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The impact of complement C1q/tumor necrosis factor-related protein 6-mediated cardiomyocyte pyroptosis on myocardial fibrosis in rats with myocardial infarction.

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Keywords: Myocardial Infarction; Pyroptosis; Fibrosis; Inflammatory Response.

Abstract. Complement C1q/tumor necrosis factor-related protein 6 (CTRP6) has anti-inflammatory and metabolic regulatory properties, but its role in ameliorating post-myocardial infarction (MI) myocardial fibrosis via pyroptosis inhibition is unclear. This study investigated whether CTRP6 improves post-MI myocardial fibrosis and cardiac dysfunction by suppressing cardiomyocyte pyroptosis through the NLRP3/caspase-1/GSDMD pathway. Thirty Sprague-Dawley rats were randomized to sham-operated (Sham), MI model (MI), or CTRP6-treated (MI+CTRP6) groups. MI was induced by left anterior descending coronary artery ligation; MI+CTRP6 rats received daily subcutaneous recombinant CTRP6 (0.2 mg/kg) from day 3 post-surgery for 28 days. Cardiac function, fibrosis markers, pyroptosis-related proteins, and inflammatory cytokines were assessed via Western blot, Masson staining, and ELISA. CTRP6 expression was lower in MI vs. Sham ($p<0.05$). CTRP6 treatment restored its expression, reduced fibrosis markers and collagen deposition, and improved cardiac function ($p<0.05$). It also downregulated pro-inflammatory cytokines and increased anti-inflammatory cytokines ($p<0.05$). In other words, exogenous CTRP6 ameliorated fibrosis and cardiac function by directly inhibiting the NLRP3/caspase-1/GSDMD pyroptosis pathway.

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Impacto de la piroptosis de cardiomiocitos mediada por CTRP6 en la fibrosis miocárdica en ratas con infarto de miocardio.

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Palabras clave: Infarto de Miocardio; Piroptosis; fibrosis; Respuesta Inflamatoria.

Resumen. La proteína 6 relacionada con el factor de necrosis del complemento C1q/tumor (CTRP6) tiene propiedades antiinflamatorias y reguladoras metabólicas, pero su papel en la reducción de la fibrosis del miocardio postinfarto (MI) mediante la inhibición de la piroptosis no está claro. Este estudio investigó si el CTRP6 mejora la fibrosis miocárdica post-MI y la disfunción cardíaca al suprimir la piroptosis de cardiomiocitos mediante la vía NLRP3/caspasa-1/GSDMD. Treinta ratas Sprague-Dawley se asignaron aleatoriamente a grupos operados con simulación (Sham), modelo MI (MI) o tratados con CTRP6 (MI + CTRP6). El MI fue inducido por ligadura de la arteria coronaria descendente anterior izquierda. Las ratas MI+CTRP6 recibieron CTRP6 recombinante por vía subcutánea diaria (0,2 mg/kg) a partir del día 3 tras la cirugía durante 28 días. La función cardíaca (ecocardiografía), los marcadores de fibrosis, las proteínas relacionadas con la piroptosis y las citocinas inflamatorias se evaluaron mediante transferencia Western, tinción de Masson y ELISA. La expresión de CTRP6 fue menor en MI que en Sham ($p<0,05$). El tratamiento con CTRP6 restableció su expresión, redujo los marcadores de fibrosis y de deposición de colágeno, y mejoró la función cardíaca ($p<0,05$). También disminuyó la regulación de las citocinas proinflamatorias y aumentó la regulación antiinflamatoria ($p<0,05$). El CTRP6 protege contra la fibrosis miocárdica post-MI inhibiendo la piroptosis de cardiomiocitos a través de la vía NLRP3/caspasa-1/GSDMD, reduciendo las citocinas proinflamatorias y la activación de fibroblastos.

