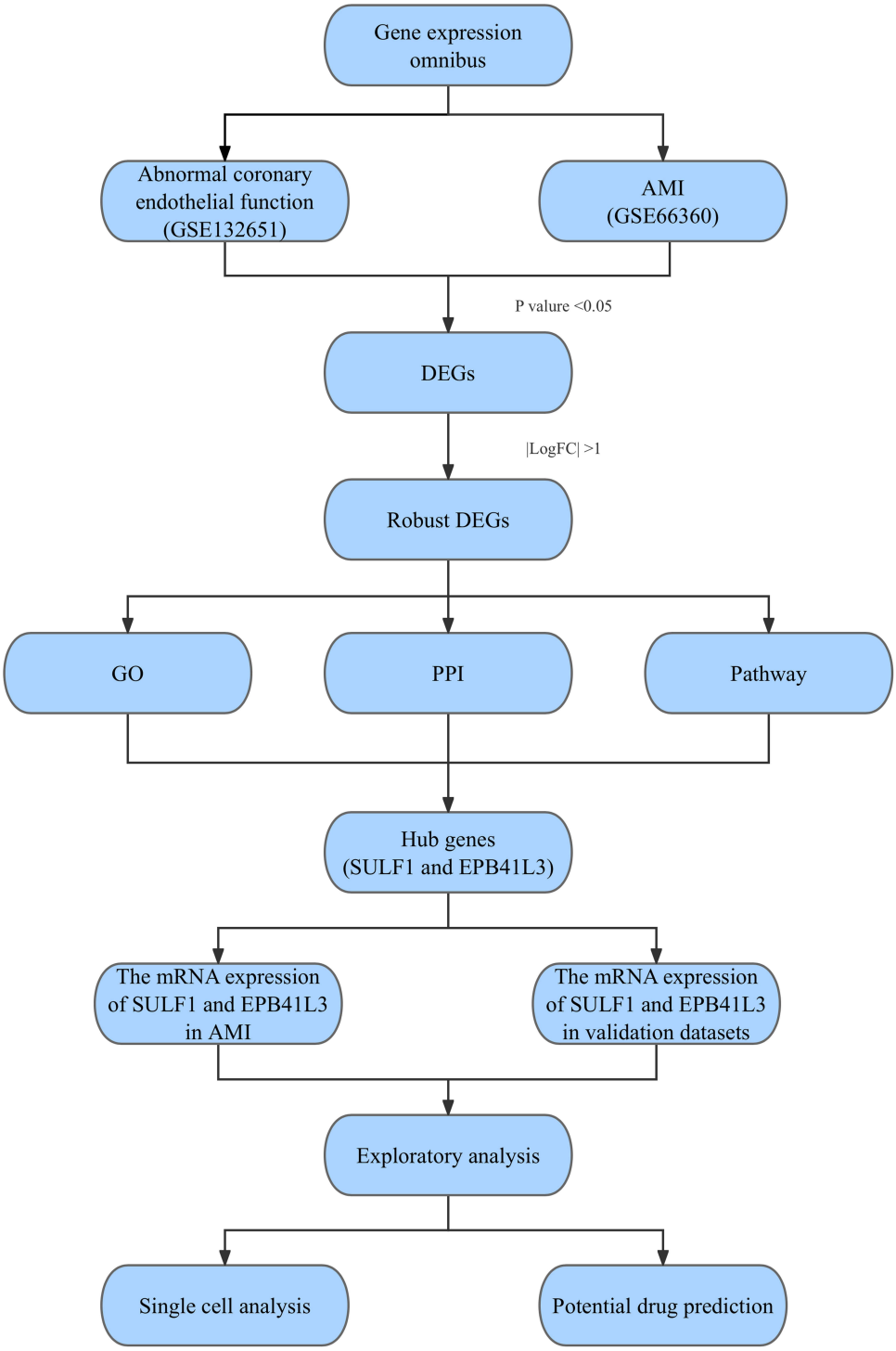

Figure 1 Study Flowchart.
Abbreviations: AMI, acute myocardial infarction; DEGs, differentially expressed genes; EPB41L3, erythrocyte membrane protein band 4.1 like 3; GO, gene ontology; GSE, gene series; PPI, protein-protein interaction; SULF1, sulfatase 1.

encompassed GO terms (Biological Process, Cellular Component, Molecular Function) and pathways from five databases (KEGG, Panther, Reactome, WP Pathway, WikiPathways). Protein-protein interactions among the differential genes were analyzed using the STRING database (https://cn.string-db.org/PPI).

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Clinical Cohort Validation

Ethical Approval, Patients, and Sample Size

This study was an exploratory clinical investigation aimed at preliminarily validating the candidate genes identified through bioinformatics screening. The sample size was determined based on feasibility: during the study period (January 2022 to January 2023), it reflected the number of patients who met strict inclusion criteria and could be recruited from two centers (Hangzhou Hospital of Traditional Chinese Medicine Affiliated to Zhejiang Chinese Medical University, and Hangzhou First People's Hospital). A total of 30 patients were initially enrolled, with one patient withdrawing, leaving 29 patients for final analysis. This study was conducted as a sub-study within the framework of two registered clinical trials (ChiCTR2200055916, ChiCTR2100054620) at the respective centers, utilizing their existing cohort resources for biomarker exploration. The study protocol strictly adhered to the Declaration of Helsinki and was approved by the Ethics Committees of Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University (Approval No. 2021LH004) and Hangzhou First People's Hospital (Approval No. IIT-20211117-0113-01).

