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BIOMEDICAL SCIENCES

# Hypoxia-inducible factor-1α attenuates myocardial inflammatory injury in rats induced by coronary microembolization

QUAN-FANG CHEN, WEI WANG, ZHOU HUANG & DONG-LING HUANG

**Abstract:** To investigated the role of HIF-1α in myocardial inflammatory injury in rats induced by CME and its possible mechanism. Forty SD rats were separated randomly and equally into four groups, i.e. CME+HIF-1α stabilizer dimethyloxalyl glycine (CME+DMOG) group, CME+HIF-1α inhibitor YC-1 (CME+YC-1) group, CME group, and Sham group. HBFP staining, myocardial enzyme assessment, and cardiac ultrasound were used to measure microinfarct, serum c-troponin I (cTnI) level, and Cardiac function. ELISA and western blot were applied for detecting NLRP3 inflammasome pathway and TLR4/MyD88/NF-κB signaling level.Pro-inflammatory factors of IL-18, IL-1β and TNF-α increased their expression levels after CME, which indicated inflammatory responses in the myocardium. Additionally, in the inflammatory process, NLRP3 inflammasome and TLR4/MyD88/NF-κB signaling were involved. DMOG reverses these effects of CME, whereas YC-1 aggravates these effects. HIF-1α may attenuate myocardial inflammatory injury induced by CME and improve cardiac function, which can perhaps be explained by the fact that TLR4/MyD88/NF-κB signaling pathway activation is inhibited.

**Key words:** HIF-1α, coronary microembolization, NLRP3 inflammasome, TLR4/MyD88/NF-κB. inflammation.

## INTRODUCTION

Coronary microembolization (CME) is a coronary microcirculation embolism and myocardial microinfarction caused by microemboli during spontaneous rupture of coronary atherosclerotic plaque or percutaneous coronary intervention (PCI) (Heusch 2016, Heusch et al. 2018). The incidence rate of this disease is 15% to 20% (Bahrmann et al. 2007). CME can induce slow flow or no reflow in the myocardiumand consequently causes local myocardial contractile dysfunction and reduces coronary and inotropic reserves, which seriously affect the heart function and prognosis of patients (Skyschally et al. 2002, Su et al. 2019). CME caused local myocardial inflammation is a substantial factor in causing progressive cardiac dysfunction according to studies (Su et al. 2018a, Dörge et al. 2002, Thielmann et al. 2002). While after CME and during the development of a myocardial immune inflammatory response, activation of the TLR4/MyD88/NF-κB signaling pathway functions as an important link. Additionally, this activation accelerates the activation of NLRP3 inflammatory bodies, promotes the inflammatory cascade, and aggravates myocardial damage. Wherefore, local myocardial inflammation caused by CME and cardiac function can be significantly improved by the inhibition of this pathway (Su et al. 2018b, Wanget al. 2017a, Ma & Xie 2017). In this sense, activation of TLR4/MyD88/NF-κB signaling pathway can causevarious inflammatory

mediators to be released in a large amount, which consequently results in a significant influence on CME-induced myocardial injury. However, its specific regulatory mechanism is not well understood.

Hypoxia-inducible factor-1α (HIF-1α), a transcriptional regulator produced by hypoxia, is degraded by proteasome under the action of proline hydroxylase (PHD) in normoxia. Under conditions of hypoxia, however, PHD activity is inhibited, so HIF-1α cannot be degraded. A complex is formed with the β subunit to regulate transcription of a plurality of target genes (Tekin et al. 2020). In the inflammatory lesions of mammalian cells and *Drosophila*, HIF-1α reduces the expression of nuclear factor-κB and inflammatory factors, thereby reducing the inflammatory response of the myocardium (Bandarra et al. 2015, Kempf et al. 2012). However, in the rat CME model, whether HIF-1α can also alleviate myocardial inflammatory injury caused by CME is not clear, and no relevant research is available. Therefore, we aim to study the mechanism underlying and the role of HIF-1α in rat CME-induced myocardial inflammatory injury to provide a novel strategy for clinical treatment and prevention of CME.

