Identification of SLED1 as a Potential Predictive Biomarker and Therapeutic Target of Post-Infarct Heart Failure by Bioinformatics Analyses

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Summary
The aim of this study was to explore potential predictive biomarkers and therapeutic targets of post-infarct heart failure (HF) using bioinformatics analyses.

CEL raw data of GSE59867 and GSE62646 were downloaded from the GEO database. Differentially expressed genes (DEGs) between patients with ST-segment elevation myocardial infarction (STEMI) and those with stable coronary artery disease (CAD) at admission and DEGs between admission and 6 months after myocardial infarction (MI) in patients with STEMI were analyzed. A gene ontology (GO) analysis and a gene set enrichment analysis (GSEA) were performed, and a protein-protein interaction network was constructed. Critical genes were further analyzed.

In total, 147 DEGs were screened between STEMI and CAD at admission, and 62 DEGs were identified in patients with STEMI between admission and 6 months after MI. The results of GO and GSEA indicate that neutrophils, neutrophil-related immunity responses, and monocytes/macrophages play important roles in MI pathogenesis. SLED1 expression was higher in patients with HF than in those without HF at admission and 1 month after MI. GSEA indicates that mTORC1 activation, E2F targets, G2M checkpoint, and MYC targets v1 inhibition may play key roles in the development of post-infarct HF. Furthermore, SLED1 may be involved in the development of post-infarct HF by activating mTORC1 and inhibiting E2F targets, G2M checkpoint, and MYC targets v1.

SLED1 may be a novel biomarker of post-infarct HF and may serve as a potential therapeutic target in this disease.

Key words: Acute myocardial infarction, Gene set enrichment analysis

Cardiovascular diseases are the leading causes of death worldwide, including in low-income and middle-income countries. In 2013, the total number of deaths resulting from cardiovascular diseases reached almost 33% of all deaths globally. Among these, ischemic heart disease accounts for 47%. Owing to the implementation of primary percutaneous coronary intervention and the prescription of evidence-based drug treatments, the prognosis of ST-segment elevation myocardial infarction (STEMI) has improved markedly over the past 20 years. Despite these advances, STEMI leads to irreversible loss of myocardial cells and adverse left ventricular remodeling. Approximately 50% of the cases demonstrate a lower ejection fraction after myocardial infarction (MI). Moreover, 20% of patients with anterior STEMI may suffer from heart failure (HF) within 1 year. The long-term prognosis of patients with STEMI remains poor. Therefore, an in-depth understanding of the pathophysiology of STEMI and post-infarct HF is still required to identify new prevention and treatment targets. In addition, effective and predictive biomarkers for post-infarct HF are urgently required for risk stratification, prognosis assessment, and individualized medicine.

The present study aimed to search for differentially expressed genes (DEGs) in patients with STEMI at admission that may be involved in the pathogenesis of STEMI and then evaluate these genes to identify reliable predictive biomarkers and therapeutic targets for post-infarct HF.

Methods

Microarray data information: CEL raw data files of GSE59867 and GSE62646 were downloaded from the GEO database, and they were all based on the GPL6244 platform of [HuGene-1.0-st] Affymetrix Human Gene 1.0 ST Array [transcript (gene) version]. The GSE59867 dataset contained 436 peripheral blood mononuclear cell
In this study, PBMC gene expression data from 139 patients with STEMI (111 from GSE59867 and 28 from GSE62646) at admission were compared with those from 60 patients with CAD (46 from GSE59867 and 14 from GSE62646) to identify DEGs in patients with STEMI at admission for subsequent analysis. Among the 139 patients with STEMI, 111 patients (83 from GSE59867 and 28 from GSE62646) had gene expression data at both admission and 6 months after STEMI. The paired data of the 111 patients were analyzed to screen for DEGs in patients with STEMI at admission for subsequent analysis. In total, complete gene expression data at four time points (admission, discharge, 1 month after MI, and 6 months after MI) were available from seven patients with HF and six patients without HF. These data were used to identify biomarkers for post-infarct HF for further analysis. The clinical characteristics and medicines of patients for post-infarct HF analysis were analyzed in the original author’s paper. There was no significant difference between patients with and without HF, except for left ventricular ejection fraction, NT proBNP, and diuretics. (Figure 1)

Microarray data preprocessing: CEL raw data of GSE59867 and GSE62646 were merged and preprocessed using the affy package in R Bioconductor for background correction, normalization, and calculation expression. The sva and limma packages in R Bioconductor were used for removal of batch effects and for normalization between arrays, respectively. The probes were converted into gene symbols according to the probe annotation information. Probes without the corresponding gene symbols were removed. If multiple probes corresponded to the same gene symbol, the probe with the highest expression value was retained.