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INTRODUCTION

Myocardial infarction (MI) represents one of the most life-threatening cardiovascular disorders globally, with its pathological hallmark being the ischemic necrosis of cardiomyocytes followed by progressive fibrosis, which ultimately culminates in heart failure and life-threatening arrhythmias [1]. Epidemiological data reveal a striking age-dependent incidence pattern, with MI affecting approximately 3.8% of the population below 60 years compared to 9.5% in individuals over 60 years [2]. While contemporary therapeutic strategies, including revascularization procedures and pharmacological interventions, have markedly enhanced acute-phase survival rates, the inexorable advancement of myocardial fibrosis continues to pose significant challenges to long-term patient outcomes and quality of life [3]. The scientific community has recently focused on elucidating the contributions of programmed cell death pathways to myocardial injury pathophysiology [4]. Among these, pyroptosis—a lytic form of cell death mediated by inflammasome activation—exacerbates local inflammatory responses and drives fibroblast activation

through the release of pro-inflammatory cytokines such as IL-1β and IL-18, potentially serving as a key trigger for myocardial fibrosis [5]. Despite these insights, the regulatory network of pyroptosis in MI and its molecular link with fibrosis remain incompletely elucidated.

Within the complement C1q/tumor necrosis factor-related protein (CTRP) family, CTRP6 has gained prominence as a multifunctional regulator, demonstrating simultaneous involvement in both glucolipid metabolism and inflammatory modulation, thereby positioning it as a molecule of particular interest in metabolic syndrome research [6]. Emerging evidence indicates that CTRP6 exerts protective effects against vascular endothelial inflammation by inhibiting the NF-κB signaling cascade and exhibits anti-fibrotic properties in the context of diabetic cardiomyopathy [7]. Notably, in myocardial ischemia-reperfusion (I/R) injury models, CTRP6 expression levels correlate positively with cardiomyocyte survival rates [8]. However, direct evidence on whether CTRP6 influences myocardial fibrosis by modulating pyroptosis remains lacking. The study by Liang et al.[9] established that serum CTRP6 levels were substantially diminished in I/R-injured rats and inversely associated with both pyroptosis markers (GSDMD-N and caspase-1) and the extent of collagen deposition, suggesting a potential role for CTRP6 in restraining fibrosis via pyroptosis inhibition. Nevertheless, the specific involvement of CTRP6 in MI pathophysiology has not yet been systematically investigated.

In this study, we present a novel conceptual framework that proposes a "CTRP6-pyroptosis-fibrosis" regulatory axis in MI. The primary objective is to delineate the molecular mechanisms by which CTRP6 attenuates cardiomyocyte pyroptosis by modulating the NLRP3/caspase-1/GSDMD signaling pathway, thereby mitigating fibroblast activation and pathological collagen accumulation. The findings are expected to yield two significant contributions: first, the identification of new therapeutic targets for combating post-MI fibrotic complications; and second, the establishment of a robust theoretical platform that supports the translational potential of CTRP6, moving it from its traditional recognition as a metabolic modulator to its emerging role as a cardiovascular protective agent.

MATERIALS AND METHODS

Animal subjects

A total of thirty male Sprague-Dawley (SD) rats, aged 4–6 weeks and weighing 200 ± 20 g, were obtained from Beijing Vitalstar Biotechnology Co., Ltd. (License No.: SCXK2023-0014). The animals were housed under standardized conditions, with free access to water, in a controlled environment (temperature: 20–25°C; relative humidity: 60–70%) under a 12-hour light/dark cycle. Following a one-week acclimatization period, the experiments were conducted in compliance with the 3Rs (Replacement, Reduction, Refinement) principles and were approved by the Institutional Animal Ethics Committee (No. 20210301002).

MI model establishment

The rats were randomly allocated into three groups (n=10 per group). In two of the groups, MI was surgically induced. Briefly, the rats were anesthetized, secured in a supine position, and intubated, after which mechanical ventilation was initiated. After thoracotomy, the heart was gently extruded, and the left anterior descending coronary artery was rapidly ligated approximately 2–3 mm distal to the aortic root, near the junction between the left auricle and the pulmonary artery cone, for MI modeling [10]. The MI model was considered successful if the left ventricular ejection fraction (LVEF) measured by Doppler echocardiography was <50%. The third group underwent an identical surgical procedure without left anterior descending ligation and served as the sham group. Among the two MI groups, one

received daily subcutaneous injections of recombinant human CTRP6 (0.2 mg/kg) starting three days post-MI induction and continuing for 28 consecutive days (CTRP6 group). The other MI group received an equivalent volume of saline and was designated the model group.