## MATERIALS AND METHODS

### Animal preparation

The Guangxi Medical University medical experimental animal center provided us with forty Sprague-Dawley rats (male, 250-300 g), with unconstrained access to tap water and laboratory chow in day-night quarters at 25°C. All experiments in this study were conducted as required by the National Institutes of Health Guidelines on the Use of Laboratory Animals, with all the procedures and protocols approved by the Institutional Animal Care and Use Committees at Guangxi Medical University.

### Establishment of the CME model and experimental grouping

Briefly, a left lateral thoracotomy was undertaken in rats at the third and fifth intercostal space. The pericardium was opened and the ascending aorta was exposed fully. A suspension of microspheres in saline solution containing about 3000 microspheres (42 μm in diameter, Biosphere Medical Inc. Rockland, USA) was injected into the left ventricle during 10s occlusion of the ascending aorta. The chest is closed in layers after a stable heartbeat is achieved. After breathing is stabilized, tracheal intubation was removed. Postoperatively, 800,000 units of penicillin were intraperitoneally injected in the rats, followed by normal feeding (Wang et al. 2017b, Lindsey et al. 2018). The forty rats were separated randomly and equally into four groups: CME+HIF-1α stabilizer dimethyloxalyl glycine (CME+DMOG) group, CME+HIF-1α inhibitor YC-1 (CME+YC-1) group, CME group, and Sham group (n = 10 per group). In the CME+DMOG group, each rat was intraperitoneally injected with 40 mg/kg DMOG (Sigma-Aldrich, St. Louis, MO, USA) at 24 hours before CME. The rats in the CME+YC-1 group were injected with 2 mg/kg YC-1 (Cayman, Ann Arbor, Michigan, USA) via tail vein 30 min before CME. Moreover, the 0.1 ml of physiological saline was injected in Sham group.

### Detection of cardiac function

At 12 h after CME, observation was performed to detect cardiac function as it was confirmed that it is at this point that the lowest cardiac function occurs (Chen et al. 2019). In this detection, cardiac output (CO), left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), and left ventricular end diagnostic diameter (LVEDd) were measured by a Hewlett Packard Sonos 7500 ultrasound instrument (Philips Technologies, Amsterdam,

NY, USA), with a 12 MHz. probe frequency. All the measured data were averaged after triple cardiac cycles. An experienced specialist conducted echocardiography.

### Measurements of serum cardiac troponin I (cTnI) levels

At 12 hours following sham or CME operation and before sacrifice, 1.0 ml blood was acquired in femoral vein, and then serum c-troponin I was detected as per the Kit instructions. (Roche, Inc., Basel, Switzerland).

### Tissue extraction and sample processing

Each rat was injected, at tail vein, with 10% potassium chlorideof 2 ml after assessing cardiac function, to stop the heart in ventricular diastolic phase, and the heart was harvested immediately. The atrium and atrial appendage were harvested. The ventricle was separated into bottom of heart and apex in the middle of left ventricle parallel to atrioventricular groove. After being frozen with liquid nitrogen the apex was immediately moved to a –80°C refrigerator. These samples were used in western blot analysis. The basal part was sliced at 4 μm thickness after being fixed for 12 h, with 4% paraformaldehyde and embedded in paraffin. Paraffin-embedded samples were used in the following staining process with hematoxylin-basic fuchsin–picric acid (HBFP).

### Measurement of myocardial microinfarct areas

In diagnosing early myocardial ischemia, HBFP staining can stain nucleus in blue color, normal myocardial cytoplasm in yellow, as well as ischemic myocardium and red blood cells in red. A DMR+Q550 pathological image analyzer (Leica, Wetzlar, Germany) was used to observe (×100 magnification) each HBFP-stained slice. For each slice, five random visual fields were selected. The Leica Qwin analysis software plane method was used for measuring the infarct area, which was then divided by gross observed area to calculate the infarct percentage (Su et al. 2015).

### Enzyme-linked immunosorbent assay (ELISA) in detection of inflammatory cytokines in serum

A specific ELISA kit (R&D Systems, Minneapolis, MN, USA) was used to examine IL-18, TNF-α, and IL-1β levels in serum as per the use manual.

