

Semaglutide ameliorates coronary microembolization-induced injury by suppressing apoptosis and inflammation via the HMGB1/RAGE/NF- κ B p65 pathway

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ABSTRACT

BACKGROUND Coronary microembolization (CME) is the major leading cause of perioperative myocardial injury during coronary revascularization. Semaglutide exerts multiple protective biological activities, but its cardioprotective effects on CME remain unclear. Thus, this experiment studied the impact of semaglutide on CME-induced myocardial injury.

METHODS A rat CME model was generated by injecting microspheres into the left ventricle while clamping the ascending aorta. A H9c2 cardiomyocyte model was constructed by stimulation of lipopolysaccharide combined with hypoxia. Semaglutide or the high mobility group box 1 (HMGB1) antagonist glycyrrhizin administrations were ahead of CME and cell modeling. Cardiac function, myocardial injury markers, cell viability and morphological alternations were detected. Apoptotic and inflammatory factors, cytosolic HMGB1 and its translocation, advanced glycosylation end-product specific receptor (RAGE), and nuclear factor kappa B p65 (NF- κ B p65) were evaluated.

RESULTS Semaglutide pretreatment ameliorated CME-induced cardiac systolic dysfunction and relieved the cardiac injury. Semaglutide attenuated myocardial apoptosis and inflammatory response following CME *in vivo* and *in vitro*. Moreover, semaglutide downregulated HMGB1 expression and suppressed its nuclear-cytoplasmic translocation. Both glycyrrhizin and semaglutide administration affected the HMGB1/RAGE/NF- κ B p65 pathway after CME.

CONCLUSIONS Semaglutide pretreatment attenuates CME-induced myocardial injury by suppressing apoptosis and inflammation through the HMGB1/RAGE/NF- κ B p65 pathway.

Coronary artery disease (CAD) is the most prevalent heart disease, inducing high mortality and complication rates worldwide. Coronary microembolization (CME), caused by the release of debris and thrombotic substances from erosion or inherent atherosclerotic plaque rupture, usually occurs spontaneously or iatrogenically by coronary revascularization in patients with acute coronary syndrome.^[1] CME could provoke cardiac contractile malfunction, ventricular microinfarction, coronary microvascular dysfunction, and fatal arrhythmia. The contractile dysfunction occurs immediately in the regional ischemic myocardium caused by microembolized occlusion. However, the cardiac movement does not recover from the recovery coronary perfusion completely, and the contractile malfunction is associated with poor clinical

outcomes.^[1] Despite the wide application of embolic protection devices, coronary vasodilator, and anti-platelets administration, there is still no effective therapy strategy for CME.^[2]

Apoptosis, the most well-studied and classical form of programmed cell death, is characterized by the caspases dependent cascade.^[3] Pro-apoptotic components like B-cell lymphoma-2-associated X protein (Bax) and anti-apoptotic factors like B-cell lymphoma-2 (Bcl-2) are stimulated to regulate the apoptosis process.^[4] Caspase-3 is one of the downstream effectors, serving as the executor of apoptosis in the cleaved form.^[5] Numerous studies have demonstrated that apoptosis involves many cardiac diseases, including acute coronary syndrome, myocardial ischemia/reperfusion injury (MI/RI), and cardiac dysfunction.^[6-8] Ac-

cumulating evidence verifies that apoptosis implicates the pathological process of losing cardiomyocytes after CME.^[9,10]

In addition to apoptosis, myocardial inflammation is another prominent mechanism involved in the pathogenesis of CME.^[11] The inflammatory reaction starts with the formation of atherosclerosis plaque and persists in the progression of CAD.^[12] Among lots of inflammatory cytokines, nuclear factor kappa B (NF- κ B) and tumor necrosis factor- α (TNF- α) are the pivotal hub factors in myocardial ischemic pathogenesis.^[13] Considerable research confirmed that the elevation of TNF- α and NF- κ B and inflammatory cells infiltrate the myocardium surrounding microinfarct lesions in the setting of CME. Moreover, the degree of regional myocardium or systemic inflammation is associated with the severity of CME.^[2] Suppression of apoptosis and inflammation could attenuate myocardial injury and improve heart function following CME.^[14,15] Therefore, interference with apoptosis and inflammatory response may be potential therapeutic value for CME-induced injury.

Glucagon-like peptide-1 receptor analog (GLP-1RA), apart from its lowering blood sugar and controlling body weight characteristics, it has special cardiac protective effects.^[16] Semaglutide, as a classical novel long-acting GLP-1 RA, numerous studies revealed that semaglutide possesses pleiotropic cardioprotective effects, including anti-atherosclerosis, reduction of apoptosis, inhibition of inflammation, and suppression of oxidative stress.^[17-19] Evidence showed that semaglutide ameliorates heart failure-related symptoms and reduces the serum C-reactive protein level in patients with heart failure with preserved ejection fraction (HFpEF), regardless of whether the patients have diabetes mellitus or not.^[20] Moreover, a recent clinical study revealed that semaglutide may reduce the in-stent restenosis rate and slow the progression of non-target lesions in CAD patients.^[21] However, whether semaglutide eases myocardial damage and heart dysfunction following CME is unknown. Considering that semaglutide possesses various cardioprotective effects, we explored its potential beneficial effects and mechanisms under the pathological conditions of CME.

As one chromatin DNA-binding non-histone protein, high mobility group box 1 (HMGB1) protein is highly conservative and exists universally. The diverse functions of HMGB1 depend on subcellular position. Under pathological conditions, HMGB1 transfers from nuclear to cytoplasm, even extracellular space, acting as a critical damage-associated molecular pattern molecule.^[22] Previous studies

reported that HMGB1 leads to myocardial apoptosis and inflammation caused by CME, and suppression of HMGB1 could relieve the myocardial injury.^[23] Advanced glycosylation end-product specific receptor (RAGE), a specific receptor for HMGB1, is activated in combination with HMGB1 and subsequently evokes NF- κ B activation that regulates cytokine and apoptosis genes transcription.^[24] However, the involvement of HMGB1/RAGE/NF- κ B p65 pathway in the CME pathological process and the effects of semaglutide on them need to be proved.

Thus, the aim of the present investigation was to explore whether semaglutide pretreatment attenuates myocardial apoptotic and inflammatory responses caused by CME and elaborate on the underlying possible mechanism. As indicated by our findings, semaglutide administration effectively ameliorated CME-induced cardiac injury by inhibiting apoptotic and inflammatory response through the HMGB1/RAGE/NF- κ B p65 pathway.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley (SD) rats (aging six-week old, weighing 200–250 g), were supplied from Guangxi Medical University Laboratory Animal Center. The animal experiments in this work were approved by the Animal Care and Welfare Committee of Guangxi Medical University (No.20-2206300). They followed the instructions of the National Institutes of Health's Guide for Care and Use of Laboratory Animals.

Rat CME Model and Animal Grouping

A rat CME model was constructed as published previously.^[25] In brief, SD rats received mechanical ventilation under anesthesia by intraperitoneal injection of sodium phenobarbital (40 mg/kg). Thoracotomy was carried out to expose the heart, the pericardium and aortic root were then separated carefully. The total volume of 100 μ L normal saline, containing almost 8000 polystyrene microspheres (diameter: 42 μ m, Polysciences, Auckland, USA), was injected into the left ventricle through the assess of cardiac apex. Concurrently, the ascending aorta was clamped for about 12 s. Subsequently, chest closure was performed with suture followed by anesthesia resuscitation and extubation.

Four groups ($n = 6$ for each group) of SD rats were equally and randomly allocated: the Sham group, the CME group, the CME + glycyrhizin (CME + Gly) group, and the CME



+ semaglutide (CME + Sem) group. The CME group was established in the manner previously mentioned. For Sham group, the microspheres were substituted for the equivalent volume of normal saline. The CME + Sem group was pretreated with subcutaneous injection of semaglutide (Novo Nordisk, Copenhagen, Denmark) 1 mg/kg once per week for four consecutive weeks before CME induction. For the CME + Gly group, rats received glycyrrhizin (MedChem Express, New Jersey, USA) 10 mg/kg via intraperitoneal injection for seven serial days.^[26] The dose of semaglutide and glycyrrhizin used in this study were referenced from relevant rat cardiac model studies and combined with equivalent conversion of body surface area between rats and humans.^[19,27-29] Subcutaneous injections with the same amount and frequency of normal saline were administrated in the CME group.

Echocardiography

Our earlier studies exhibited that the systolic heart function reached its worst level at 12 h, accompanied by the peak of inflammatory reaction and apoptosis of cardiomyocyte following CME. Hence, echocardiography was assessed 12 h after the induction of CME. A skillful sonographer, blinded to this experiment, performed the transthoracic echocardiography using an ultrasound system (MyLabSix, Esaote, Geona, Italy). Both the left ventricular diameters containing left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and the cardiac systolic function parameters containing left ventricular ejection fraction, and left ventricular fractional shortening in each group, were assessed from left parasternal long-axis section via M-mode after induction of anesthesia.