DEGs analysis: DEGs between patients with STEMI and patients with CAD at admission were identified using the limma package. The paired t-test of the limma package was used to identify DEGs between admission and 6 months after MI in patients with STEMI. A fold change of a gene expression ratio > 1.0 and adjusted P-value (adj. P) < 0.05 were used as cut-off criteria. Genes with a fold change of gene expression ratio > 2.0 were chosen as top DEGs. DEGs between HF and non-HF at the four time points were also identified using the limma package. A fold change of a gene expression ratio > 1.0 and P < 0.05 were used as the threshold value. Subsequently, DEGs of patients with STEMI at admission were visualized as vol-
Figure 2. Identification of DEGs. A: Volcano plot of mRNA expression profiles discriminating STEMI from CAD. B: Heatmap from cluster analysis of 147 DEGs between STEMI and CAD at admission. C: Volcano plot of mRNA expression profiles between admission and 6 months after MI in patients with STEMI. D: Heatmap from cluster analysis of 62 DEGs between admission and 6 months after MI in patients with STEMI. Red and blue dots in volcano plots represent upregulated and downregulated mRNAs, respectively. Green dots are the top DEGs. Each column in heatmaps represents a sample, and each row represents a gene. The gradual color change from blue to red indicates the changing process from downregulation to upregulation in heatmaps. A fold change of gene expression ratio > 1.0 and adj. \( P < 0.05 \) were considered statistically significant.

cano plots and heatmaps using the ggplot2\(^{13}\) and pheatmap \((https://cran.r-project.org/web/packages/pheatmap)\) packages, respectively, in R.

**Gene ontology (GO) functional enrichment analysis of DEGs:** To explore the potential function of DEGs in patients with STEMI, DEGs were subjected to GO enrichment analysis to determine the associated biological process (BP), molecular function (MF) and cellular component (CC) terms using the clusterProfiler package\(^{14}\) in R Bioconductor. Adj. \( P < 0.05 \) and enrichment count \( > 2 \) were used as the threshold values.

**Gene set enrichment analysis (GSEA):** GSEA\(^{15}\) is used to determine whether a predefined gene set is significantly different between two groups. In this study, GSEA was performed using hallmark gene sets (http://software.broadinstitute.org/gsea/msigdb/collections.jsp#H). To explore the mechanism of MI and post-infarct HF, GSEA was conducted using the clusterProfiler package in R Bioconductor. The entire gene lists were ranked according to the log 2 fold change of gene expression ratios between STEMI and CAD at admission and between admission and 6 months after MI in patients with STEMI, respectively. Adj. \( P < 0.05 \) was considered statistically significant.

**Protein-protein interaction (PPI) networks of DEGs:** To screen for crucial genes associated with STEMI, DEGs were mapped into the Search Tool for the Retrieval of Interacting Genes database (STRING; Version 11.0)\(^{16}\) to predict PPI pairs with a combined score \( > 0.4 \). The PPI networks were visualized using Cytoscape software (Version 3.6.1).\(^{17}\) Nodes with a degree of interaction \( \geq 10 \) were considered as hub genes. Additionally, the Molecular Complex Detection plugin (MCODE, Version 1.5.1, http://apps.cytoscape.org/apps/mcode) in Cytoscape was applied to identify a function module in the PPI network with the
Table 1. The Overlapping GO Terms Enriched by DEGs in Patients with STEMI