### Western blot analysis

10-15% SDS-PAGE was used to firstly separate the total proteins acquired from cardiomyocyte and cardiac tissue, which were then electrotransferred to PVDF membranes (Millipore, Atlanta, GA, US). Nonfat milk or 5% bovine serum albumin was used to block the membranes at room temperatures for 1.5 h before incubating these membranes overnight at 4°C by primary antibodies against GAPDH, Caspase-1, ASC, NLRP3, NF-κB p65, MyD88, TLR4, or HIF-1α. Abcam Biotech (Cambridge, UK) provided us with primary antibodies specific to ASC (1:500), NLRP3 (1:200), and TLR4 (1:500). Cell Signaling Technology (Beverly, MA, USA) provided us withprimary antibodies targeting Caspase-1 (1:1000), NF-κB p65 (1:1000), MyD88 (1:1000), and HIF-1α (1:1000). Secondary antibodies conjugated with horseradish peroxidase were used to incubatethe membranes at room temperatures for 2 h in TBST after the membranes were washed 5 times by TBS containing 0.1% Tween 20 (TBST). An enhanced chemiluminescence device (Pierce, Rockford, IL, USA) was used to detect the signals. Image Lab software of Bio-Rad was used to assess and quantify the bands for protein amounts.

### Statistical analysis

SPSS 20.0 statistical software (IBM, Chicago, IL) was used to conduct statistical analyses, in which means ± standard deviation (SD) were used to express the data. Student's t-test was used for comparison between two groups. One-way ANOVA was performed to compare among three or more groups, followed by Bonferroni's post-hoc test. $P<0.05$ was considered significant statistically.

## RESULTS

### Changes in the cardiac function of rats

LVEDd LVEF, CO, and FS values were echocardiographically detected to evaluate cardiac function. The results at 12 hours after the experiments revealed the following (Table I): 1) Cardiac function in CME group distinctly decreased than sham group, as indicated by left ventricular dilatation and myocardial systolic dysfunction: increased LVEDd ($P< 0.05$) and declined CO, FS, LVEF ($P< 0.05$). 2) The CME+DMOG group, in comparison to CME group, improved the cardiac function impairment caused by CME, as indicated by decline in LVEDd ($P<0.05$) and growth in LVEF, FS, and CO ($P<0.05$). 3) In the CME+YC-1 group ($P<0.05$), cardiac functions were decreased in rats compared with CME group.

### Detection of myocardial injury marker cTnI

1) Serum cTnI concentrations in CME+YC-1 group, CME+DMOG group, and CME group were distinctly increased ($P<0.05$) in comparison with Sham group. 2) Serum cTnI concentrations in CME+DMOG group were distinctly reduced ($P<0.05$) in comparison to CME group. 3) Serum cTnI concentrations in CME+YC-1 group were distinctly increased ($P<0.05$), relative to CME group, as shown in Fig. 1.

### Pathological observation of CME

HBFP staining: Microinfarctions were observed in the groups of CME, CME+DMOG, and CME+YC-1. While in thesham group, no obvious infarcts were noted, only with occasional subendocardial ischemia. These lesions, usually in subendocardial and left ventricle, were mostly wedge-shaped with a focal distribution, as shown in Fig. 2. The infarct size of the groups of CME, CME+DMOG, and CME+YC-1 were (11.07±3.12)%, (6.75±2.06)%, and (15.89±4.64)%, respectively. The infarct size of CME+DMOG group and CME+YC-1 group distinctly increased than Sham group ($P<0.05$). Infarct size declined in

**Table I. Changes in cardiac function ($\bar{x}$ ± s ).**

| Group | n | LVEF (%) | LVFS (%) | CO (L/min) | LVEDd (mm) |
|---|---|---|---|---|---|
| Sham | 10 | 77.68±5.59 | 42.23±4.61 | 0.182±0.028 | 5.34±0.45 |
| CME | 10 | 51.02±3.17[a] | 19.11±2.55[a] | 0.121±0.014[a] | 7.99±0.61[a] |
| CME+DMOG | 10 | 65.27±3.64[ab] | 34.86±4.57[ab] | 0.161±0.018[ab] | 6.82±0.54[ab] |
| CME+YC-1 | 10 | 42.39±2.88[ab] | 16.97±2.38[ab] | 0.094±0.012[ab] | 8.54±0.79[ab] |

**LVEF, left ventricle ejection fraction; CO, cardiac output; LVEDd, left ventricular end-diastolic diameter; LVFS, left ventricle fractional shortening; CME, coronary microembolization. [a]$P<0.05$ in comparison to Sham group; [b]$P<0.05$ in comparison to CME group.**