Samples were sourced as follows: control group samples were primarily obtained from the screening population or control arm of the relevant trial at Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University, while AMI (study group) samples were mainly derived from participants assigned to the conventional treatment arm of the relevant trial at Hangzhou First People's Hospital. All sample collection and analysis procedures followed the ethical standards of the main trials. All participants provided written informed consent, authorizing the use of their biological samples for molecular biomarker research. (Trial registration information is publicly accessible at: https://www.chictr.org.cn/). The data supporting this clinical study have been uploaded to Zenodo and can be accessed: https://doi.org/10.5281/zenodo.17989982.

Inclusion Criteria

Patients in the study group were enrolled based on the Fourth Universal Definition of Myocardial Infarction.[15] Key criteria included a dynamic change in cardiac troponin (cTn) values with at least one measurement above the 99th percentile upper reference limit, accompanied by at least one of the following: (1) symptoms of acute myocardial ischemia; (2) new ischemic electrocardiographic changes; (3) development of pathological Q waves; (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality consistent with an ischemic etiology; or (5) identification of coronary thrombus by angiography. The control group comprised patients who presented with symptoms suggestive of acute myocardial ischemia but did not show significant elevation of cTn levels, and who were subsequently confirmed via coronary angiography or computed tomography (CT) to have non-obstructive coronary artery disease. Non-obstructive disease was defined as stenosis of the left main coronary artery ≤30%, or stenosis of any other major coronary artery ≤50%.

Exclusion Criteria

The main exclusion criteria included: (1) Diabetes; (2) Known ejection fraction <30% or severe heart failure with New York Heart Association (NYHA) Class IV symptoms; (3) Severe hepatic or renal dysfunction; (4) Cancer-related diseases; (5) Connective tissue diseases; (6) Pregnant or breastfeeding subjects. Specific diagnostic criteria are detailed in Appendix 1.

Data Collection

Patient baseline data included age, gender, smoking, hypertension, hyperlipidemia, and family history of coronary heart disease. Diagnostic criteria are detailed in Appendix 1.

Real-Time Quantitative PCR

Real-time quantitative PCR (qPCR) was employed to measure the expression of SULF1 and EPB41L3 mRNA in the whole blood. Total RNA was extracted from whole blood using a commercial RNA extraction kit. Subsequently, the extracted total RNA was reverse transcribed into cDNA. A SYBR Green-based master mix was used for qPCR amplification. The reaction conditions were as follows: initial denaturation at 95 °C for 30s; 40 cycles of denaturation at 95 °C for 10s and annealing/

extension at 60 °C for 30s; followed by melting-curve analysis. Relative mRNA expression levels were calculated using the $2^{-\Delta\Delta}$Ct method with β-actin as the endogenous control. The primer sequences were: SULF1 forward 5′-TCTGTGAGTT TGCTACTGGCT-3′, reverse 5′-ATGCCTCGTTCTACCGTGTG-3′; EPB41L3 forward 5′-CCAGAAGCACCTCCCA AGAA-3′, reverse 5′-GGTGCTGGGCGATCTATCAA-3′.

External Dataset Validation

Given the established link between atherosclerosis and myocardial infarction, we searched for datasets related to atherosclerosis in the GEO database and identified GSE44461 as the target dataset. This dataset includes expression profiles from 6 patients (3 controls, 3 with TCF21-knockout related to atherosclerosis). We also selected GSE420, which includes data from 10 patients (3 controls, 7 with atherosclerosis). Differential expression analysis was performed to examine SULF1 and EPB41L3 levels in these datasets.

Exploratory Analysis

Single-Cell Analysis

Based on the results of the clinical study and validation datasets, we hypothesized that there might be differences in the expression of SULF1 and EPB41L3 across various cells. Therefore, PanglaoDB (https://panglaodb.se/#google_vignette) was used to conduct a single-cell analysis of SULF1 and EPB41L3. Initially, their distribution in single cells was directly searched based on gene names. Additionally, heart and aorta samples (since coronary arteries were not available) were selected to assess the expression of SULF1 and EPB41L3 in single cells such as endothelial cells, smooth muscle cells, cardiomyocytes, macrophages, and fibroblasts.

Drug Prediction

Using Enrichr (https://maayanlab.cloud/Enrichr/), we analyzed all drugs in the GEO database that regulate SULF1 and EPB41L3, focusing on their effects in cardiovascular contexts to explore potential therapeutic avenues.

Statistical Analysis

Bioinformatics analyses were performed using respective online tools. In the clinical component of the study, unless otherwise stated, a two-sided alpha level of 0.05 defined statistical significance for all tests. Numeric variables are summarized as mean±standard deviation and compared between groups using independent-samples t-tests. Categorical variables are presented as frequency counts and percentages, with between-group differences evaluated via Pearson's chi-square test.

To identify factors independently associated with AMI, multivariate logistic regression was employed. Clinical variables showing a between-group difference at $P < 0.10$ in univariate analysis were included as covariates. Model selection was performed using the backward likelihood ratio method. The Hosmer-Lemeshow goodness-of-fit test was applied to assess model calibration, with a P-value > 0.05 indicating adequate fit.

Given the modest sample size, the robustness of the logistic regression findings for SULF1 and EPB41L3 was evaluated using the non-parametric Bootstrap resampling method with 1000 iterations. To assess the contribution of these candidate genes to sample classification in the transcriptomic datasets, Partial Least Squares-Discriminant Analysis (PLS-DA) was conducted, and Variable Importance in Projection (VIP) scores were calculated. All analyses were performed using SPSS (version 27.0; IBM Corp.) and R software (version 4.2.3; R Foundation for Statistical Computing), with the Bootstrap procedure implemented specifically via the boot package in R.