| GO   | ID       | Description                                                                 | DEGs (MI-CAD) | DEGs (MI-Follow) |
|------|----------|------------------------------------------------------------------------------|---------------|------------------|
| BP   | GO:042119 | neutrophil activation                                                        | 17            | 12               |
| BP   | GO:0002283 | neutrophil activation involved in immune response                           | 16            | 11               |
| BP   | GO:0032103 | positive regulation of response to external stimulus                        | 13            | 10               |
| BP   | GO:0043312 | neutrophil degranulation                                                     | 16            | 11               |
| BP   | GO:0002446 | neutrophil mediated immunity                                                | 16            | 11               |
| BP   | GO:0002683 | negative regulation of the immune system process                           | 14            | 6                |
| BP   | GO:1902106 | negative regulation of leukocyte differentiation                           | 7             | 3                |
| BP   | GO:006326  | cell chemotaxis                                                             | 11            | 8                |
| BP   | GO:0050727 | regulation of the inflammatory response                                     | 13            | 11               |
| BP   | GO:0097529 | myeloid leukocyte migration                                                  | 9             | 7                |
| BP   | GO:0071677 | positive regulation of mononuclear cell migration                           | 4             | 2                |
| BP   | GO:0030595 | leukocyte chemotaxis                                                        | 9             | 7                |
| BP   | GO:0071674 | mononuclear cell migration                                                  | 6             | 4                |
| BP   | GO:1903706 | regulation of hemopoiesis                                                   | 12            | 6                |
| BP   | GO:0040588 | regulation of the innate immune response                                    | 11            | 6                |
| BP   | GO:0060670 | branching involved in the labyrinthine layer morphogenesis                 | 3             | 3                |
| BP   | GO:002548  | monocyte chemotaxis                                                        | 5             | 3                |
| BP   | GO:002688  | regulation of leukocyte chemotaxis                                          | 6             | 4                |
| BP   | GO:0014912 | negative regulation of smooth muscle cell migration                          | 4             | 2                |
| BP   | GO:1902105 | regulation of leukocyte differentiation                                      | 9             | 6                |
| BP   | GO:0071675 | regulation of mononuclear cell migration                                     | 4             | 3                |
| BP   | GO:002687  | positive regulation of leukocyte migration                                   | 6             | 4                |
| BP   | GO:0031349 | positive regulation of the defense response                                 | 11            | 7                |
| BP   | GO:0090026 | positive regulation of monocyte chemotaxis                                  | 3             | 2                |
| BP   | GO:002685  | regulation of leukocyte migration                                           | 7             | 4                |
| BP   | GO:002690  | positive regulation of leukocyte chemotaxis                                  | 5             | 3                |
| BP   | GO:0050921 | positive regulation of chemotaxis                                           | 6             | 4                |
| BP   | GO:0060713 | labyrinthine layer morphogenesis                                            | 3             | 3                |
| BP   | GO:002573  | myeloid leukocyte differentiation                                           | 7             | 4                |
| BP   | GO:0032102 | negative regulation of response to external stimulus                        | 9             | 5                |
| BP   | GO:0090025 | regulation of monocyte chemotaxis                                           | 3             | 2                |
| BP   | GO:001960  | negative regulation of the cytokine-mediated signaling pathway              | 4             | 3                |
| BP   | GO:0042063 | glio genesis                                                                | 8             | 5                |
| BP   | GO:005900  | leukocyte migration                                                         | 11            | 8                |
| BP   | GO:006700  | C21-steroid hormone biosynthetic process                                    | 3             | 2                |
| BP   | GO:0030593 | neutrophil chemotaxis                                                       | 5             | 5                |
| BP   | GO:0050920 | regulation of chemotaxis                                                    | 7             | 3                |
| BP   | GO:006669  | embryonic placenta morphogenesis                                            | 3             | 3                |
| BP   | GO:001959  | regulation of the cytokine-mediated signaling pathway                        | 6             | 4                |
| BP   | GO:0060761 | negative regulation of response to cytokine stimulus                        | 4             | 3                |
| BP   | GO:001819  | positive regulation of cytokine production                                  | 10            | 7                |
| BP   | GO:1901342 | regulation of vasculature development                                       | 10            | 9                |
| BP   | GO:004544  | fat cell differentiation                                                    | 7             | 6                |
| CC   | GO:0070820 | tertiary granule                                                             | 8             | 6                |
| CC   | GO:0042581 | specific granule                                                            | 7             | 5                |
| CC   | GO:0036667 | secretory granule membrane                                                  | 9             | 5                |
| CC   | GO:0035579 | specific granule membrane                                                   | 5             | 4                |
| CC   | GO:0101003 | ficolin-1-rich granule membrane                                             | 4             | 3                |
| MF   | GO:0038024 | cargo receptor activity                                                     | 5             | 4                |
| MF   | GO:004896  | cytokine receptor activity                                                  | 5             | 3                |