Evaluation of cardiac function

Upon completion of the treatment regimen, transthoracic echocardiography was performed on all animals using a high-resolution color Doppler ultrasound system equipped with a 15 MHz linear transducer. Key cardiac functional parameters, including LVEF, left ventricular fractional shortening (LVFS), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD), were recorded for comparative analysis.

Western blot analysis of myocardial protein expression

Following euthanasia, myocardial tissue samples were immediately collected, and total protein was extracted by homogenizing the tissues in a RIPA lysis buffer at a 1:5 ratio, followed by incubation at 4°C for 40 minutes. Protein concentrations were measured using the bicinchoninic acid (BCA) protein assay kit. Then, equal amounts of protein (30 μg per sample) were separated with 10% SDS-PAGE and transferred to polyvinylidene difluoride (PVDF) membranes using a wet transfer system. After blocking for two hours at room temperature, the membranes were incubated overnight at 4°C with primary antibodies (all diluted 1:1000 in blocking buffer): anti-CTRP6 (ab300583, Abcam), anti-Collagen III (ab7535, Abcam), anti-α-smooth muscle actin (α-SMA) (ab314895, Abcam), anti-transforming growth factor-β1 (TGF-β1) (ab315254, Abcam), anti-NOD-like receptor family pyrin domain containing 3 (NLRP3) (ab263899, Abcam), anti-cl-Caspase-1 (ab198447, Abcam), anti-gasdermin D (GSDMD) (ab219800, Abcam), anti-N terminal (NT)-GSDMD (ab215203, Abcam), anti-interleukin (IL)-1β (ab315084, Abcam), and GAPDH (ab8245, Abcam). Subsequently, the membranes were incubated with appropriate horseradish peroxidase (HRP)-conjugated secondary antibodies (goat anti-rabbit or goat anti-mouse IgG, 1:5000 dilution, ab308009, Abcam) for two hours at room temperature. Using enhanced chemiluminescence (ECL) detection reagents, protein bands were visualized and photographed. Finally, relative protein expression levels were quantified.

Histopathological examination of myocardial tissues

Cardiac tissues were fixed in 10% paraformaldehyde for 24 hours, then processed through a graded ethanol series for dehydration. After xylene clearing, tissues were embedded in paraffin and sectioned at 3-5 μm thickness. Subsequently, sections were stained with hematoxylin and eosin (H&E) and examined under a light microscope at 200× magnification to evaluate myocardial morphology (focusing on muscle fiber arrangement and ventricular wall thickness). For myocardial fibrosis assessment, tissue fixation and section preparation followed the same procedures as for H&E staining. The sections were then stained using a Masson's trichrome kit according to the manufacturer's instructions. Fibrotic changes in myocardial tissue were evaluated under light microscopy at 200× magnification, with collagen fibers appearing blue in the stained sections.

Measurement of serum inflammatory cytokines

Blood samples (3 mL) were obtained from the abdominal aorta into sterile tubes, and serum was separated by centrifugation. Serum levels of IL-1β (CSB-E08055r-IS), tumor necrosis factor-alpha (TNF-α) (CSB-E11987r), IL-6 (CSB-E04640r), IL-8 (CSB-E07451r), and IL-10 (CSB-E04595r) were measured using commercially available enzyme-linked immunosorbent assay (ELISA)

kits (Wuhan Huamei Biological Engineering Co., LTD.) according to the manufacturer's instructions.

Endpoints

The endpoints of this study included (1) a quantitative assessment of CTRP6 protein expression levels in myocardial tissues after MI, and (2) a comprehensive evaluation of CTRP6's therapeutic effects on myocardial fibrosis, histopathological damage, cardiac function, and pyroptosis.

Statistical analysis

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., USA). Continuous variables with normal distribution were presented as mean ± standard deviation ($\bar{x} \pm sd$). An independent-samples t-test was used to compare the two groups. For multiple-group comparisons, one-way repeated-measures analysis of variance (ANOVA) was employed, followed by Fisher's least significant difference (LSD) post hoc test for pairwise comparisons. A two-tailed p of less than 0.05 was considered statistically significant for all analyses.