Results

Differential Expression Gene Screening

We downloaded the GSE66360 dataset from GEO, which included 99 patients (50 controls and 49 AMI patients). We used GEO2R to calculate the DEGs between the two groups, using the criteria of P value < 0.05 and |logFC| > 1. A total of 741 DEGs were identified, including 534 upregulated and 207 downregulated genes (Figure 2A). Similarly, we

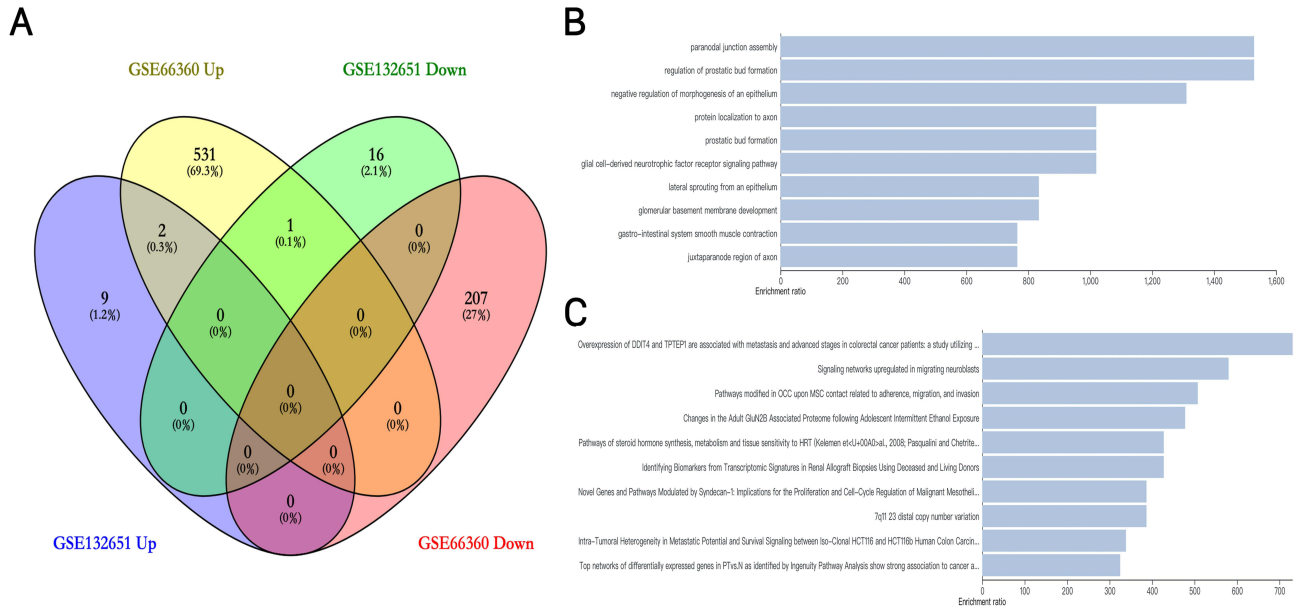

Figure 2 Differential Expression Gene Screening and Functional Annotation of Candidate Genes. (**A**) Differential Expression Gene Screening. (**B**) Gene Ontology annotation of SULF1 and EPB41L3. (**C**) Pathway analysis of SULF1 and EPB41L3.
Abbreviation: GSE, gene series.

downloaded the GSE132651 dataset from GEO, which included 19 patients (6 controls and 13 patients with coronary endothelial dysfunction). Using the same criteria, GEO2R analysis identified 28 DEGs (11 upregulated and 17 downregulated). The intersection of DEGs from both datasets yielded 3 overlapping DEGs. After excluding one gene with inconsistent regulatory directions, we identified two consistently upregulated genes and no downregulated genes. To further validate the importance of the identified candidate genes, SULF1 and EPB41L3, in sample classification, we performed PLS-DA and calculated VIP scores. In the GSE132651 dataset, SULF1 and EPB41L3 had relatively high importance for classification, with mean VIP scores of 1.724 and 1.223, respectively. In the GSE66360 dataset, the mean VIP scores for SULF1 and EPB41L3 were 0.526 and 0.578, respectively. Although these mean values did not reach the conventional significance threshold (often VIP>1), one probe for EPB41L3 (212681_at) achieved a VIP score of 1.078, suggesting that this gene may still hold classificatory value under specific conditions. These results, from a multivariate perspective, support the rationale for selecting SULF1 and EPB41L3 as potential biomarkers for AMI.

Overview of Known Functions of SULF1 and EPB41L3

To further understand the potential biological functions of SULF1 and EPB41L3, we summarized their potential involved processes by integrating annotations from public databases and existing literature. Previous studies suggest that SULF1 and EPB41L3 may be involved in processes such as cell junction assembly and the regulation of epithelial morphogenesis, respectively (Figure 2B and Supplementary Table 1). Protein-Protein Interaction (PPI) analysis revealed no direct interaction between SULF1 and EPB41L3 (Supplementary Figure 1A), indicating they might function through distinct molecular pathways. However, first-level interaction analysis showed that both genes co-express with heparan sulfate 3-O-sulfotransferase 2 (HS3ST2) (Supplementary Figure 1B), suggesting a potential indirect functional association. Furthermore, existing pathway annotations indicate that both genes are associated with various biological domains, including tumor biology, neurobehavior, and hormonal metabolic regulation (Figure 2C and Supplementary Table 2).