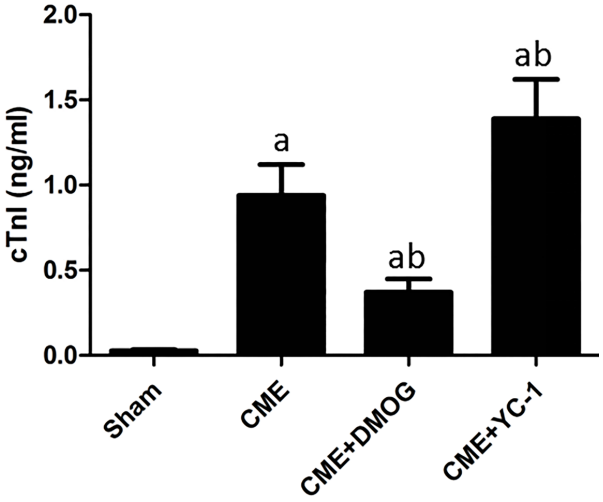


**Figure 1. Parameters of cTnI in rats of each group. Serum cTnI concentrations were increased following coronary microembolization (CME). DMOG inhibited its increase despite CME, whereas YC-1 aggravates these effects.** [a]***P*<0.05 in comparison to Sham group;** [b]***P*<0.05 in comparison to CME group. n = 10.**

CME+DMOG group in comparison to CME group (*P*<0.05). Infarct size of CME+YC-1 group distinctly increased in comparison to CME group (*P*<0.05).

## Effects of HIF-1α on serum level of IL-18, TNF-α, and IL-1β

Serum levels of pro-inflammatory cytokines in the rats were detected by ELISA in each group (Fig. 3): Levels of serum IL-18, TNF-α, and IL-1β in the groups of CME, CME+DMOG, and CME+YC-1 distinctly increased in comparison to Sham group (*P*<0.05). 2) Serum TNF-α, IL-18, and IL-1β expression levels reduced in CME+DMOG group in comparison to CME group (*P*<0.05). 3) Serum IL-18, IL-1β, and TNF-α levels in CME+YC-1 group distinctly increased in comparison to CME group (*P*<0.05).

## Effects of HIF-1α on the expression of proteins in the TLR4/MyD88/NF-κB signaling and NLRP3 inflammasome pathway

Fig. 4 indicates: 1) Myocardial levels of Caspase-1, ASC, NLRP3, NF-κB p65, HIF-1α, MyD88, and TLR4 in the groups of CME, CME+DMOG, and CME+YC-1

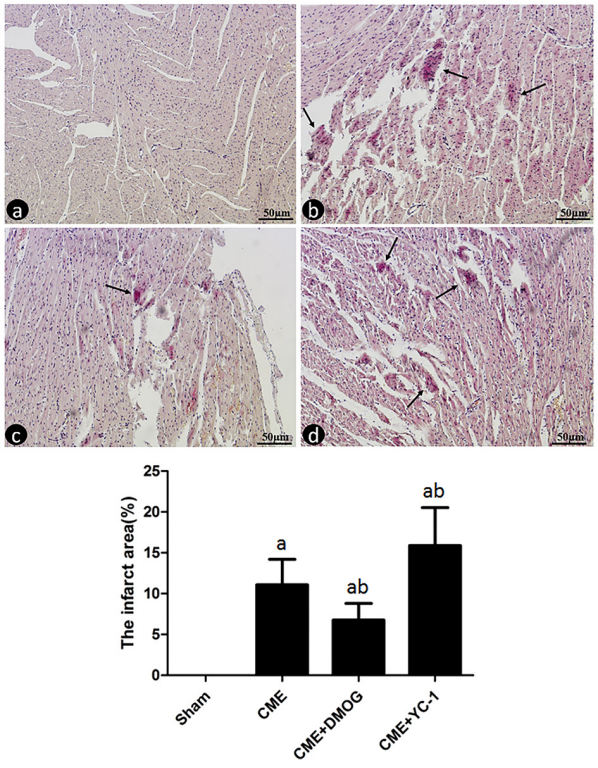


**Figure 2. Pathohistological examination by HBFP staining (magnification, ×200; bar = 50 μm) Ischemic myocardium in red. Arrow indicates microinfarct area. a: HBFP staining showed no microinfarct in the Sham group; b: Infarct was evident following coronary microembolization; c: The increase was inhibited by DMOG; d: YC-1 aggravates these effects.** [a]***P*<0.05 in comparison to Sham group;** [b]***P*<0.05 in comparison to CME group. n = 10.**