RESULTS

MI model establishment and CTRP6 expression

All rats in the sham group survived. In both the CTRP6 and model groups, one rat died in each group, while the surviving rats successfully met the MI model criteria (LVEF <50%). Western blot analysis showed that CTRP6 protein expression in myocardial tissue was significantly lower in the model group than in the sham group ($p<0.001$), indicating downregulation of CTRP6 in MI (Fig. 1).

CTRP6 attenuates myocardial fibrosis and pathological damage in MI rats

Protein expression analysis showed that although CTRP6 levels in the CTRP6 group remained lower than those in the sham controls, they were significantly higher than in the model group ($p<0.001$), confirming successful CTRP6 upregulation through recombinant human CTRP6 administration. Additionally, the model group displayed markedly increased expression of fibrotic markers, including Collagen III, α-SMA, and TGF-β1, compared with the sham group ($p<0.01$). Importantly, CTRP6 treatment significantly reduced the expression of these fibrotic proteins compared with the model group ($p<0.01$), suggesting its potential to mitigate the progression of myocardial fibrosis. Histopathological examination with H&E staining showed well-organized myocardial fibers and intact tissue structure in the sham controls. In contrast, the model group exhibited characteristic pathological changes, such as disorganized myocardial fibers and ventricular wall thinning. CTRP6 treatment markedly alleviated these abnormalities, resulting in increased ventricular wall thickness and more

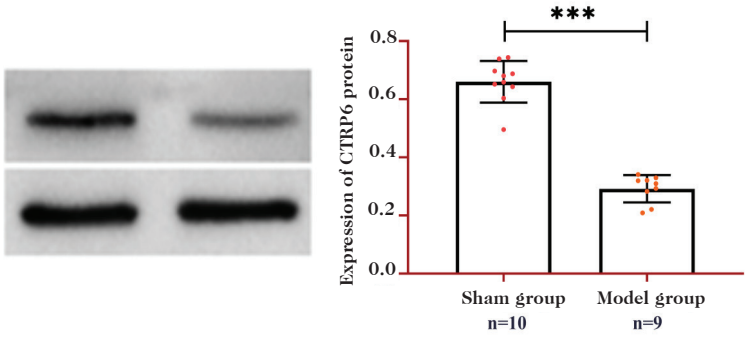

Fig. 1. CTRP6 protein expression in MI. An independent-samples t-test was used to compare groups (***$p<0.001$). CTRP6:complement C1q/tumor necrosis factor-related protein 6. MI: Myocardial infarction.

organized fiber alignment compared with untreated MI rats. Masson's trichrome staining supported these results, with the sham group showing minimal collagen deposition (indicated by blue staining). The model group exhibited extensive myocardial fibrosis, whereas CTRP6-treated animals showed significantly reduced collagen accumulation and better-preserved myocardial structure (Fig. 2).

CTRP6 ameliorates cardiac dysfunction in MI rats

The echocardiographic assessment revealed significant cardiac dysfunction in the MI model group compared to sham-operated controls. Specifically, the model group exhibited markedly reduced LVEF and LVFS, accompanied by increased LVEDD and LVESD ($p<0.05$). Notably, CTRP6 administration effectively attenuated these pathological changes, with treated animals demonstrating significantly improved LVEF and LVFS, along with reduced LVEDD and LVESD, compared with untreated MI rats ($p<0.05$; Fig. 3).

CTRP6 attenuates pyroptotic cell death in infarcted myocardium

Analysis of inflammatory mediators showed a strong pro-inflammatory state in the myocardial tissue of the model group, with significantly increased levels of IL-1β, TNF-α, IL-6,