Characteristics of Study Participants

Initially, 30 participants were enrolled in this study. Subsequently, one patient in the control group discontinued participation due to personal reasons (withdrawal of consent). Consequently, 29 patients were ultimately included in the final analysis (Supplementary Figure 2). The mean age was 57.86 years, 44.8% were female, 4 (13.8%) had a history

of smoking, 12 (41.4%) had hypertension, 2 (6.9%) had hyperlipidemia, 2 (6.9%) had cerebrovascular disease, and 2 (6.9%) had a family history of coronary heart disease (Table 1). Additionally, blood samples for SULF1 analysis from 2 participants were hemolyzed, resulting in a missing data rate of 11.8%.

Expression Levels of SULF1 and EPB41L3 mRNA

The average mRNA expression level of SULF1 was 0.95 ± 0.12 in the control group and 1.04 ± 0.10 in the AMI group, showing a statistically significant difference (P = 0.036). To reduce the interference of imbalanced baseline data (including gender and smoking), a multivariate logistic regression analysis was performed. The goodness-of-fit test indicated that the model had sufficient calibration (P=0.571), and the multivariate logistic regression results showed a statistically significant difference between the two groups (Adj.P=0.039). The robustness of this association was further validated by Bootstrap resampling analysis (1000 iterations), which yielded a consistent P-value (P=0.039) (Table 2).

The average mRNA expression level of EPB41L3 was 1.00 ± 0.08 in the control group and 1.09 ± 0.10 in the AMI group, showing a statistically significant difference (P = 0.021). The goodness-of-fit test for the multivariate logistic regression analysis indicated that the model had sufficient calibration (P=0.769), and the results showed a statistically significant difference between the two groups (Adj.P=0.034). The reliability of this finding was confirmed by Bootstrap resampling analysis (1000 iterations), which yielded a P-value of 0.040.

Validation of Datasets

We obtained the GSE44461 dataset from GEO, which consists of coronary artery smooth muscle cells from 6 patients (3 controls and 3 with atherosclerosis). GEO2R was used to identify DEGs between groups, with a significance threshold of P value < 0.05. The results showed that SULF1 was differentially expressed between the groups (P < 0.001), whereas EPB41L3 showed no significant difference (P = 0.843) (Supplementary Table 3). Additionally, we obtained the GSE420

Table 1 Clinical Characteristics

	Control (n=12)	AMI (n=17)	P value
Age, mean ± SD	57.25 ± 14.77	58.29 ± 9.87	0.821
Female, no. (%)	8 (66.7)	5 (29.4)	0.047
Smoking, no. (%)	0 (0)	4 (23.5)	0.070
Hypertension, no. (%)	4 (33.3)	8 (47.1)	0.460
Hyperlipidemia, no. (%)	1 (8.3)	1 (5.9)	0.798
CBVD, no. (%)	0 (0)	2 (11.8)	0.218
Family history of CHD, no. (%)	0 (0)	2 (11.8)	0.218

Note: Values are numbers (%) or means ± SD.
Abbreviations: AMI, acute myocardial infarction; CBVD, cerebral vascular disease; CHD, coronary heart disease; SD, standard deviation.

Table 2 Gene Expression of SULF1 and EPB41L3

Gene	Control (n=12)	AMI (n=15)	P value	Adj.P value*	Bootstrap P value
SULF1, mean ± SD	0.95 ± 0.12	1.04 ± 0.10	0.036	0.039	0.039
	Control (n=12)	AMI (n=17)			
EPB41L3, mean ± SD	1.00 ± 0.08	1.09 ± 0.10	0.021	0.034	0.040

Notes: *The p-value was adjusted for gender and smoking through backward likelihood ratio method. Values are means ± SD.
Abbreviations: AMI, acute myocardial infarction; EPB41L3, erythrocyte membrane protein band 4.1 like 3; SULF1, sulfatase 1; SD, standard deviation.

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dataset, which includes aortic samples from 10 patients (4 controls and 6 with atherosclerosis). Analysis with the same threshold revealed that SULF1 was differentially expressed (P = 0.045), while EPB41L3 was not detected. In summary, external dataset validation revealed a key contrast: SULF1 consistently showed differential expression in atherosclerotic vascular tissues, whereas EPB41L3 did not. This finding contrasts with their synchronized upregulation in whole blood, suggesting they may be involved in AMI through distinct cellular origins or biological pathways.

Single-Cell Analysis

PanglaoDB results indicated that SULF1 was primarily distributed in germ cells, fibroblasts, mesothelial cells, basal cells, and endothelial cells, while EPB41L3 was mainly found in germ cells, oligodendrocytes, fibroblasts, adipocytes, basal cells, and neurons (Figure 3A and B). We further examined their distribution in cardiac tissue (SRA745744) (Figure 3C). SULF1 displayed prominent expression in fibroblasts, endothelial cells, and smooth muscle cells, with expression also detected in cardiomyocytes, mesothelial cells, and pericytes (Figure 3D). EPB41L3 was predominantly expressed in cardiomyocytes, fibroblasts, and pericytes, and was also present in endothelial cells, smooth muscle cells, mesothelial cells, and macrophages (Figure 3E). In aortic tissue (SRA734405) (Figure 3F), SULF1 showed significant expression in endothelial cells and fibroblasts, with additional expression in macrophages and B cells (Figure 3G), whereas EPB41L3 was primarily expressed in fibroblasts, with some expression in endothelial cells (Figure 3H).