distinctly increased in comparison to Sham group (*P*<0.05). 2) In CME+DMOG group, relative HIF-1α protein expression distinctly increased in comparison to CME group, whereas relative Caspase-1, ASC, NLRP3, NF-κB p65, MyD88, and TLR4 protein expressions distinctly decreased (*P*<0.05); 3) In CME+YC-1 group, the relative protein expression of HIF-1α was significantly reduced in comparison to CME group, whereas relative Caspase-1, ASC, NLRP3, NF-κB p65, MyD88, and TLR4 protein expressions were increased significantly (*P*<0.05).

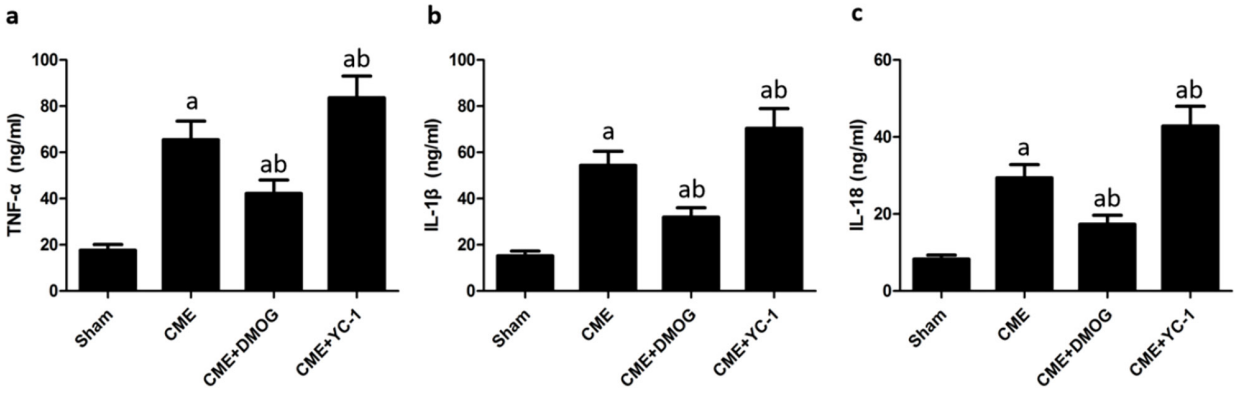


**Figure 3. Effects of HIF-1α on serum levels of TNF-α (a), IL-1β (b), and IL-18 (c). Serum TNF-α, IL-18, and IL-1β expression levels were increased following coronary microembolization (CME). DMOG inhibited its increase despite CME, whereas YC-1 aggravates these effects.** [a]*P*<0.05 in comparison to Sham group; [b]*P*<0.05 in comparison to CME group. n = 10.

## DISCUSSION

To investigate the changes in myocardial inflammation after DMOG pretreatment, a rat CME model was established in this study. HIF-1α reversed the increase in inflammatory cell infiltration and inflammatory factors IL-18, IL-1β, and TNF-αinduced by CME in rats. Simultaneously, HIF-1α reduced the expressions of Caspase-1, ASC, NLRP3, NF-κB p65, MyD88, TLR4, and other proteins related to inflammation, thereby reducing myocardial injury. Thus, HIF-1α attenuates myocardial inflammation induced by CME in rats and may be related to inhibition of TLR4/MyD88/NF-κB signaling and the NLRP3 inflammasome pathway.