Sample Collection and Handling

After evaluation of echocardiography, SD rats received excessive anesthesia by overdose intraperitoneal injection of sodium phenobarbital (70 mg/kg) immediately. Serums were isolated by centrifuging blood samples from the abdominal aorta and then preserved at -80°C . Rat ventricles were removed and rinsed with ice-cold phosphate-buffered saline after cardiac arrest. The left ventricles were divided averagely into apex, middle, and basal parts along the long axis. The apex and middle parts of the hearts were preserved in liquid nitrogen for additional examination. The basal part tissues perpendicular to the heart along the axis were soaked in 4% paraformaldehyde (Biosharp, Hebei, China), embedded with paraffin, and cut into serially 4 μm -thick sections.

Hematoxylin Eosin (HE) Staining and Hematoxylin-basic Fuchsin-picric Acid (HBFP) Staining

After dewaxing and hydration, the heart section slices were stained using HE dye (Servicebio, Wuhan, China). For microinfarct area assessment, the sections slices were stained with the HBFP dye solutions kit (Servicebio, Wuhan, China). The myocardium HE and HBFP staining images were taken from a microscope system (Axio Imager2, Zeiss, Oberkochen, Germany).

Transmission Electron Microscopy Observation

The myocardium, taken freshly from left ventricles, were cut into sections about 1.0 mm^3 pieces, then fixed in 2.5% glutaric dialdehyde solution (Servicebio, Wuhan, China) at 4°C overnight and fixed in 1% osmic acid solution at room temperature for 4 h followed. Then dehydrated in gradient ethanol and acetone. After penetration, embedding and aggregation, the tissue was sliced into sections 60 nm thick, stained with 2% uranyl acetate, and then followed 2.6% lead citrate solution. The pictures were captured using an electron microscope (JEM-1400, JEOL, Tokyo, Japan).

Cell Culture and Modeling

The rat H9c2 cardiomyocytes (purchased from Zhong Qiao Xin Zhou Biotechnology, Co., Ltd, Shanghai, China) were seeded in the cellular culture plates, and were incubated with Dulbecco's Modified Eagle Medium (Wisent Inc., Nanjing, China) containing 10% fetal bovine serum (Wisent Inc., Nanjing, China) and penicillin (100 U/mL) and streptomycin (100 $\mu\text{g}/\text{mL}$). The H9c2 cells were cultivated in the incubator at 37°C in an atmosphere containing 5% CO_2 . Our previous studies applied the H9c2 subjected to lipopolysaccharide (LPS) and hypoxia to imitate the ischemic and injury micro-environment of CME *in vitro*. Briefly, the control group H9c2 cells were cultured under normal conditions with the same amount of solvent. The LPS + hypoxia model group cells suffered from LPS (10 $\mu\text{g}/\text{mL}$, Solarbio, Beijing, China) in combination with hypoxia for 12 h. Prior to modeling, the semaglutide group cells were pre-treated with semaglutide (5 mmol/L , MedChem-Express, New Jersey, USA), and the glycyrrhizin group cells were pre-treated with glycyrrhizin^[30] (10 $\mu\text{mol}/\text{L}$, MedChemExpress, New Jersey, USA) for 2 h.

Cell Viability and Lactate Dehydrogenase (LDH) Activity Measurement

Cell viability was measured by a cell counting kit (CCK)-



8 solution (Solarbio, Beijing, China). Approximately 103 cells per well were seeded in 96-well plates and cultured. After treatment of intervention agents and addition of CCK-8 solution, cells were measured at an absorbance of 450 nm using a microplate reader. H9c2 cells LDH activity was measured using a commercial LDH detection kit (Jianchen Bioengineering, Nanjing, China) following the manufacturer's directions.

Terminal Deoxynucleotidyl Transferase-mediated dUTP Nick-end Labeling (TUNEL) Detection

Following dewaxing and hydration, myocardial sections were treated with 4% sodium citrate solution (Solarbio, Beijing, China) in a microwave oven for 8 min for retrieval. Then, myocardial slices and H9c2 cell culture coverslips were incubated with TUNEL reaction buffer (Roche, Basel, Switzerland) for 1 h at 37 °C in the absence of light. Then, the nuclei were stained with DAPI staining (Solarbio, Beijing, China) solution after rinsing with phosphate-buffered saline, and the slices were examined using the fluorescence microscope (Axio Imager2, Zeiss, Oberkochen, Germany).

Enzyme-linked Immunosorbent Assay

The serum concentrations of cardiac troponin T (cTnT), creatine kinase MB isoenzyme (CK-MB), TNF- α and interleukin-1 β were determined using commercial enzyme-linked immunosorbent assay kits (Bioswamp, Wuhan, China) in accordance with the manufacturer's instructions. The LDH activity was evaluated by an LDH assay kit (Jianchen Bioengineering Institute, Nanjing, China).

Immunohistochemistry (IHC) and Immunofluorescence (IF)

After antigen retrieval, the myocardial sections and cell-attached slides were received permeated with 0.3% Triton X-100, and subsequently incubated with 5% bovine serum albumin (Beyotime Biotechnology, Shanghai, China). Then IHC was performed utilizing an IHC kit (Maxim Biotechnologies, Fuzhou, China) and the slices of myocardium were incubated with TNF- α (dilution 1:200, Proteintech, Wuhan, China) and IL-1 β (dilution 1:500, Abcam, UK) primary antibodies, following visualized by diaminobenzidine reaction (Maxim Biotechnologies, Fuzhou, China). The IHC slices were examined by the microscope system (BX53, Olympus, Tokyo, Japan). For the IF detection, the sections were incubated with HMGB1 (dilution 1:500, Abcam, UK), phosphorylated-NF- κ B p65 (dilution 1:800, Cell Signaling Technology, USA) primary antibody overnight at 4 °C. Then, secti-

Table 1 List of qPCR primer sequences.

Gene	Primer sequence 5'→3'
HMGB1	5'-CCAGTGTGTCGAAGCCATTGCTTTT-3'
	5'-GCGCGGAAAATTACAAGAACGCT-3'
TNF- α	5'-ACTGAACTTCGGGGTGATCG-3'
	5'-TGGTGGTTTGCTACGACGTG-3'
IL-1 β	5'-GGGATGATGACGACCTGCTA-3'
	5'-TGTCGTTGCTTGCTCTCTCT-3'
β -actin	5'-TGTCACCAACTGGGACGATA-3'
	5'-GGGGTGTGAAGGTCTCAAA-3'

HMGB1: high mobility group box 1; IL-1 β : interleukin-1 β ; qPCR: quantitative real-time polymerase chain reaction; TNF- α : tumor necrosis factor- α .

ons were labeled with Cy3-conjugated secondary antibody (dilution 1:100, Proteintech, Wuhan, China) for 1 h. Cellular nuclei were stained with a DAPI staining solution (Solarbio, Beijing, China). All the IF slides were observed under a fluorescence microscope (Axio Imager2, Zeiss, Oberkochen, Germany).

Quantitative Real-time Polymerase Chain Reaction (qPCR)

Total RNAs were extracted by RNAiso Plus (Takara, Dalian, China), measured by Nanodrop 2000 (ThermoFisher Scientific, USA), and reverse transcribed into cDNA with RT Reagent Kit with gDNA Eraser (Takara, Dalian, China). The qPCR was performed using SYBR Green Premix (Takara, Dalian, China) on Applied Biosystem 7500 (ThermoFisher, Scientific, USA). β -actin served as the internal reference. The primers were ordered and synthesized from Tsingke Biotech (Nanning Synthetic Department, China). All primer sequences are listed in Table 1.

Immunoblotting

Total proteins were extracted from left ventricles and H9c2 cells using radioimmunoprecipitation assay lysate, including protease and phosphatase inhibitors (Solarbio, Beijing, China), and the cytoplasmic proteins in fresh myocardium were isolated using nuclear and cytoplasmic protein extraction kits (Beyotime, Shanghai, China). Using bicinchoninic acid assay (Solarbio, Beijing, China), the concentrations of protein samples were quantified and denatured. The proteins underwent separation using sodium dodecyl sulfate-polyacrylamide gel electrophoresis and were transferred onto polyvinylidene fluoride (PVDF) membranes (Millipore, USA). Then, the PVDF membranes (Millipore, USA) were blocked with 5% bovine serum albumin (Be-



yotime Biotechnology, Shanghai, China) for 1 h. The diluted primary antibodies, including HMGB1 (dilution 1:2000, Abcam, UK), TNF- α (dilution 1:2000, Proteintech, China), IL-1 β (dilution 1:1000, Abcam, UK), Caspase-3/Cleaved Caspase-3 (dilution 1:1000, Wanlei, China), Bax (dilution 1:2000, Abcam, UK), Bcl-2 (dilution 1:1000, Abcam, UK), RAGE (dilution 1:1000, Abcam, UK), phosphorylated-NF- κ B p65 (dilution 1:1000, Cell Signaling Technology, USA), NF- κ B p65 (dilution 1:1000, Cell Signaling Technology, USA), and β -actin (dilution 1:8000, Proteintech, China), were used to incubated with the PVDF membrane (Millipore, USA) overnight at 4 °C. Followed by horseradish peroxidase-conjugated secondary antibody (dilution 1:10000, Santa Cruz Biotechnology, USA) incubation for 1 h at room temperature the following day. Then, blots were examined with the chemiluminescence method using the automatic image analysis system (FluorChem M, Protein Simple, USA), and the relative expression levels of proteins were determined by Image J software (NIH, MD, USA).