Drug Prediction Analysis

Enrichr was used to analyze all regulatory drugs for SULF1 and EPB41L3 in the GEO database, focusing on cardiovascular samples and related therapeutics (Supplementary Tables 4 and 5). After filtering the dataset for duplicates and non-human samples, we found that in the drug-upregulation group, metoprolol upregulated SULF1 in coronary artery smooth muscle cells. In the drug-downregulation group, paclitaxel downregulated SULF1 in the left internal mammary artery (Table 3). Further exploration identified etanercept as having the highest Combined Score for upregulating both SULF1 and EPB41L3 (315,246.2), and carboplatin as having the highest Combined Score for downregulating SULF1 (454.8).

Discussion

Through integrated analysis of public databases and clinical samples, this study identified an upregulated expression pattern of SULF1 and EPB41L3 in the whole blood of patients with AMI, which remained significant after adjusting for confounding factors. This finding provides new clues for exploring the molecular mechanisms of AMI. It is well established that endothelial dysfunction serves as both the initiating event and a core component of the inflammatory response in atherosclerosis. Further validation analysis strengthened the potential link between SULF1 and arteriosclerosis. Exploratory analysis revealed the baseline expression distribution of SULF1 and EPB41L3 across different cell types, suggesting their potential involvement in distinct biological contexts. Regarding pharmacological regulation, metoprolol and paclitaxel were predicted as potential modulators of SULF1 expression, while etanercept and carboplatin demonstrated stronger predicted regulatory potential for both genes, offering potential directions for future research.

Previous studies have highlighted the critical impact of coronary endothelial dysfunction on the coronary circulation system.[16–18] The endothelium serves not only as a physical barrier for the coronary arteries but also plays a central role in regulating vascular tone, blood fluidity, and thrombosis. Its dysfunction is often accompanied by the activation of inflammatory processes, such as leukocyte adhesion and the release of pro-inflammatory factors, which may represent one of the pathological mechanisms through which it influences MI.[5–7] To further explore the underlying molecular mechanisms, we initially conducted a bioinformatics analysis of GEO datasets, identifying two DEGs in the coronary endothelium: SULF1 and EPB41L3. A review of the existing literature on the known functions of these genes revealed that SULF1 and EPB41L3 are involved in processes such as cell adhesion, signal transduction, and cytoskeletal organization. These functions are related to maintaining vascular integrity and endothelial function, and dysregulation of these processes is closely linked to the initiation and perpetuation of vascular inflammation. For instance, the regulation of epithelial morphogenesis involves cell proliferation and differentiation, which may be associated with the repair processes following coronary endothelial injury.[19–21] Furthermore, their potential roles in hormonal and metabolic regulation are also linked to risk factors for cardiovascular diseases.[22–24] Their known functions in tumor biology also