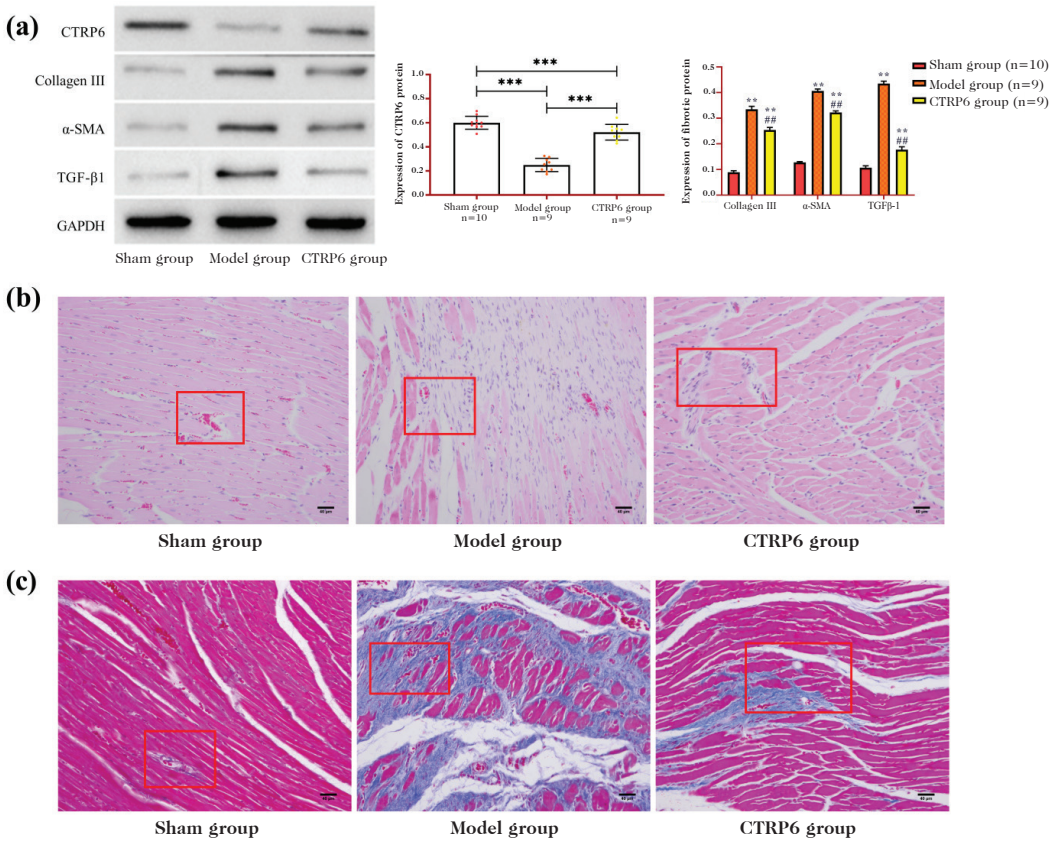

Fig. 2. Effect of CTRP6 on myocardial fibrosis and tissue damage in MI rats. (a) Measurement of myocardial fibrosis-related protein expression in MI rats treated with exogenous CTRP6. (b) Hematoxylin and eosin (H&E) staining of myocardial tissue (200×). (c) Masson staining of myocardial tissue (200×). Repeated-measures analysis of variance and LSD intra-group tests were used to compare multiple groups: ***$p<0.001$ compared with the sham group; **$p<0.01$ compared with the model group; ##$p<0.01$. Complement C1q/tumor necrosis factor-related protein 6 (CTRP6), α-smooth muscle actin (α-SMA), and transforming growth factor-β1 (TGF-β1). The portion of inflammatory cell infiltration is highlighted in the figure. MI: Myocardial infarction.

and IL-8, alongside decreased IL-10, compared to sham controls ($p<0.05$). CTRP6 treatment effectively adjusted this inflammatory imbalance, significantly reducing pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, and IL-8) while boosting anti-inflammatory IL-10 expression ($p<0.05$). Regarding pyroptosis-related proteins, western blot analysis revealed substantial upregulation of NLRP3, cleaved Caspase-1, GSDMD, NT-GSDMD, and IL-1β in both the model and CTRP6 groups compared to the sham group ($p<0.05$); however, their levels were lower in the CTRP6 group than in the control group ($p<0.05$). These findings suggest that CTRP6 suppresses myocardial pyroptosis in MI rats (Fig 4).

