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Downregulation of interferon-induced protein with tetratricopeptide repeats 3 relieves the inflammatory response and myocardial fibrosis of mice with myocardial infarction and improves their cardiac function

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Abstract: Myocardial infarction (MI) is a common cardiovascular disease with high morbidity and mortality. In this study, we explored the role of interferon-induced protein with tetratricopeptide repeats 3 (IFIT3) in MI. MI was induced by ligation of the left anterior descending coronary artery. Lentivirus-mediated RNA interference of IFIT3 expression was performed by tail vein injection 72 h before MI modeling. Cardiac injury indexes and inflammatory response were examined 3 days after MI. Cardiac function indexes, infarct size, and cardiac fibrosis were assessed 4 weeks after MI. IFIT3 expression was upregulated in myocardial tissues at both 3 days and 4 weeks after MI. Knockdown of IFIT3 significantly relieved the myocardial injury, as evidenced by the decrease in serum levels of cTnI and CK-MB. In addition, IFIT3 knockdown significantly reduced the number of $CD68^+$ macrophages and the levels of interleukin-1β, interleukin-6, and tumor necrosis factor-α, indicating that the inflammatory response was relieved. Moreover, IFIT3 silencing also significantly improved cardiac function and reduced infarct size, myocardial fibrosis, and collagen content in mice with MI. Mechanically, the present study showed that the activation of the mitogen-activated protein kinase (MAPK) pathway was observed in myocardial tissues of MI mice, which was blocked by IFIT3 knockdown, as indicated by the decreased phosphorylation of JNK, p-38, and ERK. Collectively, our results revealed the role of IFIT3 in the inflammatory response and myocardial fibrosis after MI, indicating that IFIT3 might be a potential target for MI treatment.

Key words: fibrosis, inflammation, interferon-induced protein with tetratricopeptide repeats 3 (IFIT3), mitogen-activated protein kinase (MAPK) pathway, myocardial infarction

Introduction

Myocardial infarction (MI) is the cardiovascular disease with the highest morbidity and mortality worldwide [1]. It is characterized by ventricular damage and impaired cardiac function caused by prolonged ischemia and myocardial hypoxia [2]. Previous studies showed that the inflammatory response and cardiac fibrosis participated in the pathophysiological process after MI [3]. Therefore, exploring the potential targets that regulate the inflammatory response and cardiac fibrosis may provide new ideas for the clinical treatment of MI.

Interferon-induced protein with tetratricopeptide repeats 3 (IFIT3) belongs to the family of interferon-stimulated genes (ISGs), which are involved in various biological functions, including innate immunity, antivi-

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ral immune response, and inflammatory response [4]. In the past decade, the understanding of the role and underlying mechanism of IFIT3 has been limited to the antiviral immune response and innate immunity [5, 6]. Recently, it was found that IFIT3 participated in the progression and metastasis of some types of cancer [7–9]. In addition, Guan *et al.* reported that IFIT3 was upregulated in ischemic-reperfused liver tissues of liver transplant patients, and downregulation of IFIT3 ameliorated the hepatic ischemia-reperfusion injury and suppressed the release of inflammatory cytokines [10], indicating the potential role of IFIT3 in ischemic diseases.

Moreover, a study based on transcriptional profile analysis showed that upregulated IFIT3 expression was observed in human ischemic cardiac hypertrophy and MI animal models [11]. Furthermore, RNA sequencing using blood samples from patients with MI and normal controls showed that IFIT3 was upregulated in the MI patients and might be potentially relevant to the pathology of MI [12]. However, the function of IFIT3 in MI has not been reported yet.

According to previous studies, the activation of mitogen-activated protein kinase (MAPK) activities was observed in animal models of MI [13, 14]. Suppression of this pathway was reported to have a protective effect on MI [15–17]. In pancreatic cancer cells, IFIT3 showed binding to c-Jun N-terminal kinase (JNK) [18], which belonged to the MAPK family and was involved in the impaired cardiomyocyte contractility in a post-MI model of cardiac dysfunction [19]. However, the correlation between IFIT3 and the MAPK pathway in MI has not been studied yet.

Therefore, in the present study, we mainly focused on the role and potential mechanism of IFIT3 in MI, hoping the findings could provide new evidence for the potential clinical application of IFIT3 in MI treatment.