**DEGs (MI-CAD)** indicates DEGs between STEMI and coronary artery disease at admission; **DEGs (MI-Follow)**, DEGs between admission and 6 months after myocardial infarction in patients with STEMI; **BP**, biological process; **CC**, cellular component; **DEGs**, differentially expressed genes; **GO**, gene ontology; **MF**, molecular function; and **STEMI**, ST-segment elevation myocardial infarction.

Following parameters: degree cut-off: 2, node score cut-off: 0.2, k-core: 2, maximum depth: 100. Modules with MCODE scores ≥ 4.5 and nodes ≥ 5 were used for further analysis.

**Biomarker screening for post-infarct HF and function analysis:** To seek biomarkers of post-infarct HF, top DEGs, hub genes, and genes in the selected function modules were further analyzed to elucidate their roles in post-infarct HF during follow-up. Biomarkers were screened by crossing these genes with DEGs between patients with HF and those without HF at four time points. The biomarkers were further subjected to GSEA to ex-
plore their function in HF. The entire gene lists were ranked according to the correlation coefficient of a biomarker and other genes of gene expression ratio between patients with and without HF at admission. Adj. \( P < 0.05 \) was considered statistically significant.

**Results**

**Identification of DEGs:** Raw data comprised 32,321 probes. A total of 18,822 genes remained following data preprocessing. Subsequently, 147 DEGs were screened between STEMI and CAD at admission, including 79 upregulated and 68 downregulated genes (Figure 2A and B). As shown in Figure 2A, SOCS3, ERCP, and HP were the top DEGs. There were 62 DEGs in patients with STEMI between admission and 6 months after MI. Interestingly, 95% (59 out of 62) of the DEGs were upregulated. SOCS3, HP, and SLED1 were identified as the top DEGs. The results are presented in volcano plots and heatmaps in Figure 2C and D.

**Mechanism analysis of STEMI:** 66 GO terms were enriched in DEGs between STEMI and CAD, whereas 319 GO terms were enriched in DEGs between admission and 6 months after MI in patients with STEMI. There were 50 overlapping GO terms between the two sets of DEGs (Table I), which more likely indicate the functions of DEGs in STEMI. The top 8 enrichment terms are shown in graphs for each part of the GO analyses (if any) for the two sets of DEGs (Figure 3A and B). As illustrated in Figure 3A and B, BP enrichment analyses show that DEGs chiefly participated in neutrophil-related biological processes, such as neutrophil activation, neutrophil degranulation, and neutrophil-mediated immunity. In CC enrichment analysis, DEGs were predominantly involved in the construction of tertiary granule, specific granule, and secretory granule membrane. In MF terms, DEGs were mainly related to cargo receptor activity.

**Twenty-seven hallmark gene sets were chosen for STEMI when compared with CAD, and 30 hallmark gene sets were screened for STEMI when compared with 6 months after MI. There were 21 overlapping hallmark gene sets enriched in STEMI (Table II), which may be related to the development of MI. As illustrated in Figure 3C and D, the overlapping activated hallmark gene sets mainly included TNF-\( \alpha \) signaling via NF-kB, the inflammatory response, the P53 pathway, complement, and glycolysis. By contrast, E2F targets, the interferon alpha response, and allograft rejection were the overlapping suppressed hallmark gene sets.**

**PPI network construction and analysis:** A PPI network
was constructed using STRING with DEGs between STEMI and CAD, including 72 (49 upregulated and 23 downregulated) nodes and 150 edges (Figure 4A). Furthermore, seven hub genes and two modules were screened from the PPI network (Figure 4B). Another PPI network was built with DEGs between admission and 6 months after MI in patients with STEMI, including 43 (41 upregulated and 2 downregulated) nodes and 105 edges (Figure 4C). In addition, five hub genes and one module were chosen from the PPI network (Figure 4D).