Statistical Analysis

Results were displayed as mean $\pm$ SD. The data were assessed employing one-way analysis of variance, and statistical differences among groups were compared using a *post-hoc* analysis. A probability value ≤ 0.05 indicated a significant difference. GraphPad Prism 9.0 statistical software (GraphPad Software Inc., San Diego, CA, USA) was adopted for data analysis in this study.

RESULTS

Semaglutide Ameliorated CME-induced Cardiac Insufficiency

Echocardiography was used to detect the effects of semaglutide or glycyrrhizin on heart systolic function of CME rats. The echocardiography was conducted at 12 h after the surgical procedure. The cardiac systolic function in the CME group was impaired, manifested as lower left ventricular ejection fraction and left ventricular fractional shortening but larger left ventricular end-diastolic diameter and left ventricular end-systolic diameter when compared to the Sham group (Figure 1A & 1B). Remarkably, both glycyrrhizin pretreatment and semaglutide pretreatment mitigated the heart systolic dysfunction caused by CME (Figure 1A & 1B). Moreover, the enhancement of cardiac function in the CME + Sem group was surpassed that of the CME + Gly group (Figure 1A & 1B).

Semaglutide Alleviated Myocardial Injury Caused by CME

After CME induction, the histopathological myocardial damage was evaluated by HE staining and HBFp staining. In the CME group, the myocardium around the microspheres was swollen, and the infiltrations of erythrocytes and leukocytes in the arterial lumen were noted under HE staining observation. Conversely, pretreatments with glycyrrhizin or semaglutide decreased the severity of swelling and infiltration of blood cells (Figure 2A). The scattered microinfarctions indicated by positive staining of HBFp were observed after CME (Figure 2B). Moreover, the transmission electron microscopy scan results showed that the ventricular muscle fibers were disorganized and moderately damaged following CME, some mitochondria exhibited swollen and damaged cristae (Figure 2C). The serum concentrations of cTnT, CK-MB, and serum LDH activity were elevated in the CME group compared with the Sham group, and pretreatments either with glycyrrhizin or with semaglutide reduced the myocardial injury biomarkers (Figure 2E–2G). All these results suggested notable cardiac morphological changes and myocardial damages following CME. Significantly, compared to the CME group, the degree of myocardial edema, accumulation of inflammatory cells, microinfarct area, and cardiac biomarkers levels were reduced in the CME + Gly group and the CME + Sem group. Furthermore, the CME + Sem group presented lower expression of cardiac biomarkers, fewer microinfarctions, swollen myocardium, inflammatory cells and ultrastructural impaired changes. The H9c2 cell model established by LPS plus hypoxia was used to simulate an ischemic and biochemical microenvironment similar to that of CME *in vivo*. The CCK-8 assay indicates that the cell viability of H9c2 cells was decreased in the LPS + Hypo group, while enhanced by semaglutide pretreatment within a specific range (Figure 2I). The concentration of glycyrrhizin on H9c2 cells was referred to related research. The detection of CK-MB and LDH activity showed that semaglutide alleviates the H9c2 cell injury (Figure 2J & 2K). Glycyrrhizin, possessing cardioprotective effects, could reduce the H9c2 cell injury in this model (Figure 2J & 2K). These findings provided evidence that semaglutide could protect against CME-induced myocardial injury.

Semaglutide Attenuated Myocardial Apoptosis in Rats After CME

The apoptotic myocytes were assessed with a TUNEL assay. Our previous study showed that these reactions rea-



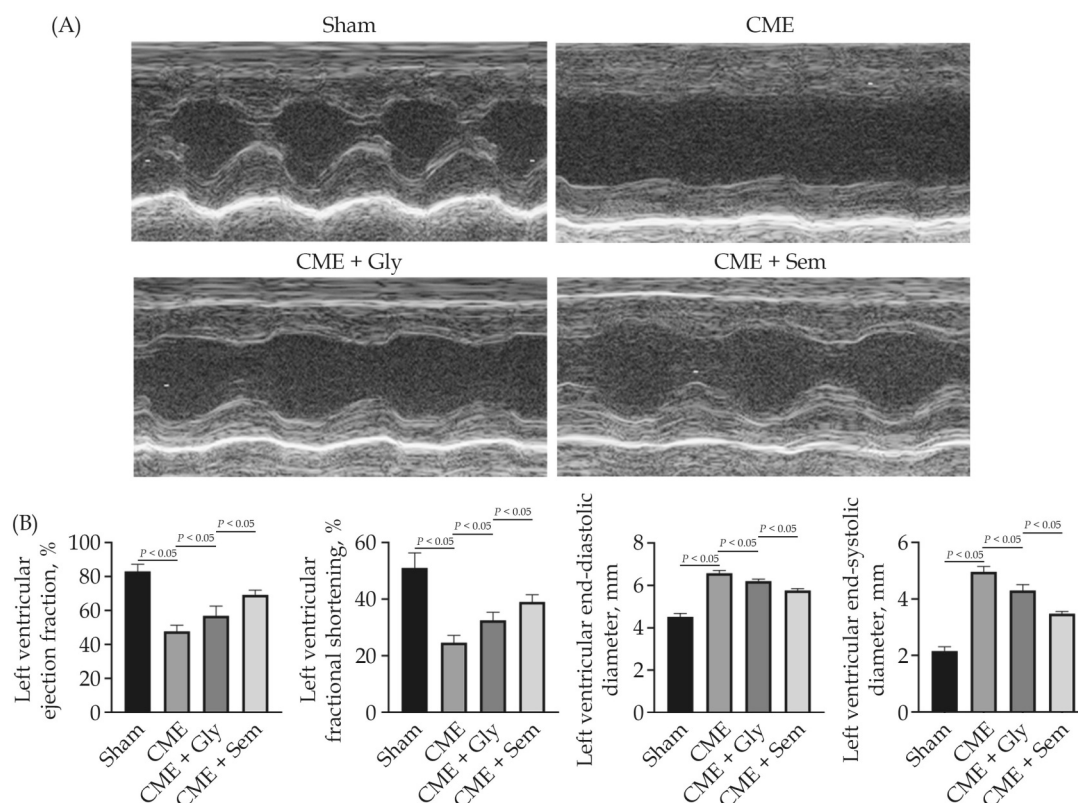


Figure 1 Semaglutide improved CME-induced heart dysfunction. (A) Typical echocardiograms within all groups; and (B) left ventricular ejection fraction, left ventricular fractional shortening, left ventricular end-diastolic diameter, and left ventricular end-systolic diameter among groups. $n = 5$ per group. CME: coronary microembolization.

ched peak at 12 h after CME.^[3] The results pointed out that the apoptotic cell rate was greater in the CME group compared to the Sham group (Figure 3A & 3B). In the cellular model, the apoptotic cell rate of the LPS + Hypo group was significantly increased compared with the Control group (Figure 4A & 4B). In contrast, the apoptotic cardiomyocyte rates in the CME + Gly group and the CME + Sem group decreased compared to that of the CME group. In comparison to the CME + Gly group, the apoptotic cell rate in the CME + Sem group was reduced (Figure 3A & 3B). The similar phenomenon was observed in the H9c2 cell model (Figure 4A & 4B).

The relative expressions of apoptosis-related factors in the myocardium and H9c2 cells, such as cleaved Caspase-3, Bax, and Bcl-2, were detected with immunoblot. The results were consistent with TUNEL detection (Figure 3C). When compared with the Control group, the cleaved Caspase-3 and Bax expressions were increased in the LPS + Hypo group, whereas the Bcl-2 expression was decreased. By contrast, pretreatment with glycyrrhizin or semaglutide partially reduced the upregulated cleaved Caspase-3 and Bax,

while enhancing the reduced Bcl-2 expression (Figure 4C). These findings indicated that semaglutide possessed anti-apoptotic effects in cardiomyocyte.

Semaglutide Relieved Myocardial Inflammatory Response in Rats After CME

The inflammatory factor levels within all groups, such as TNF- α and IL-1 β , reflecting the myocardial inflammation, were measured by qPCR, immunoblot, and IHC detection. The myocardial TNF- α and IL-1 β mRNA and protein expressions were significantly raised in the CME group compared with the Sham group (Figure 5A & 5C & 5D). The inflammatory reaction was further assessed in an H9c2 cell model study. In comparison to the Control group, the expressions of TNF- α and IL-1 β in the LPS + Hypo group cells were increased (Figure 6A–6E).