Materials and Methods

Animals and MI model

This study was approved by Tangshan Gongren Hospital. The animal experimental procedures were carried out in strict accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The mouse model of MI was established by ligation of the left anterior descending coronary artery (LAD) in 8-week-old C57BL/6 male mice as described previously [20, 21]. Model establishment was identified by the rapid formation of a pale region on the left ventricle. Sham-operated mice underwent identical operations without ligating the coronary artery. Seventy-two hours before MI modeling, the mice received 2×10^7 transducing units of IFIT3 shRNA lentivirus (LV-shIFIT3) or control lentivirus (LV-shNC) by tail vein injection. The mice were sacrificed at 3 days or 4 weeks after MI, and the serum and tissue samples were harvested for further analysis. The target sequences of *IFIT3* shRNA and NC shRNA were as follows: 5'-GGAAGUAUGUCCAGUCAUAUG-3' (*IFIT3* shRNA); 5'-UUCUCCGAACGUGUCACGU-3' (NC shRNA). The Tet-pLKO-Puro lentiviral plasmids were purchased from Fenghui Biotechnology Co., Ltd. (China). The possibility of *IFIT3* shRNA targeting other members of the IFIT family has been ruled out (Supplementary Figs. 1A and B).

ELISA

The serum levels of cardiac troponin-I (cTnI) and creatine kinase-MB (CK-MB) were measured using a mouse cTnI ELISA kit (EM1466, FineTest, Wuhan, China) and mouse CK-MB ELISA kit (EM0929, FineTest) according to the manufacturer's instructions.

Echocardiographic assessment

Echocardiography was performed 4 weeks after MI modeling. The left ventricular end-diastolic diameter (LVIDd), the left ventricular end-systolic diameter (LVIDs), the ejection fraction (EF), and the fractional shortening (FS) were recorded to assess the cardiac function. Optical density (OD) values were analyzed by microplate reader (Biotek, Winooski, VT, USA) at a wavelength of 450 nm.

Histological analysis and immunofluorescence staining

Haematoxylin and eosin (HE) staining was used for the histopathological analysis of heart tissues. Masson staining was performed to assess myocardial fibrosis. Images were captured at 200× magnification using a microscope (Olympus, Tokyo, Japan). To observe the macrophages, immunofluorescence staining was performed using an antibody against CD68 (1:200; A13286, ABclonal, Wuhan, China) at 4°C overnight. Then the sections were incubated with a Cy3-linked goat anti-rabbit antibody (1:200; A0516, Beyotime, Shanghai, China) for one hour at room temperature. Afterward, the samples were stained with 4',6-diamidino-2-phenylindole (DAPI, Beyotime). Images were captured at 400× magnification using a fluorescence microscope (Olympus). Staining with 2,3,5-Triphenylte-tetrazolium chloride (TTC) was performed for the determination of the infarct size. The normal cardiac tissues were red while the MI area was pale. The percentage of infarct size was

calculated.

Western blot

Protein lysates were harvested from heart tissues. The proteins were separated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene difluoride (PVDF, MilliporeSigma, Burlington, MA, USA) membranes. After being blocked with 5% non-at milk, the membranes were incubated with the following primary antibodies: anti-IFIT3 (1:1,000; A3924, ABclonal), anti-JNK (1:1,000; AF6318, Affinity, Changzhou, China), anti-p-JNK (1:1,000; AF3318, Affinity), p38 (1:1,000; AF6456, Affinity), p-p38 (1:1,000; AF4001, Affinity), ERK (1:1,000; AF0155, Affinity), p-ERK (1:1,000; AF1015, Affinity), collagen I (1:1,000; AF0134, Affinity), collagen III (1:1,000; AF0136, Affinity), α-SMA (1:1,000; AF1032, Affinity), and anti-β-actin (1:1,000; sc-47778, Santa Cruz Biotechnology, Dallas, TX, USA) at 4°C overnight. Next, the membranes were incubated with horseradish peroxidase (HRP) goat anti-rabbit IgG and HRP goat anti-mouse IgG (1:5,000; A0208/A0216, Beyotime) at 37°C for 45 min. Finally, the protein bands were visualized by using enhanced chemiluminescence liquid (ECL, Beyotime), and the OD values were analyzed by a Gel-Pro Analyzer (Liuyi, Beijing, China).

Quantitative real-time PCR (qRT-PCR)

Total RNA was isolated from heart tissue samples using TRIpure (BioTeke, Wuxi, China) according to the manufacturer's instructions. Next, RNAs were reverse transcribed to cDNAs using the Super M-MLV reverse transcriptase and RNase inhibitor (BioTeke, Wuxi, China). qRT-PCR was performed using 2×Taq PCR MasterMix and SYBR Green (Solarbio, Beijing, China) in an Exicycler 96 PCR instrument (Bioneer, Daejeon, South Korea). The following primers were utilized to detect the indicated gene transcripts: IFIT3 forward, 5'-ATGGCAGAACTGAGACGAT-3'; IFIT3 reverse, 5'-GTGGTACTCCTGGAGGTTG-3'; IL-1β forward, 5'-CTCAACTGTGAAATGCCACC-3'; IL-1β reverse, 5'-GAGTGATACTGCCTGCCTGA-3'; IL-6 forward, 5'-ATGGCAATTCTGATTGTATG-3'; IL-6 reverse, 5'-GACTCTGGCTTTGTCTTTCT-3'; TNF-α forward, 5'-CAGGCGGTGCCTATGTCTCA-3', TNF-α reverse, 5'-GCTCCTCCACTTGGTGGTTT-3'; β-actin forward, 5'-CTGTGCCCATCTACGAGGGCTAT-3', β-actin reverse, 5'-TTTGATGTCACGCACGATTTCC-3'. The relative gene expression was measured according to the $2^{-\Delta\Delta Ct}$ method. β-actin was considered as the internal control.