**Mechanism analysis of post-infarct HF:** GSEA indicated that 29 hallmark gene sets were enriched in patients with HF. The top 15 gene sets are depicted in Figure 5D. Compared with GSEA between STEMI and CAD, mTORC1 signaling activation was specific for post-infarct HF. In addition, E2F targets, G2M checkpoint, and MYC targets v1 were the suppressed hallmark gene sets.

**Biomarkers of post-infarct HF and function analysis:** A total of 29 genes, including top DEGs, hub genes, and genes in the selected function modules, were selected for further analysis to elucidate their role in post-infarct HF. At admission, the expression levels of CD163, FPR2, IL1R2, SLED1, and VSG4 were higher in patients with HF than in those without it (Figure 5A). Patients with HF showed higher expression of FOS and lower expression of KLRF1 than those in patients without HF at discharge (Figure 5B). The expressions of PTGS2 and SLED1 were upregulated in patients with HF 1 month after MI compared to those in patients without HF (Figure 5C). There was no expression difference among the 29 genes between patients with and without HF 6 months after MI. SLED1 was upregulated in patients with HF at admission and 1 month after MI when compared to that in patients without HF. Therefore, SLED1 may be a potential biomarker of post-infarct HF.

GSEA of SLED1 was carried out between patients with and without HF at admission to explore the function of SLED1 in post-infarct HF, which showed that 32 hallmark gene sets were related to SLED1. Interestingly, there were 28 overlapping hallmark gene sets (including mTOR 1 signaling) between the hallmark gene sets associated with SLED1 and those enriched in HF (Table III). Moreover, the overlapping hallmark gene sets activated and inhibited in HF were also positively and negatively correlated with SLED1 expression, respectively (Figures 5D, 5E). As illustrated in Figures 5D, 5E, the hallmark gene sets inhibited in HF and SLED1 were completely consistent, including E2F targets, the G2M checkpoint, and MYC targets v1.

**Discussion**

In the present study, 147 DEGs were identified between STEMI and CAD at admission, and 62 DEGs were screened for STEMI between admission and 6 months after MI. GO functional enrichment analyses were conducted to explore the potential functions of the two sets of DEGs. There were 50 overlapping GO terms between the two sets of DEGs, indicating that DEGs for STEMI were chiefly involved in neutrophil-related biological processes, such as neutrophil activation, neutrophil degranulation, and neutrophil-mediated immunity. GSEA revealed that most overlapping hallmark gene sets for STEMI were related to activation and/or infiltration of monocytes/macrophages. These results suggest that neutrophils and monocytes/macrophages may play vital roles in the pathogene-

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Table II. The Overlapping Hallmark Gene Sets Enriched in Patients with STEMI