Hypoxia is closely linked to inflammation. In hypoxia, HIF-1α converts oxidative phosphorylation into a glycolysis process to generate energy to maintain cell physiology. In periosteal cells lacking HIF-1α, periosteal cells are damaged by inflammation due to insufficient energy (Peyssonnaux et al. 2005). In the inflammatory injury caused by arthritis and myocardial ischemia, DMOG, a drug inhibitor of PHD, reduces the inflammatory response (Cummins et al. 2006). In addition, DMOG also alleviates expressions of TNF-α, IL-6, and IL-1β in macrophages induced by lipopolysaccharide (Takeda et al. 2009). This work suggests that CME-induced myocardial inflammation will be alleviated upon DMOG pretreatment. In addition, inflammatory factors, e.g. IL-18, TNF-α, and IL-1β distinctly reduced, and cardiac function was improved. In contrast, when pretreated with the HIF-1α inhibitor YC-1, CME-induced myocardial inflammation was aggravated, and cardiac function was further aggravated. These results confirmed the anti-inflammatory effect of HIF-1α in CME.

TLR4 is the first TLR-associated protein to be discovered and exhibits the highest expression in the heart. At external stimuli, the body firstly activates the innate immune response and TLR4 expression, promotes the acquired immune response, and induces NF-κB activation through its dependent linker protein MyD88 and signal transduction pathway (Zhang et al. 2017a). Through the activation of TLR4 receptors, some endogenous ligands activate NF-κB. Wherefore, pro-inflammatory factors will be released, e.g. IL-1β, and TNF-α (O'Neill & Bowie 2007), which further activate NF-κB, causing activation of NLRP3 inflammatory bodies, initial amplification