Glycyrrhizin or semaglutide pretreatment reduced the expression levels of TNF- α and IL-1 β compared with the CME group (Figure 5A & 5C & 5D). Moreover, the serum concentrations of TNF- α and IL-1 β were consistent with that in the myocardium (Figure 5B). The expression levels of TNF

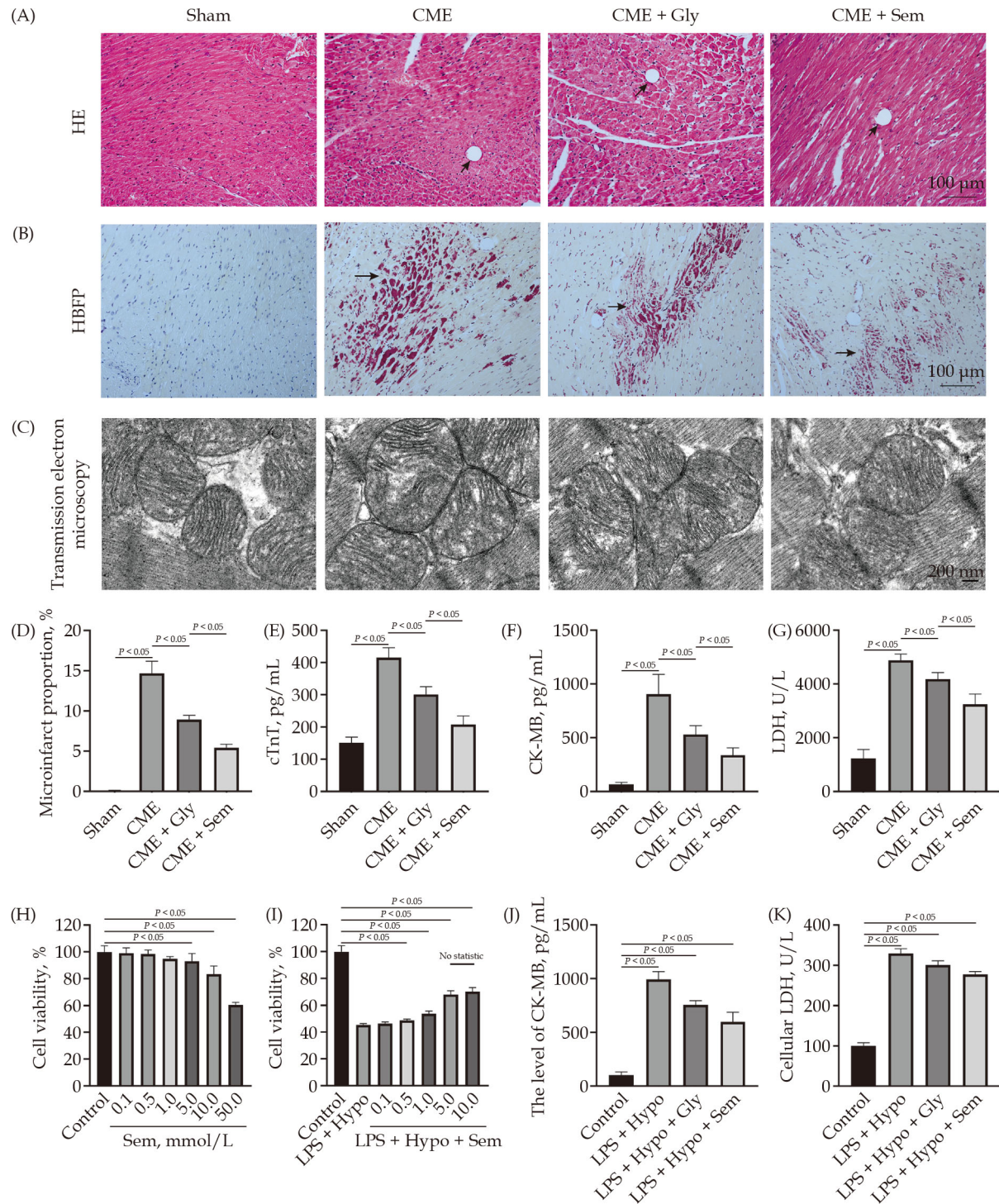


Figure 2 Semaglutide alleviated myocardial injury caused by CME and lessened the H9c2 cardiomyocyte injury. (A) Representative HE staining images within all groups. (Magnification 200 ×; Scale bar = 100 μm). The black arrows refer to the embolic microspheres; (B) HBFP staining of myocardium within all groups. (Magnification 200 ×; Scale bar = 100 μm). The black arrows refer to the microinfarct regions; (C) transmission electron microscopy scan images within all groups (Scale bar = 200 nm); (D) quantification of microinfarct region within all groups; (E-G) serum levels of cTnT, CK-MB, and LDH. $n = 5$ per group; (H & I) the changes in cell viability of H9c2 cells under semaglutide interventions; and (J & K) cell supernatant levels of CK-MB and LDH. $n = 5$ per group. CK-MB: creatine kinase MB isoenzyme; CME: coronary microembolization; cTnT: cardiac troponin T; HBFP: hematoxylin-basic fuchsin-picric acid; HE: hematoxylin eosin; LDH: lactate dehydrogenase; LPS: lipopolysaccharide.

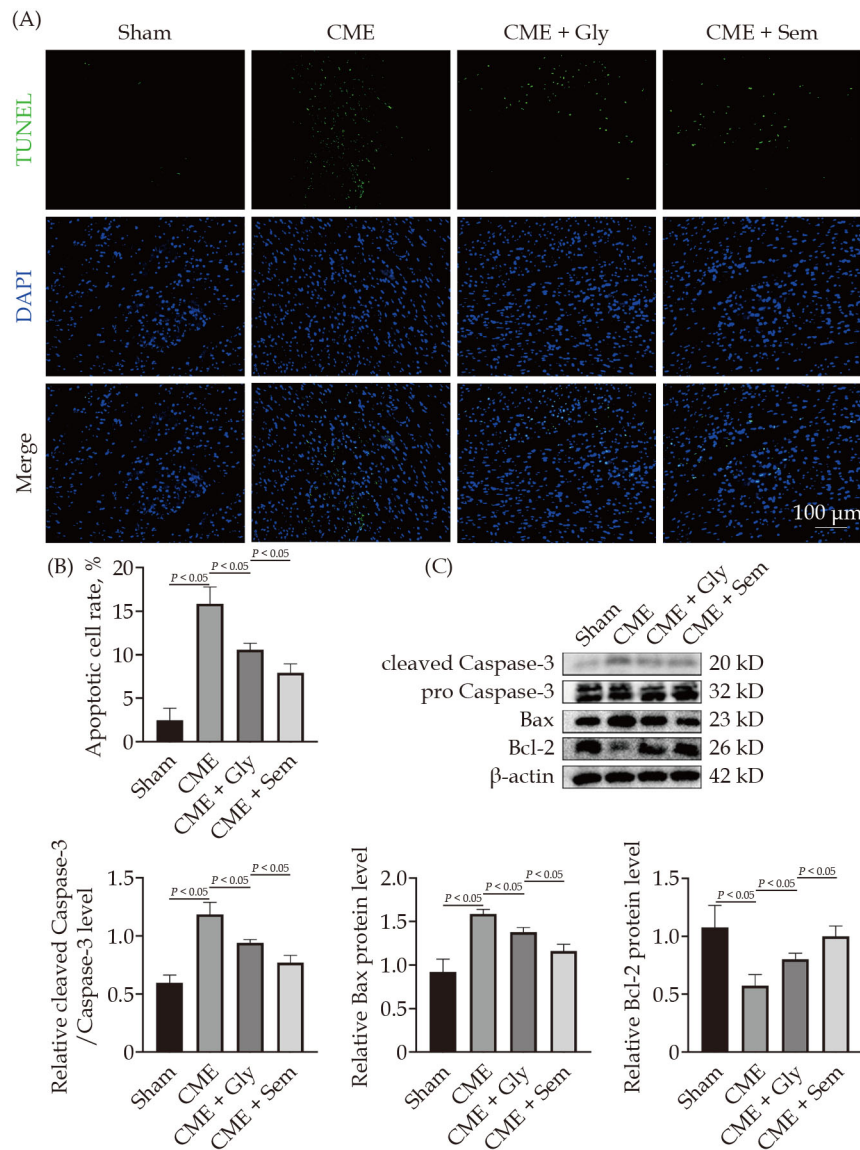


Figure 3 Semaglutide attenuated myocardial apoptosis in the CME. (A) The TUNEL detection within all groups. (Magnification 200 ×; Scale bar = 100 μm); (B) the myocardial apoptosis rate within all groups; and (C) relative expressions of Bax, Bcl-2, and cleaved Caspase-3 in the myocardium. Bax: B-cell lymphoma-2-associated X protein; Bcl-2: B-cell lymphoma-2; CME: coronary microembolization; TUNEL: terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling.

-α and IL-1β in the CME + Sem group were lower than those in the CME + Gly group (Figure 5A–5D). Glycyrrhizin or semaglutide pretreatments also led to marked downregulations of TNF-α and IL-1β in H9c2 cells (Figure 6A–6E). Collectively, these data reveal that semaglutide reduces inflammation caused by CME.