| Description | MI-CAD enrichmentScore | adj. P | MI-Follow enrichmentScore | adj. P |
|-------------|------------------------|-------|---------------------------|-------|
| HALLMARK_TNFA_SIGNALING_VIA_NFKB | 0.522071286 | 0.00628457 | 0.69898769 | 0.00448029 |
| HALLMARK_IL6_JAK_STAT3_SIGNALING | 0.49293494 | 0.00628457 | 0.593658188 | 0.00448029 |
| HALLMARK_INFLAMMATORY_RESPONSE | 0.482613528 | 0.00628457 | 0.595852774 | 0.00448029 |
| HALLMARK_REACTIVE_OXGEN_SPECIES_PATHWAY | 0.477174119 | 0.01036055 | 0.685752564 | 0.00448029 |
| HALLMARK_P53_PATHWAY | 0.445908687 | 0.00628457 | 0.575465712 | 0.00448029 |
| HALLMARK_XENOBIOTIC_METABOLISM | 0.40940348 | 0.00628457 | 0.536417408 | 0.00448029 |
| HALLMARK_MYOGENESIS | 0.4032688 | 0.00628457 | 0.373873455 | 0.02232855 |
| HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION | 0.393257704 | 0.00628457 | 0.478674746 | 0.00448029 |
| HALLMARK_HYPOXIA | 0.388079457 | 0.00628457 | 0.5407072 | 0.00448029 |
| HALLMARK_COAGULATION | 0.387177088 | 0.00628457 | 0.461673775 | 0.00448029 |
| HALLMARK_COMPLEMENT | 0.381198929 | 0.00628457 | 0.49184231 | 0.00448029 |
| HALLMARK_UV_RESPONSE_UP | 0.37520927 | 0.00628457 | 0.510961287 | 0.00448029 |
| HALLMARK_ADIPOGENESIS | 0.369588076 | 0.00628457 | 0.578606962 | 0.00448029 |
| HALLMARK_DNA_REPAIR | 0.334003156 | 0.02342579 | 0.415918467 | 0.02076412 |
| HALLMARK_GLYCOLYSIS | 0.32919185 | 0.01034381 | 0.486867788 | 0.00448029 |
| HALLMARK_ESTROGEN_RESPONSE_LATE | 0.320294174 | 0.01506932 | 0.430635724 | 0.00448029 |
| HALLMARK_APOPTOSIS | 0.309286511 | 0.03063726 | 0.438760087 | 0.00448029 |
| HALLMARK_KRAS_SIGNALING_UP | 0.291704593 | 0.03238866 | 0.422024238 | 0.00448029 |
| HALLMARK_ALLOGRAFT_REJECTION | -0.343867483 | 0.00628457 | -0.365514253 | 0.01707262 |
| HALLMARK_INTERFERON_ALPHA_RESPONSE | -0.370888157 | 0.01036055 | -0.57575037 | 0.0062873 |
| HALLMARK_E2F_TARGETS | -0.44598593 | 0.00628457 | -0.360133485 | 0.0128621 |

MI-CAD indicates a gene set enrichment analysis between STEMI and coronary artery disease at admission; MI-Follow, a gene set enrichment analysis between admission and 6 months after myocardial infarction in patients with STEMI; and STEMI, ST-segment elevation myocardial infarction.
Figure 4. PPI networks construction of DEGs. A: The PPI network of DEGs between STEMI and CAD at admission was constructed using Cytoscape. B: Top two significant modules were obtained from PPI of DEGs between STEMI and CAD with scores of 4.8 and 4.5, respectively. C: The PPI network of DEGs between admission and 6 months after MI in patients with STEMI was built. D: The top significant module (score = 5.0) was selected from PPI of DEGs between admission and 6 months after MI in patients with STEMI. The nodes represent the genes, whereas the lines represent interactions between genes. The gradual color change of nodes from blue to red indicates the changing process of genes from downregulation to upregulation. The width of the line denotes the combined score of the predicted interaction. The size of the nodes indicates the degree of interaction in the PPI network (A, B). Nodes with the black outline stand for the hub genes.

sis of MI. After MI, neutrophils are the first cell line to massively invade the myocardium, followed by monocytes, which further differentiate into M1 or M2 macrophages. Neutrophils and the M1 subtype dominate the early inflammatory phase and secrete pro-inflammatory cytokines, causing damage and removing dead cells and debris, whereas the M2 subtype accumulates during the resolution of inflammation, promoting wound healing. However, excessive neutrophil activation may release toxic products such as proteolytic enzymes and oxygen radicals, thus, injuring cardiomyocytes. A clinical study revealed that a high neutrophil-to-lymphocyte ratio predicts large infarct sizes and poor clinical outcomes in patients with AMI who undergo PCI. Animal experiments have indicated that neutrophil depletion reduces the myocardial infarct size, suggesting neutrophil-mediated injury. Besides, previous studies indicated that excessive activation of M1 macrophages promotes ventricular remodeling and
Biomarkers and mechanism analysis of post-infarct HF. DEGs between patients with and without HF were identified from 29 crucial genes at admission (A), discharge (B), and 1 month after MI (C). P < 0.05 was considered statistically significant. D: GSEA of entire genes according to the log2 fold change of the gene expression ratio between patients with HF and those without HF at admission. E: GSEA of entire genes according to the correlation coefficient of SLED1 and other genes of the gene expression ratio between patients with and without HF at admission. The size and the color intensity of a circle represent the numbers of enriched genes and adj. P, respectively (D, E). Adj. P < 0.05 was considered statistically significant.