Statistical analysis

The data are represented as the mean ± SD. Statistical analysis was performed using the GraphPad Prism software (version 8.0). One-way ANOVA and Tukey's multiple comparisons test were used to compare data differences among groups. $P<0.05$ was considered statistically significant.

Results

IFIT3 expression was elevated in myocardial tissues of mice at both 3 days and 4 weeks after MI

To investigate the association of IFIT3 expression with MI, the mRNA and protein levels of IFIT3 in myocardial tissues were examined using qRT-PCR and western blot. We found that *IFIT3* expression was significantly increased in heart tissues at both 3 days (Figs. 1A and B) and 4 weeks (Figs. 1C and D) after MI compared with sham-operated animals. Moreover, in heart tissues at 4 weeks after MI, the protein level of IFIT3 in the infarct area was significantly higher than that of the non-infarcted area (Supplementary Fig. 1C). However, IFIT3 RNA-interfering lentivirus markedly decreased the level of IFIT3 in myocardial tissues of mice with MI (Figs. 1A–D).

IFIT3 knockdown relieved myocardial injury and inflammatory response

To evaluate the role of IFIT3 in myocardial injury, the serum levels of cTnI and CK-MB were examined. As shown in Figs. 2A and B, knockdown of IFIT3 dramatically alleviated the myocardial injury, as evidenced by the decreased serum levels of cTnI and CK-MB 3 days after MI. HE results showed that knockdown of IFIT3 significantly relieved the myocardial injury and inflammatory infiltration in heart tissues (Fig. 2C). In addition, IFIT3 knockdown markedly reduced the amount of CD68-positive macrophages (Fig. 2D) and levels of inflammatory cytokines (IL-1β, IL-6, and TNF-α; Fig. 2E) in myocardial tissues 3 days after MI. Taken together, these results indicated that knockdown of IFIT3 relieved the myocardial injury and inflammatory response 3 days after MI.

IFIT3 knockdown improved cardiac function and reduced the infarct size

To further investigate the effects of IFIT3 on cardiac function after MI, the cardiac function indexes were measured by echocardiography 4 weeks after MI. As shown in Figs. 3A–D, the impaired cardiac function was observed in MI mice, while knockdown of IFIT3 dramatically improved the cardiac function, as evidenced