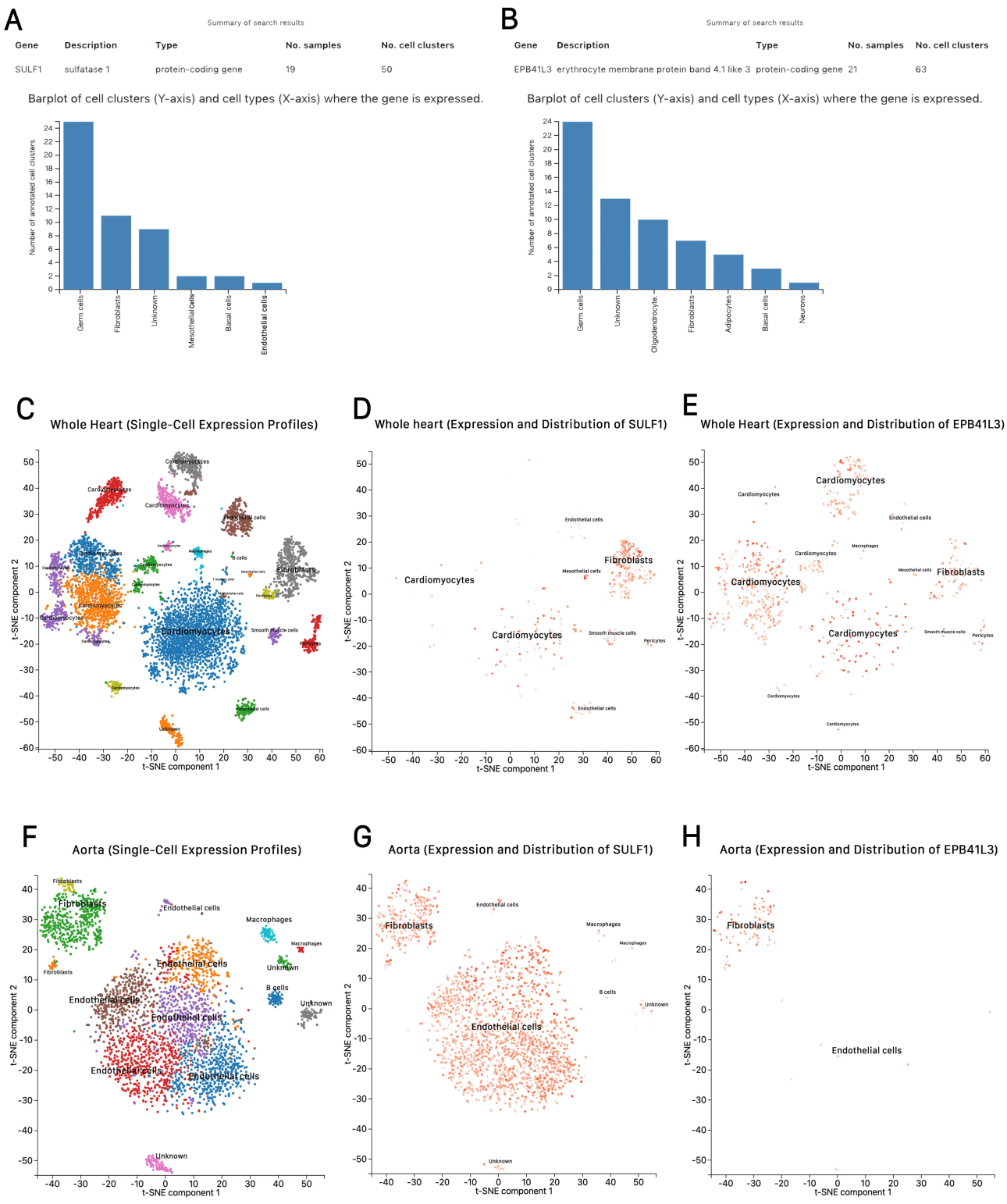

Figure 3 Single-Cell Analysis. (**A**) Bar Chart of SULF1 Distribution Across Different Cell Types. (**B**) Bar Chart of EPB41L3 Distribution Across Different Cell Types. (**C**) Cellular Distribution Map of the Whole Heart. (**D**) Distribution of SULF1 in Various Cell Types Throughout the Whole Heart. (**E**) Distribution of EPB41L3 in Various Cell Types Throughout the Whole Heart. (**F**) Cellular Distribution Map of the Aorta. (**G**) Distribution of SULF1 in Various Cell Types Throughout the Aorta. (**H**) Distribution of EPB41L3 in Various Cell Types Throughout the Aorta.

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Table 3 Prediction of Drugs Regulating SULF1 and EPB41L3

Potential Drug	Intervention Target	Gene Expression Omnibus	Regulatory Direction	P-value	Adj. P-value*	Odds Ratio†	Combined Score‡	Genes
Etanercept	Psoriasis lesions	GSE47751	Up	< 0.001	0.013	39,276.0	315,246.2	EPB41L3; SULF1
PLX4032	Melanoma cell	GSE24862	Up	0.021	0.045	96.1	373.0	SULF1
Adenosine triphosphate	Acute myeloblastic leukemia cell	GSE30903	Up	0.024	0.045	80.6	299.2	EPB41L3
Alfacalcidol	Non-tumorigenic prostate epithelial cell	GSE15947	Up	0.026	0.045	74.5	270.6	SULF1
Nickel	Nickel-allergic patients	GSE6281	Up	0.029	0.045	66.8	235.6	SULF1
Cediranib	Metastatic Alveolar Soft Part Sarcoma	GSE32569	Up	0.030	0.045	66.1	232.5	SULF1
Celecoxib	Primary colorectal adenocarcinomas	GSE11237	Up	0.030	0.045	65.7	230.5	SULF1
Imatinib	CD34+ cells	GSE1418	Up	0.030	0.045	65.4	229.5	EPB41L3
Isotretinoin	Immortalized sebocytes	GSE10432	Up	0.031	0.045	64.1	223.7	SULF1
Estradiol	Breast adenocarcinoma cells	GSE24592	Up	0.031	0.045	63.7	221.8	EPB41L3
Cycloheximide	Breast cancer cells	GSE8597	Up	0.032	0.045	61.7	212.8	SULF1
Retinoic acid	Squamous cell carcinoma cell	GSE54464	Up	0.032	0.045	60.9	209.4	SULF1
Vemurafenib	Melanoma cell	GSE42872	Up	0.033	0.045	59.6	203.6	SULF1
Interferon beta	Peripheral blood mononuclear cell	GSE26104	Up	0.033	0.045	59.2	202.0	EPB41L3
Azathioprine	Ulcerative colitis patients	GSE38713	Up	0.036	0.045	54.6	181.7	SULF1
Lipopolysaccharide	Peripheral blood derived monocytes	GSE5504	Up	0.037	0.045	52.3	172.2	EPB41L3
Metoprolol	Coronary smooth muscle cells	GSE3356	Up	0.046	0.046	41.7	128.2	SULF1
Carboplatin	36M2 ovarian cancer cells	GSE13525	Down	0.018	0.041	112.6	454.8	SULF1
Sevoflurane	Atrial samples	GSE4386	Down	0.021	0.041	94.7	366.3	SULF1
Etanercept	Whole-blood leukocytes	GSE36177	Down	0.022	0.041	89.1	339.3	EPB41L3

(*Continued*)

Table 3 (Continued).

Potential Drug	Intervention Target	Gene Expression Omnibus	Regulatory Direction	P-value	Adj. P-value*	Odds Ratio†	Combined Score‡	Genes
Cholestyramine	Ulcerative colitis	GSE11223	Down	0.025	0.041	78.7	290.1	EPB41L3
Etanercept	Psoriasis	GSE11903	Down	0.026	0.041	75.6	275.9	EPB41L3
Lipopolysaccharide	Adult peripheral and cord blood mononuclear cells	GSE3140	Down	0.027	0.041	73.3	265.4	EPB41L3
Propofol	Atrial samples	GSE4386	Down	0.028	0.041	71.5	256.8	SULF1
Ascorbic acid	Skin fibroblasts	GSE11919	Down	0.028	0.041	68.9	245.2	SULF1
Hydrocortisone	Keloid fibroblasts	GSE7890	Down	0.029	0.041	67.0	236.6	SULF1
Ascorbyl-2-phosphate	Skin fibroblasts	GSE11919	Down	0.029	0.041	66.8	235.6	SULF1
Cigarette Smoke	Alveolar macrophages	GSE8823	Down	0.031	0.041	63.9	222.8	EPB41L3
Cisplatin	Ovarian carcinoma cell lines	GSE47856	Down	0.031	0.041	63.5	220.9	EPB41L3
Resveratrol	Subcutaneous abdominal adipose tissue and skeletal muscle	GSE41168	Down	0.031	0.041	63.3	220.0	SULF1
Resveratrol	Breast cancer cells	GSE25412	Down	0.035	0.041	56.3	189.2	SULF1
Isotretinoin	Skin	GSE10433	Down	0.035	0.041	55.5	185.7	SULF1
Paclitaxel	Left internal mammary artery	GSE19136	Down	0.036	0.041	54.7	182.3	SULF1
O-ethyl S-[2-(diisopropylamino) ethyl] methylphosphonothiolate	Hepatocytes	GSE33606	Down	0.036	0.041	53.6	177.8	EPB41L3
Estradiol	Osteosarcoma cells	GSE1153	Down	0.044	0.044	44.2	138.4	EPB41L3