Semaglutide Reduced HMGB1 Expression and Its Nuclear-cytoplasmic Translocation

HMGB1 is crucial in the processes of apoptosis and inflammation, with its cellular location is tightly associated with

biological functions. Cytosolic HMGB1 in the myocardium and extracellular HMGB1 expression levels were determined with immunoblot and enzyme-linked immunosorbent assay, respectively. Both cytosolic and extracellular levels of HMGB1 raised in the CME group (Figure 7A & 7B). Consistently, the upregulated HMGB1 expressions were suppressed in the CME + Gly group and the CME + Sem group. Between the CME + Gly group and the CME + Sem group, the inhibitory effects on HMGB1 expression and nucleocytoplasmic translocation were more significant in the CME + Gly group (Figure 7A & 7B). Compared to the Sham

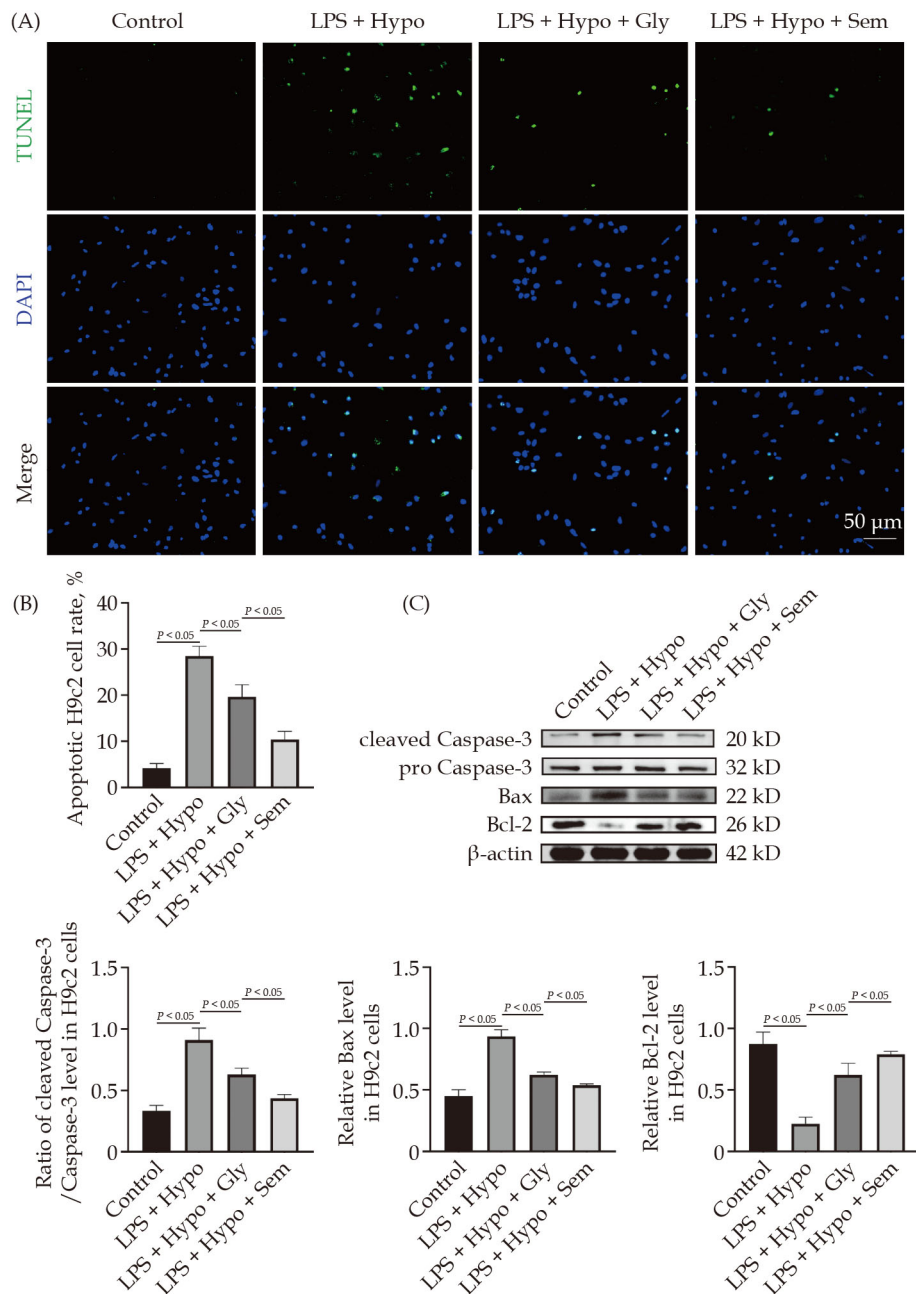


Figure 4 Semaglutide attenuated H9c2 cells apoptosis caused by LPS and hypoxia. (A) Representative image TUNEL staining of apoptotic H9c2 cells. (Magnification 200 $\times$; Scale bar = 50 μ m); (B) the apoptosis rate in H9c2 cells; and (C) relative expressions of Bax, Bcl-2, and cleaved Caspase-3 in H9c2 cells. Bax: B-cell lymphoma-2-associated X protein; Bcl-2: B-cell lymphoma-2; LPS: lipopolysaccharide; TUNEL: terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling.

group, the upregulated *HMGB1* mRNA at the transcriptional level was also detected in myocardium of the CME group. Interventions with glycyrrhizin or semaglutide repressed the *HMGB1* upregulation (Figure 7C).

IF was used to confirm the positional change of *HMGB1* in the myocardium following CME. In the Sham group, *HMGB1* was primarily located in the nuclei of cardiomyocytes

(Figure 7D). In contrast, *HMGB1* accumulated in the cytoplasm of cardiomyocytes and was delivered into the extracellular space after CME induction. However, glycyrrhizin pretreatment profoundly reduced the *HMGB1* translocation from nuclear to cytoplasm. The inhibitory effect on *HMGB1* nucleocytoplasmic translocation was also observed in semaglutide administration (Figure 7D). The ch-