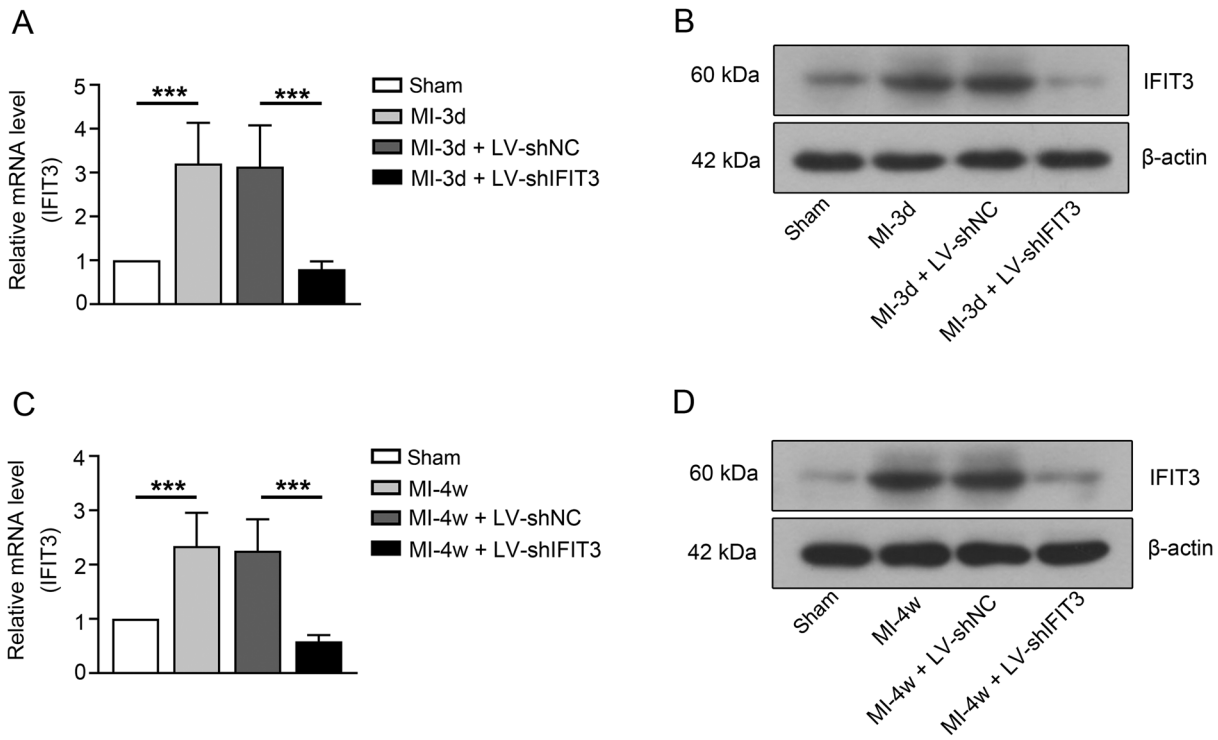

Fig. 1. Elevated interferon-induced protein with tetratricopeptide repeats 3 (IFIT3) expression in myocardial tissues after myocardial infarction (MI) was decreased by lentivirus-mediated RNA interference of IFIT3 expression. quantitative real-time PCR (qRT-PCR) and western blot were performed to examine IFIT3 mRNA and protein levels at 3 days (A and B) and 4 weeks (C and D) after MI. β-actin served as the internal control. The data are expressed as the mean ± SD (n=6 per group). ***P<0.001.

by the decrease in LVIDd and LVIDs and the increase in EF and FS. In addition, TTC staining showed that IFIT3 knockdown markedly reduced the infarct size (Figs. 3E and F). These results suggested the protective effects of IFIT3 knockdown on the heart after MI.

IFIT3 knockdown reduced myocardial fibrosis 4 weeks after MI

As shown by the Masson staining in Fig. 4A, the collagen fibers (blue staining) were diffusely distributed in myocardial tissues 4 weeks after MI, while IFIT3 knockdown significantly decreased the content of collagen. Western blot analysis further proved that knockdown of IFIT3 markedly reduced the expression levels of collagen I, collagen III, and α-SMA in myocardial tissues of MI mice (Fig. 4B). These results indicated that IFIT3 knockdown reduced myocardial fibrosis 4 weeks after MI.

IFIT3 knockdown inhibited activation of the MAPK pathway

To further explore the underlying mechanism of the role of IFIT3 in MI, we measured the activation of the MAPK pathway in heart tissues of mice by using western blot analysis. We found that the MAPK pathway was significantly activated in myocardial tissues of MI mice, while knockdown of IFIT3 inhibited the activation, as evidenced by the decreased phosphorylation of JNK, p-38, and ERK (Fig. 5), suggesting that the MAPK pathway might be involved in the role of IFIT3 in MI.

Discussion

Our work demonstrated for the first time that IFIT3 exhibited an important role in the pathophysiological process after MI, particularly in the inflammatory response and myocardial fibrosis. We found that knockdown of IFIT3 relieved the inflammatory response and fibrosis in myocardial tissues and improved the cardiac function of mice with MI, and blockade of the MAPK pathway might be involved in these beneficial effects.

In our work, IFIT3 expression was significantly upregulated in myocardial tissues after MI. Hypoxia-reoxygenation is the cause of MI and induces myocardial injury. Previous studies reported that in the hypoxia/reoxygenation (HR) model, the expression of IFIT3 in macrophages was significantly increased [10]. In this study, we observed significant macrophage infiltration in the heart tissues of mice with MI. Therefore, the high expression of IFIT3 in macrophages may partly explain