Notes: *The adjusted p-value was computed using the Benjamini-Hochberg method for correction for multiple hypotheses testing. †The rank based ranking was derived from running the Fisher exact test for many random gene sets in order to compute a mean rank and standard deviation from the expected rank for each term in the gene-set library and finally calculating a z-score to assess the deviation from the expected rank. ‡Combined score was computed by taking the log of the p-value from the Fisherexact test and multiplying that by the z-score of the deviation from theexpected rank.
Abbreviations: EPB41L3, erythrocyte membrane protein band 4.1 like 3; GSE, Gene Series; SULF1, sulfatase 1.

suggest their potential involvement in pathological processes analogous to those in vascular endothelial cells, such as atherosclerosis.[25–27] PPI analysis indicated no direct interaction between SULF1 and EPB41L3, which is more consistent with the notion that they may participate in the disease process through independent rather than synergistic pathways. Although first-layer interaction analysis revealed co-expression of both genes with HS3ST2, suggesting a potential indirect associations,[28–30] its specific biological significance remains unclear. A more plausible explanatory model is that SULF1 and EPB41L3 may function as parallel functional units, respectively influencing different aspects of endothelial cell function and collectively contributing to the complex pathophysiology of myocardial infarction, rather than operating as a unified complex.

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Although the known functions of SULF1 and EPB41L3 suggest their potential involvement in the molecular mechanisms linking endothelial dysfunction to myocardial infarction, direct clinical evidence is currently lacking. This study provides the first preliminary validation in patients with coronary artery disease. By comparing the expression levels of SULF1 and EPB41L3 in the whole blood of patients with AMI versus those with non-obstructive coronary artery disease, we found that both genes were significantly upregulated in AMI patients. This difference remained significant even after adjusting for relevant confounding factors and upon Bootstrap resampling analysis, offering new clinical clues regarding the association between SULF1/EPB41L3 and myocardial infarction.

However, their specific mechanisms of action are complex and may vary depending on the cellular context. For instance, research by Glaser et al[31] indicated that upregulation of SULF1 might promote the loss of endothelial function, whereas Korf-Klingebiel et al[32] found that deficiency of SULF1 could exacerbate impaired cardiac repair post-myocardial infarction, suggesting that SULF1 may possess multiple, even seemingly contradictory, functions in the processes of cardiac injury and repair. Currently, there are few reports on the relationship between EPB41L3 and myocardial infarction. To further assess their relevance to atherosclerosis, we queried the GEO database and found that SULF1 was differentially expressed in both coronary artery and aortic atherosclerosis samples, supporting its potential involvement in the atherosclerotic process. Notably, no differential expression of EPB41L3 was detected in GSE420 (human aorta), and it was not even detected in GSE44461 (human smooth muscle cells). This finding is inconsistent with our observations in whole blood, suggesting that EPB41L3 expression exhibits significant tissue and cell type specificity, and may be highly sensitive to the pathological state and cellular origin. As a cytoskeletal linker protein, its differential expression may reflect the distinct reprogramming of adhesion and signal transduction pathways in different cell types (such as circulating immune cells and activated stromal cells) in response to the systemic stress of AMI. Therefore, the upregulation observed in whole blood likely primarily reflects the systemic inflammatory response and immune cell activation triggered by AMI, rather than direct local vascular expression changes. Contextual differences must be fully considered when interpreting its pathological significance, and the robustness of EPB41L3 as a biomarker still requires further validation in future, larger-scale, homogeneous clinical cohorts.

To gain a deeper, cell-level understanding of this specificity, we analyzed existing single-cell datasets using the PanglaoDB platform. The results showed that within integrated data from multiple tissue types, fibroblasts were the primary cell type exhibiting co-expression of SULF1 and EPB41L3, suggesting their potential involvement in cardiac fibrosis or tissue repair processes. Fibrosis itself represents the terminal stage of chronic inflammation.[31,32] Notably, SULF1 showed significant expression in endothelial cells, whereas EPB41L3 expression levels in endothelial cells were relatively low. Further focusing on cardiac tissue revealed that SULF1 is highly expressed in fibroblasts, endothelial cells, and smooth muscle cells, while EPB41L3 is primarily expressed in cardiomyocytes, fibroblasts, and pericytes.