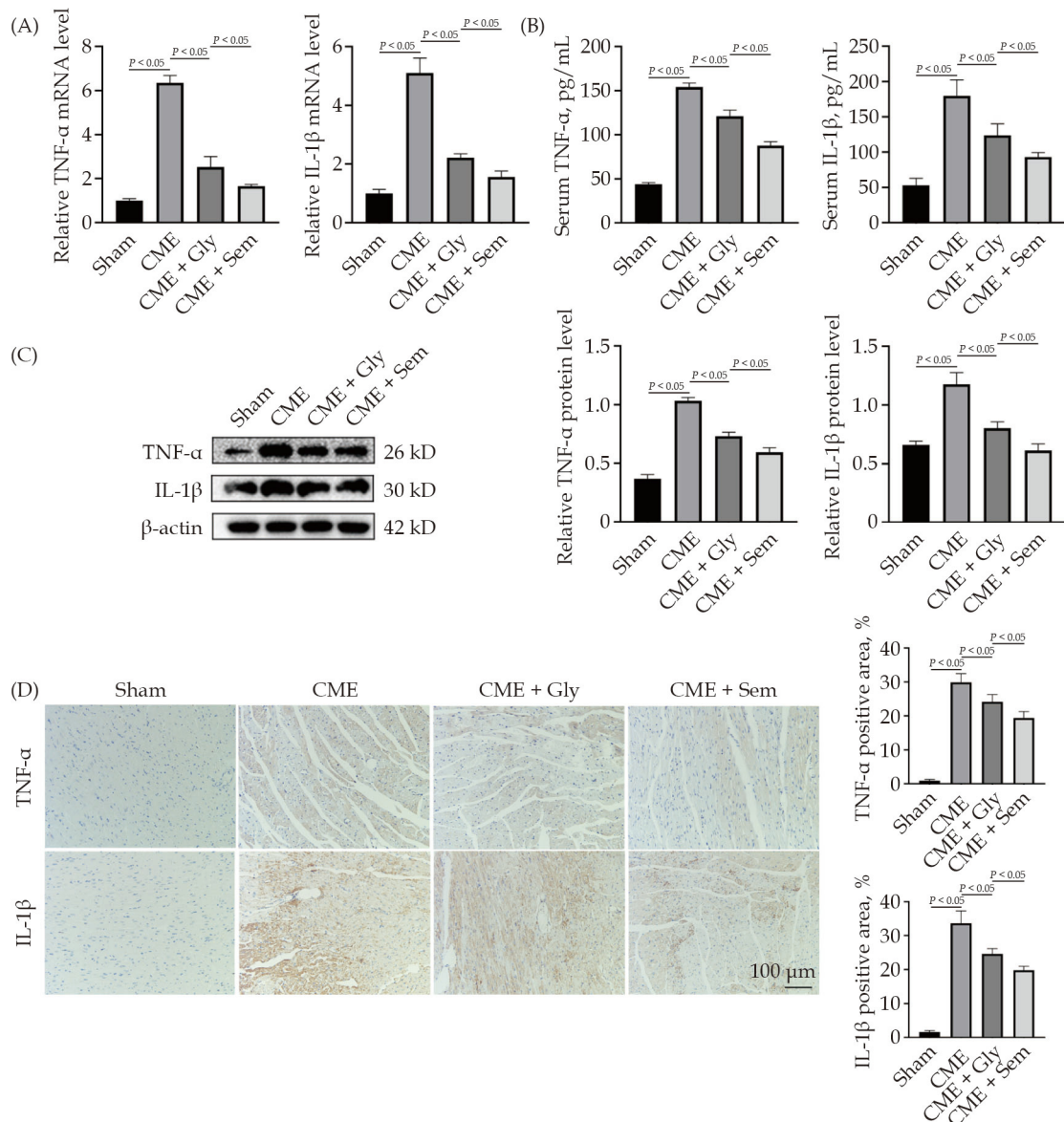


Figure 5 Semaglutide relieved myocardial inflammation in the CME. (A) *TNF-α* mRNA and *IL-1β* mRNA in the myocardium within all groups; (B) serum concentrations of *TNF-α* and *IL-1β* in the myocardium; (C) relative expressions of *TNF-α* and *IL-1β* in the myocardium; and (D) representative immunohistochemistry images of *TNF-α* and *IL-1β* within all groups. CME: coronary microembolization; *IL-1β*: interleukin-1beta; *TNF-α*: tumor necrosis factor-alpha.

anges in expression and translocation of HMGB1 were confirmed in the H9c2 cell model subjected to LPS plus hypoxia stimulation. Compared to the controls, the cytosolic and extracellular HMGB1 increased in the LPS + Hypo group cells (Figure 7E-7G). Inhibiting HMGB1 by glycyrrhizin or semaglutide reversed the HMGB1 nuclear-cytoplasmic translocation and depressed the upregulated extracellular HMGB1 contents (Figure 7E-7G). Overall, these findings suggest that the effects of semaglutide on CME are related to HMGB1 expression.

Semaglutide Restrained Apoptosis and Inflammation Through the HMGB1/RAGE/NF-κB Pathway

It is well known that HMGB1 binds to its receptors, such as RAGE, and then activates NF-κB p65 to increase the produce and release of inflammatory cytokines. In other word, pro-inflammatory effect of HMGB1 depends on the activation of downstream inflammatory signaling pathway. To further address the mechanism that semaglutide improved CME, the levels of RAGE, NF-κB p65, and phosphate-NF-κB p65 were detected using western blot as described.

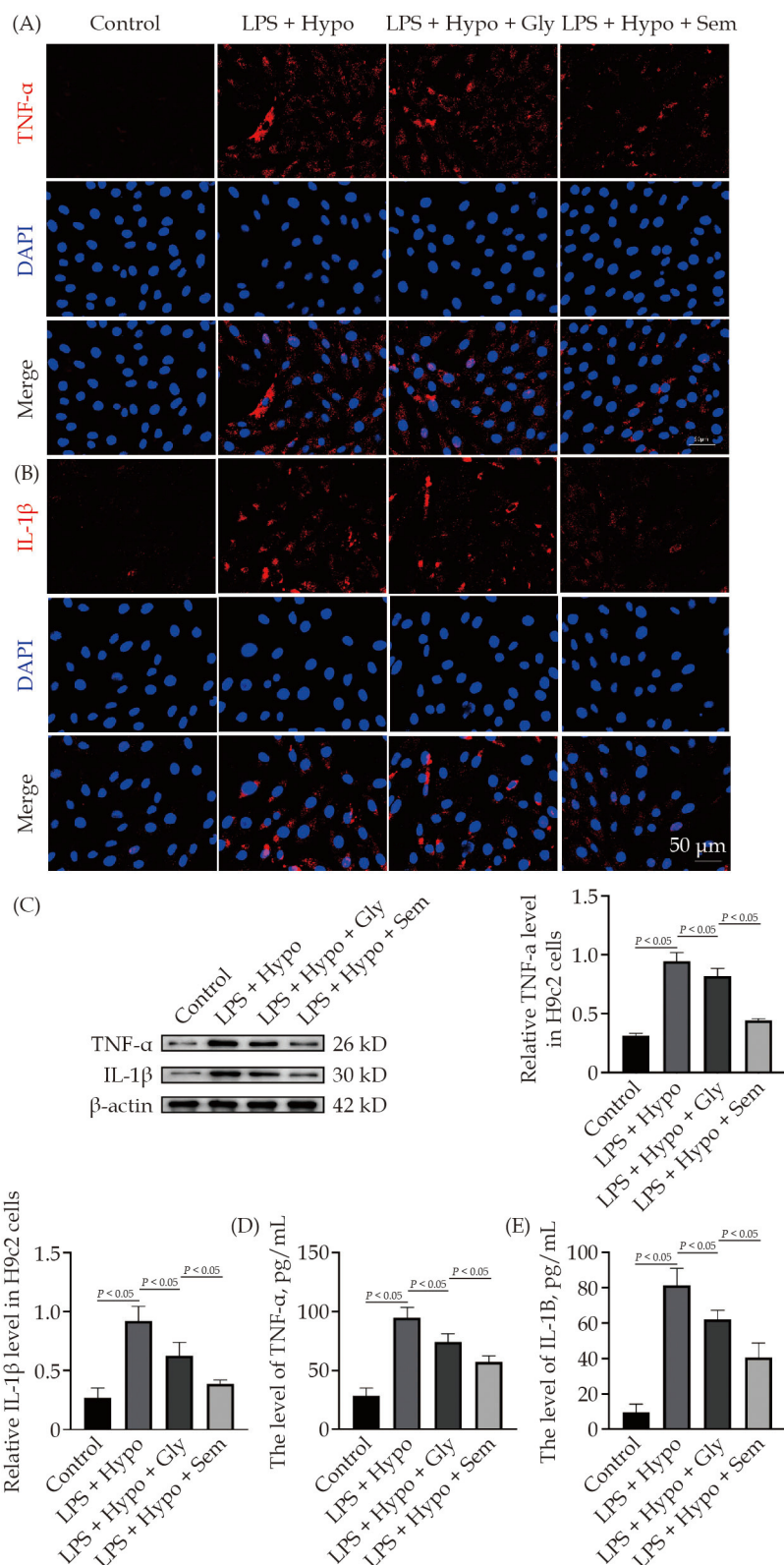


Figure 6 Semaglutide relieved H9c2 cells inflammation caused by LPS and hypoxia. (A & B) Representative immunofluorescence images of TNF- α and IL-1 β in H9c2 cells; (C) relative expressions of TNF- α and IL-1 β in H9c2 cells; and (D & E) cell supernatant levels of TNF- α and IL-1 β . IL-1 β : interleukin-1beta; LPS: lipopolysaccharide; TNF- α : tumor necrosis factor-alpha.