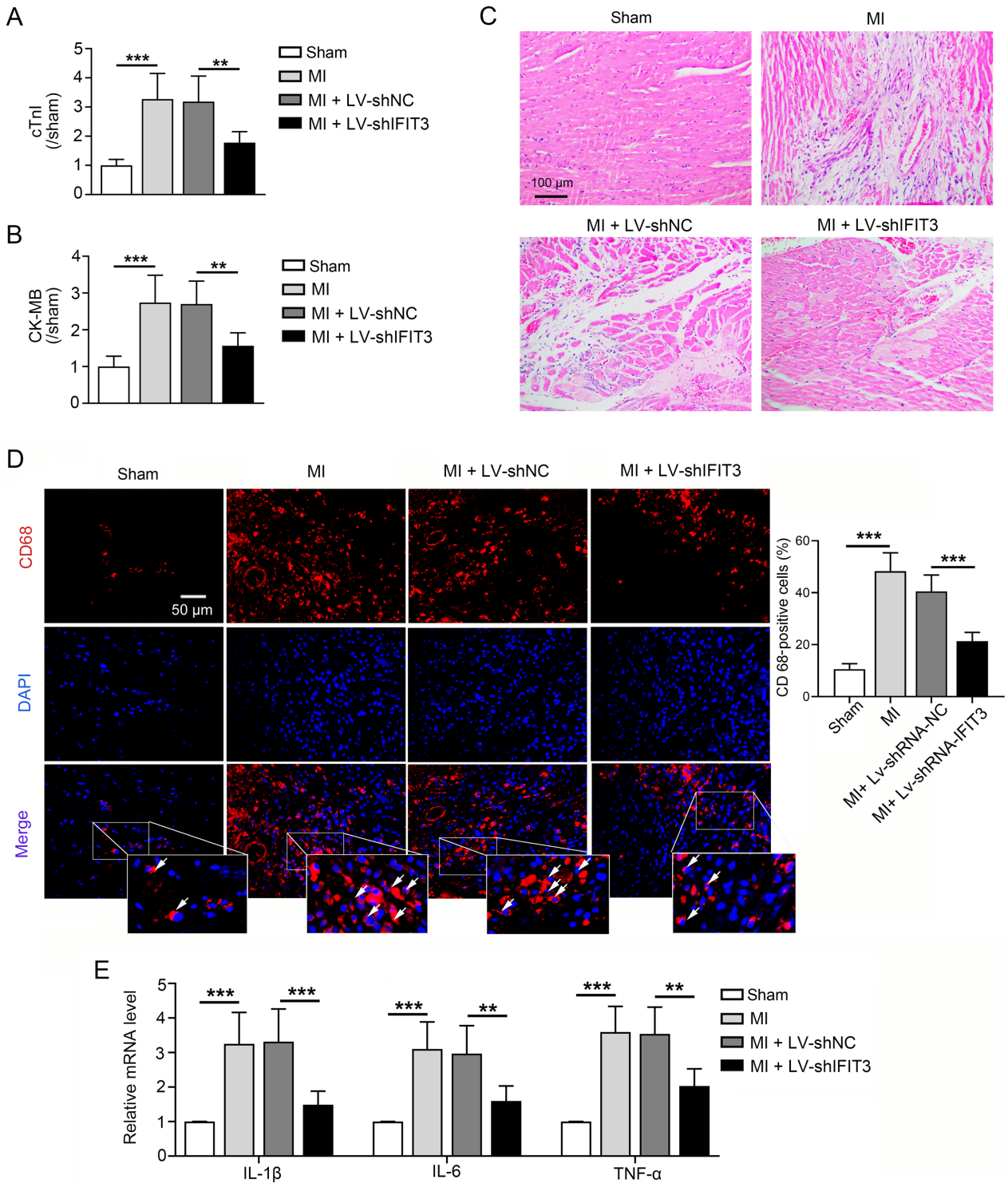

Fig. 2. Interferon-induced protein with tetratricopeptide repeats 3 (IFIT3) knockdown alleviated cardiac injury and the inflammatory response 3 days after myocardial infarction (MI). (A, B) The levels of cTnI and CK-MB in serum were detected using commercial ELISA kits. (C) Representative images of myocardial tissues stained with HE (magnification ×200, scale bar=100 μm). (D) Representative fluorescent immunostaining images of $CD68^+$ macrophages and quantification of CD68-positive cells (magnification ×400, scale bar=50 μm). (E) Relative mRNA levels of inflammatory cytokines were determined using quantitative real-time PCR (qRT-PCR). β-actin served as the internal control. The data are expressed as the mean ± SD (n=6 per group). **P<0.01; ***P<0.001.

the overexpression of IFIT3 in the myocardial tissues of mice with MI. However, whether IFIT3 is dysregulated in other cells in myocardial tissues needs to be further explored in future studies. Additionally, the dysregulation of gene expression is affected by many factors, such as the methylation of DNA, transcription and translation regulation, and protein interaction. It has been reported that NF-κB p65 could directly bind to the IFIT3 pro-