These distribution differences suggest that SULF1 and EPB41L3 may play distinct roles in the pathological process of myocardial infarction. Based on this, we integrate the current findings to propose a speculative staged working hypothesis: in the initial phase of the disease, endothelial cell-associated SULF1 may contribute to the onset of endothelial dysfunction by activating pro-inflammatory signals. In the phase following ischemic injury, EPB41L3—primarily expressed in cardiomyocytes and fibroblasts—may play a more significant role in inflammation resolution, cardiac remodeling, and repair. This staged model integrates the seemingly contradictory cellular distributions into a continuous pathological process, providing a more refined framework for understanding the potential roles of SULF1 and EPB41L3 in AMI. In aortic tissue, SULF1 is mainly expressed in endothelial cells and fibroblasts, while EPB41L3 remains predominantly expressed in fibroblasts. The low expression of EPB41L3 in endothelial and smooth muscle cells may partially explain the lack of significant differential expression in vascular tissue datasets. In summary, when exploring the mechanisms by which endothelial dysfunction influences myocardial infarction, it is crucial to consider the cell-specificity of gene expression and their potential roles at different stages of the disease.

To explore potential future research directions and generate testable hypotheses, we conducted a predictive drug–gene interaction analysis using the Enrichr platform, aiming to identify candidate compounds that might regulate SULF1 and EPB41L3 The results indicated that metoprolol and nebivolol may upregulate SULF1 expression in coronary artery smooth muscle cells. Given that beta-blockers are known to possess certain anti-inflammatory effects, whether this represents a potential mechanism for their regulation of SULF1 warrants further investigation. Notably, despite ongoing mechanistic

research, conclusions from several recent large-scale clinical trials regarding the universal efficacy of beta-blockers in AMI, particularly in patients with heart failure with preserved ejection fraction (HFpEF), remain controversial.[33] Conversely, the use of paclitaxel-eluting stents was associated with downregulation of SULF1 expression in coronary arteries, suggesting that these drugs might influence vascular response processes by modulating SULF1.[34] Additionally, the tumor necrosis factor-alpha (TNF-α) inhibitor etanercept and carboplatin showed relatively high predictive scores for the overall regulation of SULF1 and EPB41L3, respectively. Particularly for etanercept, its known anti-inflammatory mechanisms intersect with the biological processes potentially involving SULF1/EPB41L3, suggesting a hypothesis worthy of future validation: namely, these genes may mediate certain inflammation-related pathways. However, it must be emphasized that all the above analyses are based on bioinformatic predictions. The upregulation of SULF1 and EPB41L3 in MI could be a cause, a consequence, or merely an epiphenomenon of the disease; their causal relationship with AMI remains unclear. Therefore, the predicted effects of these drugs remain highly hypothetical and require step-by-step validation through subsequent gene intervention experiments and functional studies.

As an exploratory study, this research has several main limitations. Firstly, the GEO datasets used for the bioinformatic analysis have inherent limitations regarding the precise match between their sample sources and our study objectives. Furthermore, the key validation qPCR experiments were based on peripheral blood samples; their results reflect systemic expression profiles and cannot directly represent specific changes in coronary endothelial cells. Secondly, the limited sample size of this clinical validation study constrains statistical power and the ability to detect small effect sizes (even with internal validation using Bootstrap resampling). Thus, we did not perform diagnostic performance analyses (such as ROC curve analysis) or evaluate the correlation of their expression with established clinical gold standards (eg, cardiac troponin). Additionally, this study did not directly measure local or systemic inflammatory markers associated with SULF1/EPB41L3 expression. Therefore, the diagnostic performance of these genes as biomarkers, their precise relationship with inflammation, and their potential incremental value all require systematic evaluation in future, larger, and more rigorously designed cohorts, which represents a key objective for subsequent validation studies. Finally, the core aim of this study was hypothesis generation, and the evidence obtained remains preliminary. The association between SULF1 and EPB41L3—particularly EPB41L3, which has a weaker foundation in previous research—and AMI urgently requires validation in future, larger independent cohorts, supplemented by detailed functional experiments to provide evidence for causal mechanisms. The proposed staged functional model is also merely speculative based on cross-sectional data and awaits validation through longitudinal studies (including determining the optimal detection time window for their expression dynamics).

Conclusion

This study confirms that SULF1 and EPB41L3 are potential biomarkers associated with AMI. Their upregulation in the peripheral blood of patients suggests they may participate in the vascular inflammatory process of AMI by influencing endothelial function. Considering their distinct expression patterns in endothelial cells, cardiomyocytes, and fibroblasts, we propose a hypothesis awaiting validation: they may play roles at different stages of ischemic injury and repair. Furthermore, the regulatory drugs predicted by this study provide preliminary clues—requiring validation through functional experiments—for future exploration of intervention strategies targeting these molecules. The primary value of this study lies in providing directional guidance for subsequent in-depth mechanistic exploration.

Data Sharing Statement

The bioinformatics data in this study are from publicly available datasets, and all raw data can be found on the corresponding websites. Additionally, the data supporting this clinical study have been uploaded to Zenodo and can be accessed through the following link upon reasonable request: https://zenodo.org/records/14249531.

Ethical Approval and Consent to Participate

All procedures performed in studies involving human participants were following the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for Publication

Informed consent was obtained from all individual participants included in the study.

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Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Author Contributions

Conceptualization: J.H., T.C., B.G., H.Z.; Data curation: C.Y., S.W.; Formal analysis: X.Z.; Investigation: B.G., J.Z., C. B., H.Z., L.C, Q.C., X.F.; Resources: B.G., J.Z., C.B., Validation: H.Z., L.C.; Methodology: J.H., T.C., B.G., X.X., Q.C., X.F.; Writing – original draft: H.Z., X.X.; Writing – review & editing: Q.C., X.F. Houyong Zhu, Xiaoqun Xu, Xinyu Zhu, and Jinyu Huang contributed equally to this work. All authors took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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