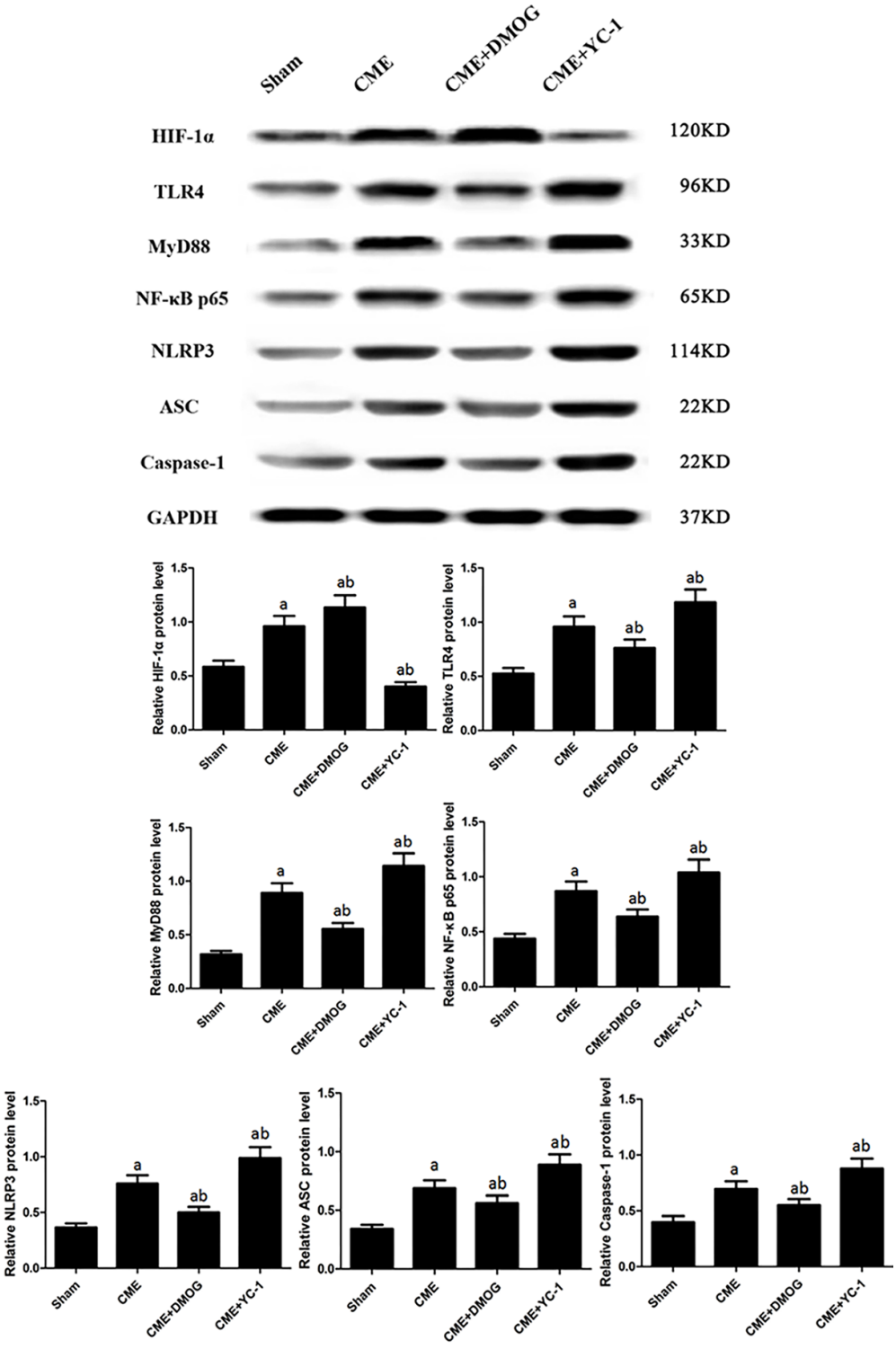


**Figure 4.** Effects of HIF-1α on TLR4/MyD88/NF-κB signaling and NLRP3 inflammasome pathway. HIF-1α expression was decreased, and the expression of TLR4, MyD88, NF-κB p65, NLRP3, ASC and Caspase-1 was increased following coronary microembolization (CME). DMOG reversed the expression of CME on the expression of these proteins, whereas YC-1 aggravates these effects.[a]*P*<0.05 in comparison to sham group; [b]*P*<0.05 in comparison to CME group. n = 10.

of the inflammatory signal, and triggering an inflammatory cascade of chains (Zhang et al. 2017b). In a previous study, we found that, involvement of CME in the myocardium inflammatory response significantly activated the TLR4/MyD88/NF-κB signaling pathway, causing a reduction in cardiac function in rats and consequently leading to myocardial injury. Additionally, TLR4/MyD88/NF-κB was distinctly inhibited when the TLR4-specific inhibitor TAK-242 was used. In addition, the NLRP3 inflammatory body activation was decreased, and expression levels of inflammatory elements, e.g. IL-18, TNF-α, and IL-1β were also decreased, which could improve cardiac functions through significantly reducing CME-induced myocardial injuries (Su et al. 2018b). This work demonstrates that stable expression of HIF-1α can inhibit the TLR4/MyD88/NF-κB signaling pathway, as well as the NLRP3 inflammasome pathway. These findings also verify that HIF-1α can protect CME-induced myocardial inflammatory injury.

Our study has these deficiencies: Firstly a plastic microsphere is adopted as microembolic agent for CME modeling. This material could cause microvascular embolism though, it does not exhibit biological properties, e.g. inflammation, chemotaxis, vasoactive activity, and thrombus activity. Moreover, since a number of factors are involved in clinical microvascular embolization, e.g. white blood cells, platelets, red blood cells, and components of atherosclerotic plaques, the modeling in this work cannot identically represent CME caused by clinical plaque rupture.

As a summary, this work suggests that high expression of HIF-1α exhibits a protective effect on CME-induced myocardial injury, which can perhaps be explained by the fact that TLR4/MyD88/NF-κB signaling pathway and NLRP3 inflammasome pathway are inhibited, thereby reducing myocardial inflammatory injury. Therefore, increasing HIF-1α expression in myocardial tissue is expected to become a new development target in prevention and treatment of CME-induced myocardial injury.

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**QUAN-FANG CHEN**[1]
http://orcid.org/0000-0003-1862-4551

**WEI WANG**[2]
http://orcid.org/0000-0003-1613-7717

**ZHOU HUANG**[2]
http://orcid.org/0000-0001-9385-0597

**DONG-LING HUANG**[2]
http://orcid.org/0000-0003-1587-6825

[1]Institute of Respiratory Disease, the First Affiliated Hospital, Guangxi Medical University, 6 Shuangyong Road, Nanning 530021, Guangxi, People's Republic of China

[2]Department of Emergency, the First Affiliated Hospital, Guangxi Medical University, 6 Shuangyong Road, Nanning 530021, Guangxi, People's Republic of China

Correspondence to: **Wei Wang**
*E-mail: drweiwang@yeah.net*

## Author contributions

W.W designed the research. Q.F.C and W.W carried out the experiments. Z.H and D.L.H analysed the data. Q.F.C wrote the manuscript. All authors read and approved the final manuscript.