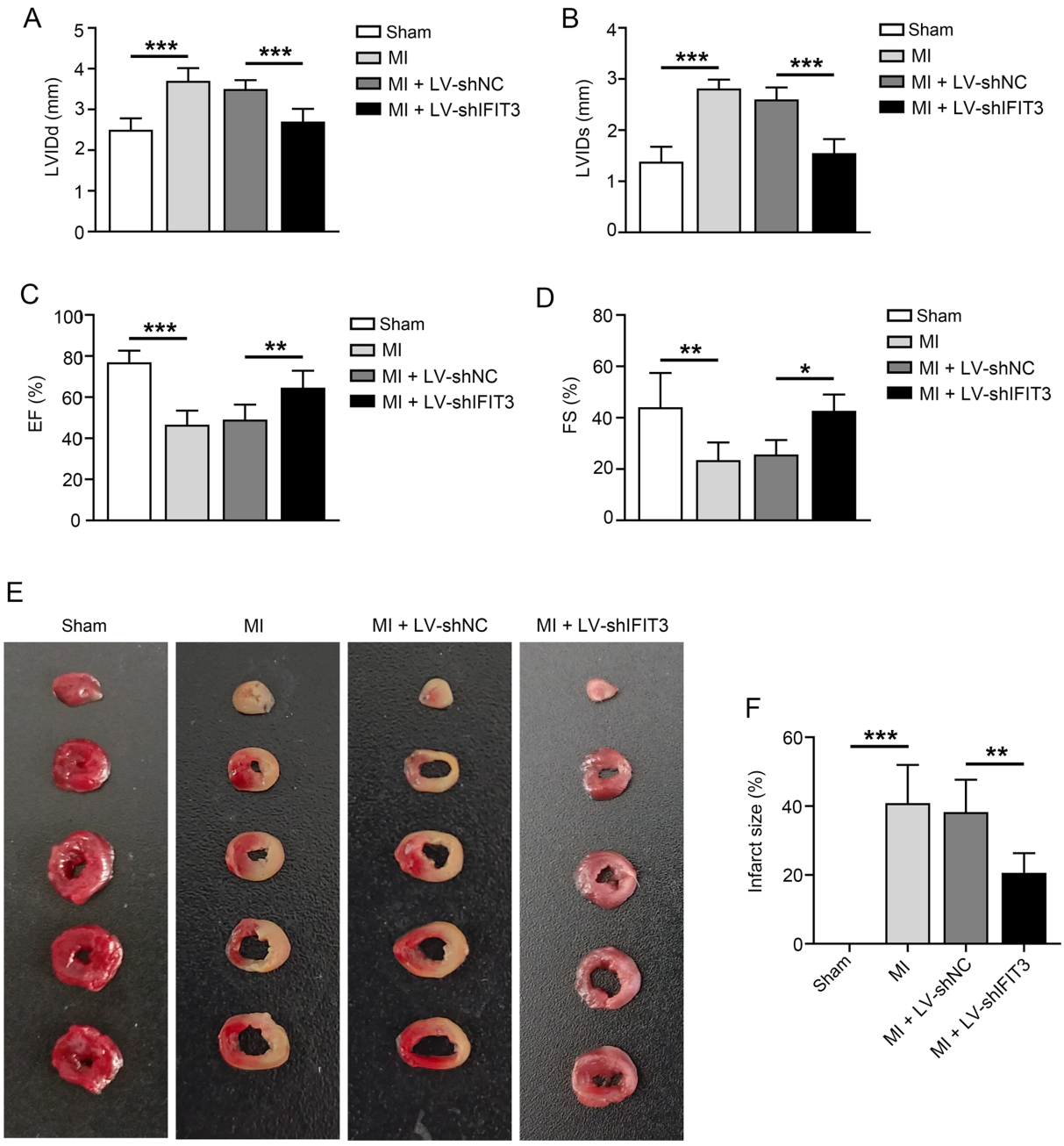

Fig. 3. Interferon-induced protein with tetratricopeptide repeats 3 (IFIT3) knockdown improved cardiac function 4 weeks after myocardial infarction (MI). (A–D) Echocardiography was used to measure the cardiac function indexes, including the left ventricular end-diastolic diameter (LVIDd), the left ventricular end-systolic diameter (LVIDs), the ejection fraction (EF), and the fractional shortening (FS). (E, F) Representative images of 2,3,5-Triphenylte-tetrazolium chloride (TTC) staining and quantification of the infarct size. The data are expressed as the mean ± SD (n=6 per group). **P*<0.05; ***P*<0.01; ****P*<0.001.

moter to drive IFIT3 transcription [22]. Furthermore, another study reported a significant increase in the nuclear expression of NF-κB p65 in the myocardial tissues of rats with MI [23]. Additionally, IFIT3 has been reported to interact with signal transducer and activator of transcription 1 (STAT1) in pancreatic cancer cells, and STAT1 inhibition significantly reduced IFIT3 expression [18]. Studies have also shown a significant elevation of STAT1 expression in hypoxia-induced cardiomyocytes, and STAT1 knockout relieved cardiac damage MI mice [24, 25]. Therefore, the dysregulation of IFIT3 expression in the myocardial tissues of mice with MI may be regulated by transcription factors, such as NF-κB p65, or interacting proteins, such as STAT1.

Elevated cTnI and CK-MB levels have been widely applied in the clinical diagnosis of cardiac injury and have served as major early markers reflecting myocardial injury in laboratory animal models of MI [26–28].