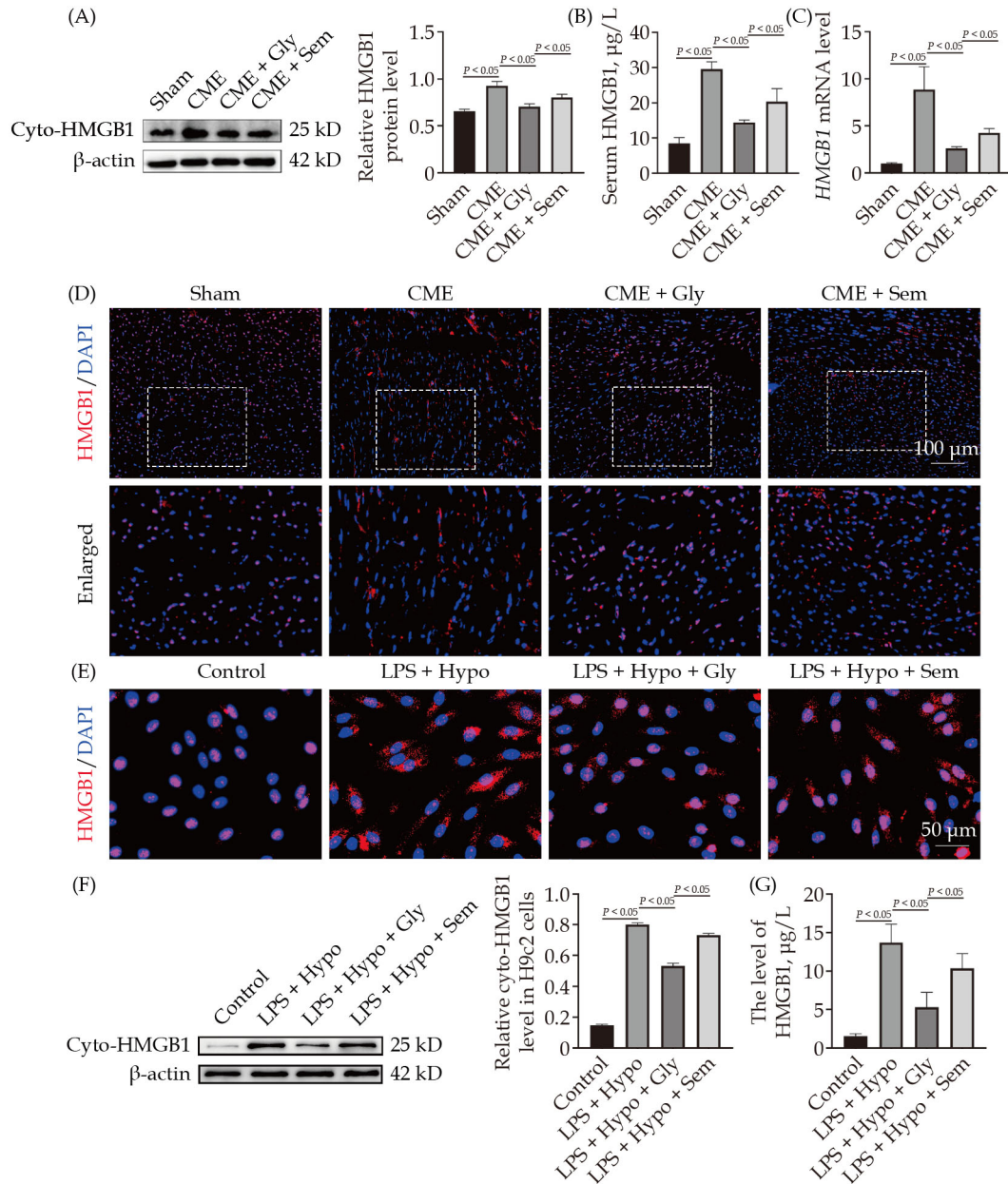


Figure 7 Semaglutide inhibited HMGB1 expression and nuclear-cytoplasmic translocation after CME *in vivo* and *in vitro*. (A) Relative expression of cytoplasmic HMGB1 in the myocardium; (B) serum HMGB1 levels within all groups; (C) HMGB1 mRNA in the myocardium; (D) HMGB1 immunofluorescence images in the myocardium (Magnification 200 $\times$; Scale bar = 100 μm); (E) representative HMGB1 immunofluorescence images in H9c2 cells (Magnification 200 $\times$; Scale bar = 50 μm); (F) relative expression of cytoplasmic HMGB1 in H9c2 cells; and (G) the level of HMGB1 in cell supernatant. CME: coronary microembolization; HMGB1: high mobility group box 1; LPS: lipopolysaccharide.

ed in methods. Compared with the Sham group, the RAGE and phosphate-NF- κ B p65 expressions were both upregulated in the CME group. Pretreatments with semaglutide or glycyrrhizin reduced the RAGE and phosphate-NF- κ B p65 expression levels following CME (Figure 8A). IF detection confirmed the increased myocardial nuclear translocation of phosphate-NF- κ B p65 in the CME group but reduced in the

CME + Gly group and the CME + Sem group (Figure 8B). These findings were similar to immunoblots results. Simultaneously, both the immunoblot and IF detections of H9c2 cell model *in vitro* were consistent with the findings of CME model *in vivo* (Figure 8C & 8D). Thus, the results indicate that semaglutide reduces RAGE expression and affects NF- κ B p65 pathway in CME settings.

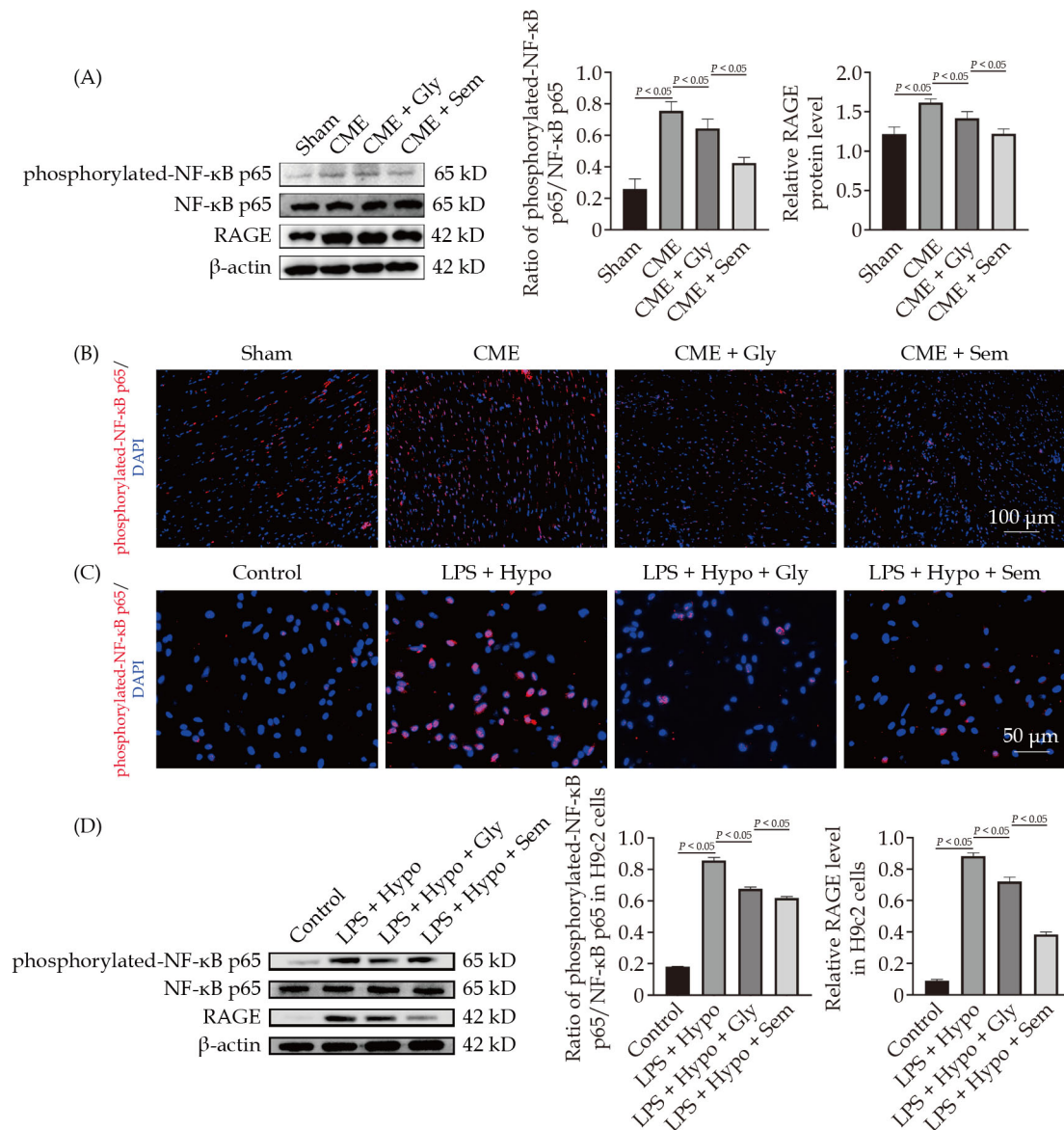


Figure 8 Semaglutide protected against CME-induced apoptosis and inflammation through the RAGE/NF-κB p65 pathway. (A) Relative expressions of phosphate-NF-κB p65 and RAGE in the myocardium; (B) phosphate-NF-κB p65 immunofluorescence images within all groups (Magnification 200 ×; Scale bar = 100 μm); (C) representative phosphate-NF-κB p65 immunofluorescence images in H9c2 cells (Magnification 200 ×; Scale bar = 50 μm); and (D) relative expressions of phosphate-NF-κB p65 and RAGE in H9c2 cells. CME: coronary microembolization; LPS: lipopolysaccharide; NF-κB p65: nuclear factor kappa B p65; RAGE: advanced glycosylation end-product specific receptor.

DISCUSSION

In the current study, we established a rat CME model, and the results showed activations of apoptosis and inflammatory response, upregulation and translocation of HMGB1, which cause myocardial injury and contractile dysfunction by activating RAGE/NF-κB p65 pathway. Semaglutide pretreatment remarkably reduced the cardiac injury and improved the impaired heart function after CME. This study also examined the inhibitory effects of semaglutide on

apoptosis and inflammation mediated by suppressing the expression of HMGB1 and its nucleocytoplasmic translocation.