HF after MI, and strategies modulating macrophage polarization have been proven to improve ejection fraction after MI,26,27) suggesting a pivotal role of M1 macrophages in post-infarct HF.

SLED1 is a pseudogene of the lncRNA class. This study demonstrated that SLED1 was upregulated in patients with post-infarct HF. Ishii and her colleagues found that SLED1 was significantly upregulated in peripheral blood cells of patients with systemic lupus erythematosus and speculated that it may be associated with systemic inflammation.28) Also, the inflammatory response plays an important role in adverse remodeling and heart failure following MI.29,30) Therefore, we speculate that SLED1 may contribute in the progression of post-infarct HF through the inflammatory response. In the present study, we found that activation of mTORC1 is specific for post-infarct HF, and SLED1 might activate mTORC1. Interestingly, mTORC1 activity is increased in both SLE and HF, and its blockade is therapeutic.31,32) Studies indicated that mTORC1 regulates macrophage polarization by promoting the M1 subtype and inhibiting the M2 subtype.33,34) Disruption of mTORC1 activation in macrophages inhibits M1 macrophage-mediated inflammation.35) Considering a key role of M1 macrophages in post-infarct HF, we considered that SLED1 may promote M1 macrophage polarization and inflammation by activating mTORC1, leading to post-infarct HF. Autophagy is generally considered to be cardioprotective. mTORC1 has been shown to inhibit autophagy and promote heart failure, whereas inhibition of mTORC1 activation enhances autophagy and then mitigates HF.36) Obviously, SLED1 may also promote heart failure after MI by regulating autophagy.

In addition, GSEA showed that genes involved in E2F targets, the G2M checkpoint, and MYC targets v1 were inhibited in post-infarct HF. All of these are involved in cell cycle regulation. For example, the E2F family
regulates cell cycle progression through the G1/S transition, and inhibition of E2F targets may lead to cell cycle arrest. The G2M checkpoint prevents damaged cells and thus prevented them from entering the mitotic M phase. The G2M checkpoint arrest induces cells to directly enter the M phase without repair and poses a high risk of apoptosis. Abbate and colleagues have confirmed by autopsy that the apoptotic rate at infarct sites in patients with post-infarct HF was almost four times that in patients without HF, indicating a disorder and apoptosis may play a pathophysiological role in post-infarct HF. Collectively, these data suggest that cell cycle disorder and apoptosis may play a pathophysiological role in post-infarct HF. Surprisingly, the inhibited hallmark gene sets involved in HF and SLED1 were completely consistent, suggesting that upregulated SLED1 may also be involved in HF attack by interfering with cell cycle and promoting apoptosis through inhibiting E2F targets, the G2M checkpoint, and MYC targets v1.

These data indicate that SLED1 may be a novel biomarker for post-infarct HF. Owing to its roles in the development of post-infarct HF, SLED1 may also serve as a potential therapeutic target in this disease. However, we did not conduct experiments to validate our conclusions. Further extensive investigation and experimentation are thus warranted to confirm whether SLED1 could be a biomarker of post-infarct HF and to clarify its potential mechanisms and therapeutic value.

**Conclusions**

Patients with STEMI and high SLED1 expression at admission may be at a higher risk of HF and are more likely to suffer from HF during follow-up. Furthermore, upregulated SLED1 may be involved in the development of post-infarct HF by activating mTORC1 and inhibiting E2F targets, the G2M checkpoint, and MYC targets v1. In summary, SLED1 may be a novel biomarker of post-infarct HF and a potential therapeutic target for this disease.

**Disclosure**

**Conflicts of interest:** None.

**Ethical approval:** This article does not contain any studies with human participants or animals performed by any of the authors.

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