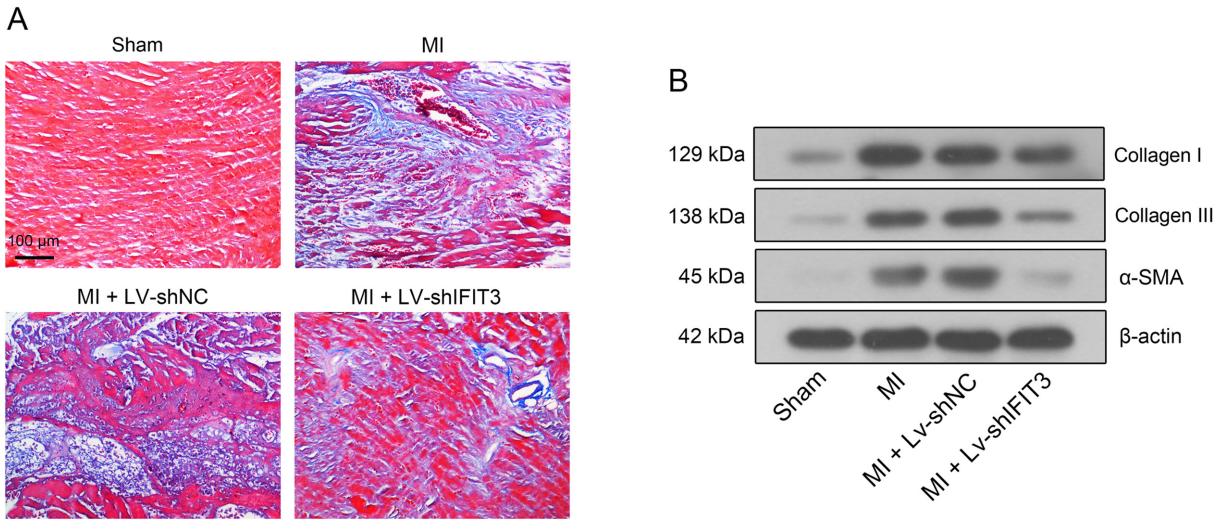

Fig. 4. Interferon-induced protein with tetratricopeptide repeats 3 (IFIT3) knockdown reduced myocardial fibrosis 4 weeks after myocardial infarction (MI). (A) Representative images of myocardial tissues with Masson staining (magnification ×200, scale bar=100 μm). Blue staining indicates the collagen. (B) Western blot analysis of collagen I, collagen III, and α-SMA in myocardial tissues. β-actin served as the loading control.

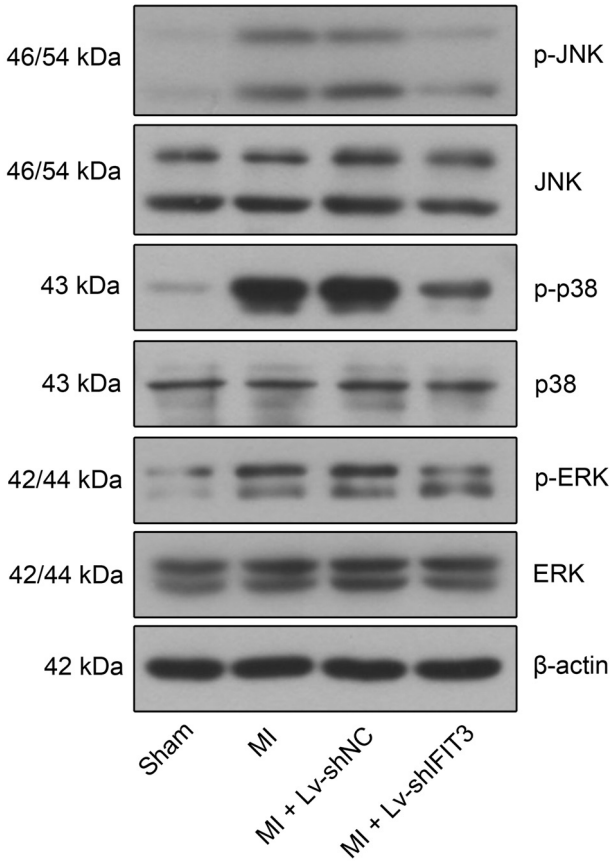

Fig. 5. Interferon-induced protein with tetratricopeptide repeats 3 (IFIT3) knockdown inhibited the activation of the mitogen-activated protein kinase (MAPK) pathway 3 days after myocardial infarction (MI). The expression levels of p-JNK, c-Jun N-terminal kinase (JNK), p-p38, p-38, p-ERK, and ERK were determined using western blot analysis. β-actin served as the loading control.

In addition, the serum level of cTnI has a prognostic value for infarct size, as a significant correlation between cTnI level and the infarct expansion index has been observed [29]. The present study proved that the serum levels of cTnI and CK-MB were significantly increased 3 days after MI, indicating that the MI model was well established. Furthermore, IFTI3 knockdown significantly decreased the elevated cTnI and CK-MB levels 3 days after MI, indicating that IFIT3 might relieve the cardiac injury after MI.