Interventional manipulation is widely applied in CAD therapy. However, the periprocedural myocardial injury, which was attributed to CME partially, remains an ordinary problem after coronary revascularization. The highly complex pathogenesis and underlying mechanism of CME are not fully understood. The inflammation occurs the en-

tire process from atherosclerosis to plaque rupture. And inflammatory response is triggered and amplified due to physical occlusion of microcirculatory vessels, contributes to contractile dysfunction, and aggravates cardiomyocyte damage in the surrounding myocardium around the microinfarct.^[2] Recent research has revealed that disturbed homeostasis occurs after CME, and then the numerous forms of programmed cell death play a pivotal role during the CME progression.^[32-34] Apoptosis, the most investigated form of programmed cell death with elevated pro-apoptotic factors such as Bax and Bad and decreased anti-apoptotic factors like Bcl-2, exacerbates the loss of survival cardiomyocytes and cardiac dysfunction after CME. Our previous studies have revealed that both apoptosis and inflammation were activated and engaged in the myocardial injury in rat CME model, as interference targets could relieve the damages.^[35] Similarly, the inflammatory cells infiltration in the adjacent zone of microinfarct factors and elevated expression of pro-apoptotic factor Bax and executor cleaved Caspase-3, inflammatory genes (like TNF- α and IL-1 β), and down-regulated anti-apoptotic Bcl-2 in myocardium were observed in the CME group. The present study results were consistent with earlier studies on the CME model, strengthening the involvement of apoptosis and inflammation in the development of the CME.

Metabolic disorders such as diabetes mellitus and obesity are major risk factors of CAD and affect the patients' outcomes, and the GLP-1RAs are effective agents for controlling metabolic disturbances.^[36,37] Semaglutide, one novel GLP-1RAs, has attracted our attention owing to its potential protective action on multiple organs beyond its original hypoglycemic property. The STEP-HFpEF clinical trial showed that administering semaglutide could improve physical limitation, ease heart failure symptoms, and reduce systemic inflammation in patients with HFpEF.^[20] Experimental studies suggested that GLP-1RAs alleviate inflammatory response and oxidative stress in the cardiomyocyte under several stimulated conditions *in vivo* and *in vitro*.^[19,38] Zhu, *et al.*^[27] have reported that semaglutide could protect against MI/RI by suppressing myocardial apoptosis. Network pharmacology analysis revealed that GLP-1RA exerts cardiac benefit by interfering with different targets and pathways related to atherosclerosis, myocardial remodeling, thrombosis, etc.^[39] However, relatively little is understood about the effects and potential mechanisms through which semaglutide impacts on cardiac injury after CME. Our results showed that semaglutide pretreatment attenuated the myocardial pathological damages, reduced the myo-

cardial infarct size, microinfarct area, relieved mitochondria morphological damages and myocardial injury, and improved cardiac dysfunction. In addition, the downregulated apoptosis was reflected by fewer positive TUNEL detection cells and the downregulation of cleaved Caspase-3 and Bax, accompanied by upregulation of Bcl-2. Besides, mitigatory inflammatory response manifested by fewer inflammatory cell infiltration and reduced inflammatory cytokines. All these changes indicate that semaglutide exerted cardioprotective effects on myocardial injury through the suppression of apoptosis and inflammatory response in rat CME model.

HMGB1, a ubiquitous nuclear protein, is essential for maintaining the balance between cellular survival and death. It has been demonstrated that HMGB1 transfers from nuclear to cytoplasm or shifts into extracellular spaces, and it serves as a pro-inflammatory alarmin under stimulated conditions.^[22] However, the extracellular level of HMGB1 and its subcellular location change after CME remains unknown. The current study found that both cytosolic and serum HMGB1 expression levels were increased, and more HMGB1 transferred from nuclear to the cytoplasm in the myocardium following CME. This change implies HMGB1 migrates from nuclear to cytoplasm and extracellular space under pathological conditions by CME. At the same time, pretreatment with semaglutide suppressed the upregulation of cytosolic and serum HMGB1 expression and nucleocytoplasmic translocation of HMGB1.

It is widely recognized that extranuclear HMGB1 plays a detrimental role in diverse pathological processes, including MI/RI and acute myocardial infarction.^[40,41] Chen, *et al.*^[23] have revealed that myocardial HMGB1 contributes to myocardial injury by inducing apoptosis and enhancing endoplasmic reticulum stress in this rat CME model. Another rat CME experiment has uncovered that inhibiting HMGB1 with glycyrrhizin alleviates myocardial apoptosis and inflammation caused by CME.^[28] With a combination of principal pattern recognition receptors like toll-like receptor 4 and RAGE, HMGB1 activates subsequent pathways and triggers inflammatory response and programmed cell deaths.^[42] A recent study revealed that the HMGB1/RAGE axis exacerbates apoptosis induced by MI/RI in a diabetic mouse model.^[41] In this study, the RAGE expression and the expression elevation of cytosolic HMGB1 and nucleocytoplasmic translocation of HMGB1 after CME induction were upregulated. Similar to the ligand HMGB1, the expression of RAGE was repressed by semaglutide or glycyrrhizin pretreatment in CME. NF- κ B is the cru-



cial mediator in the RAGE-associated pathways; its activation and upregulation cause the release of pro-inflammatory cytokines and coordinate varied programmed cell death processes.^[43] Inhibiting NF- κ B pathway could impede the inflammation in atherosclerosis mice.^[44] It has been validated that suppressing the RAGE/NF- κ B axis mediated apoptosis and inflammation attenuate ischemia myocardial injury induced by isoproterenol.^[45] Our previous studies confirmed that activated and upregulated NF- κ B signaling pathways engage in the pathogenesis of CME.^[46] This study found an elevation in the phosphorylation level and the entry of nuclei of phosphorylated-NF- κ B p65 in the myocytes after CME. These changes were restored by pretreatment with semaglutide, and the alternations of expression and translocation of phosphorylated-NF- κ B p65 indicated semaglutide could restrain NF- κ B p65 phosphorylation and nuclear entry in myocardium induced by CME. Accordingly, we speculated that semaglutide might inhibit the HMGB1/RAGE/NF- κ B p65 pathway, thus mitigating the CME-induced damages. Glycyrrhizin decreased RAGE and phosphorylated-NF- κ B p65 expressions and translocation, as well as HMGB1 and its nucleocytoplasmic translocation following CME induction. Additionally, the pretreatment with semaglutide altered the expressions of the HMGB1/RAGE/NF- κ B pathway, similar to the effects of HMGB1 antagonist glycyrrhizin. Therefore, semaglutide may suppress the apoptotic and inflammatory re-

sponse by inhibiting the HMGB1 translocation and expression and its downstream RAGE/NF- κ B p65 pathway, thus ameliorating myocardial injury and cardiac dysfunction.

LIMITATIONS

Though the current study extended the pleiotropic cardioprotective effects of semaglutide, some limitations should be considered. On the one hand, this study used a rodent CME model instead of large mammals like pigs and sheep that share more similarities in cardiac anatomic and physiological features with humans. On the other hand, this study explored the application of semaglutide on cardiac injury after CME *in vivo*. Still, the detailed molecular mechanisms modulating HMGB1 by semaglutide require further investigation.

CONCLUSIONS

In conclusion, this study provides new evidence that semaglutide protects against myocardial injury following CME by inhibiting apoptosis and inflammatory response via suppressing cytoplasmic HMGB1 expression and nucleocytoplasmic translocation (Figure 9). These results suggest that semaglutide exerts protective effects on myocardial injury. This study represents a potential strategy for preventing and treating perioperative myocardial injury.

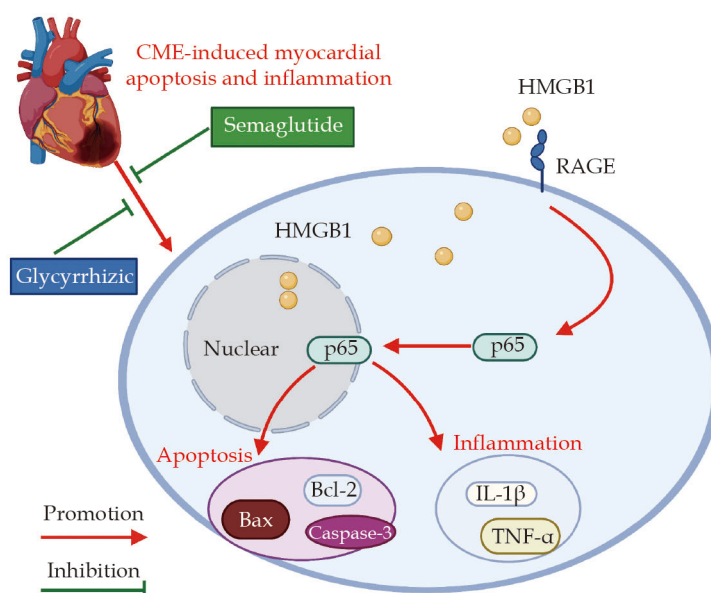


Figure 9 An overview of the mechanism by which semaglutide mitigates myocardial apoptosis and inflammation via inhibition of HMGB1 translocation and RAGE/NF- κ B p65 pathway (Created in BioRender, <https://BioRender.com/g91p100>). Bax: B-cell lymphoma-2-associated X protein; Bcl-2: B-cell lymphoma-2; CME: coronary microembolization; HMGB1: high mobility group box 1; IL-1 β : interleukin-1beta; NF- κ B p65: nuclear factor kappa B p65; RAGE: advanced glycosylation end-product specific receptor; TNF- α : tumor necrosis factor-alpha.

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