Since adult mammalian cardiomyocytes cannot regenerate after MI, the injured tissues and necrotic cardiomyocytes release signals that activate innate immune pathways and lead to the inflammatory response [30, 31]. However, excessive inflammation could be harmful. According to previous studies, the continued upregulation of inflammation indicators (such as high-sensitivity C-reactive protein [32] and IL-6 [33]) in plasma of patients with MI predicted worse outcomes. Some macrophages have also been reported to damage the heart function and lead to a poor prognosis after MI [34]. Consistently, the anti-inflammatory therapy was reported to have beneficial effects after MI. For example, a randomized controlled trial showed that anti-inflammatory therapy with Canakinumab, a monoclonal antibody inhibiting IL-1β, reduced the risk of the composite endpoint of death from MI [35]. Therefore, regulation of the inflammatory response was of great significance in the treatment of MI.

Though most reports have mainly focused on the antiviral effect of type I interferons and ISGs, emerging evidence suggests that they might also play a role in the inflammatory response after MI. For example, Sc-RNA

seq detection of white blood cells in the infarct area of the acute phase after MI in mice showed that a group of macrophages was regulated by interferon regulator factor 3 (IRF3), and completely knockout of the gene encoding IRF3 or type I interferon receptor significantly improved the survival rate and myocardial repair of mice after MI [36]. This indicated that the repair and improvement of heart function after MI could be promoted by regulating the function and number of macrophages, and type I interferons might be involved in the regulation of macrophages. In our work, knockdown of IFIT3 dramatically alleviated the infiltration of immune cells, reduced the number of macrophages and the inflammatory cytokine levels, and improved cardiac function. These results implied that IFIT3 was critical in the inflammatory response after MI and that regulation of inflammatory response might help improve cardiac function after MI.

After the resolution of inflammation, myofibroblast proliferation, collagen deposition, scar formation, and neovascularization follow, thereby resulting in wound healing [37]. As reported previously, under the mediation of macrophages, myocardial fibroblasts proliferated and migrated to the infarct area to produce collagen I and collagen III [38, 39]. However, myocardial fibrosis could damage the systolic and diastolic function of the heart and contribute to the adverse ventricular remodeling, which is considered a poor prognosis after MI. Hence, myocardial fibrosis treatment to slow down or reduce the adverse ventricular remodeling is of great clinical significance [2, 39]. In our work, IFIT3 knockdown markedly reduced the content of collagen in infarcted hearts and decreased the level of collagen I, collagen III, and α-SMA 4 weeks after MI, which might contribute to the preservation of cardiac function. In agreement with our findings, reduced myocardial fibrosis was found to be involved in the function of several potential therapeutic agents after MI [40–42].

In the present work, we revealed that IFIT3 knockdown significantly inhibited the activation of the MAPK pathway in MI mice. It has been shown that overexpression of IFIT3 increases the phosphorylation level of AKT in oral squamous cell carcinoma cells [7]. Phosphorylated AKT is an upstream regulator of the MAPK pathway and activates the MAPK pathway [43]. Furthermore, the knockdown of IFIT3 reduces the phosphorylation level of STAT1 [10]. In hepatocellular carcinoma, STAT1 positively regulates the MAPK pathway [44]. Moreover, IFIT3 has been reported to interact with JNK protein in pancreatic cancer [18]. Therefore, the regulation of the MAPK pathway by IFIT3 may be mediated by AKT, STAT1, or some other mediator, or IFIT3 may directly regulate the MAPK pathway. The function of the MAPK pathway in the pathophysiological process after MI has been reported by several studies. For instance, in MI models, inhibition of the MAPK pathway was reported to improve MI [14, 45, 46], including inhibition of the release of pro-inflammatory factors, macrophage infiltration, and myocardial fibrosis. Altogether, this study demonstrates that IFIT3 may affect inflammation and myocardial fibrosis in myocardial tissues of mice with MI by activating the MAPK pathway. Moreover, downregulation of IFIT3 was reported to inhibit the phosphorylation of STAT2 and protected the liver from ischemia-reperfusion injury [10]. Therefore, whether other pathways are involved in the role of IFIT3 in MI needs to be further explored.

Conclusion

Collectively, IFIT3 might exhibit a critical role in MI. Knockdown of IFIT3 improved cardiac function, alleviated myocardial injury and the inflammatory response and reduced myocardial fibrosis, which might be associated with the MAPK pathway. This finding suggested that IFTI3 might be a promising target for the prevention and treatment of MI.

Sources of Funding

None.

Conflict of Interest

The authors declare that they have no competing interests.

Author Contribution

Jianhua Sun and Xiaoming Shang conceived and designed the experiments and wrote the paper. Qi Zhang and Xiaokun Liu performed the experiments and analyzed the data.

Acknowledgments

None.

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