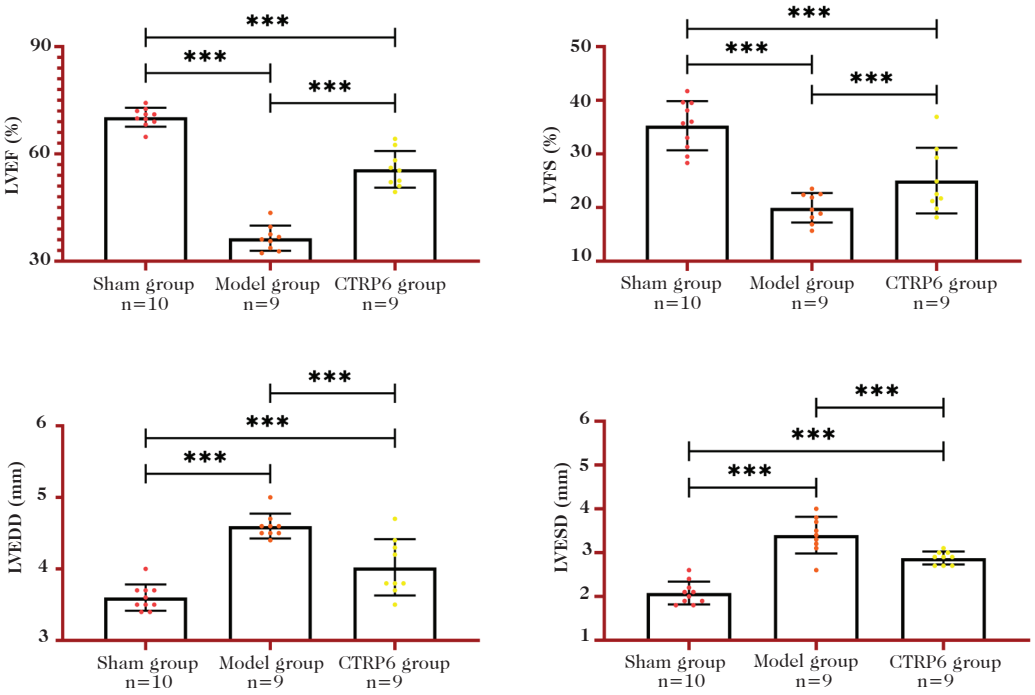

Fig. 3. Effect of CTRP6 on cardiac function (LVEF, LVFS, LVEDD, LVESD) in MI rats. Repeated-measures analysis of variance and LSD intra-group tests were used to compare multiple groups; ****p<0.001*. Left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD). MI: Myocardial infarction; CTRP6: Complement C1q/tumor necrosis factor-related protein 6.

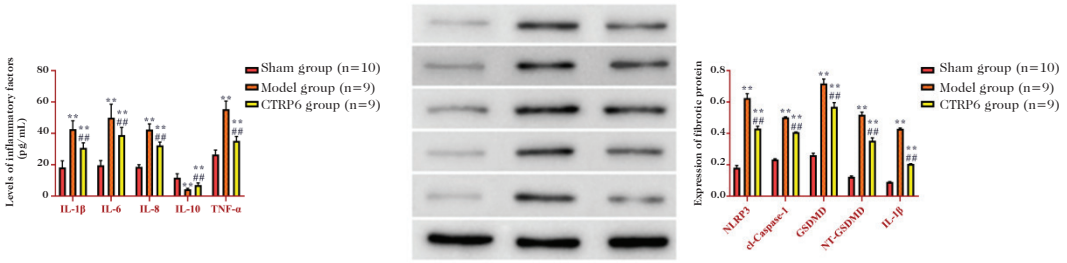

Fig. 4. Effect of CTRP6 on myocardial pyroptosis in MI rats. (a) Effect of CTRP6 on the levels of inflammatory factors (IL-1β, TNF-α, IL-6, IL-8, IL-10) in myocardial tissues of MI rats. (b) Effect of CTRP6 on the expression of focal death proteins (NLRP3, cl-Caspase-1, GSDMD, NT-GSDMD, IL-1β) in myocardial tissues of MI rats. Repeated-measures analysis of variance and LSD intra-group tests were used to compare multiple groups, compared with the sham group **$p<0.01$, and the model group *##p<0.01*. NOD-like receptor family pyrin domain containing 3 (NLRP3), gasdermin D (GSDMD), N-terminal (NT), interleukin (IL), tumor necrosis factor-α (TNF-α). MI: Myocardial infarction; CTRP6: Complement C1q/tumor necrosis factor-related protein 6.

DISCUSSION

Through MI modeling in rats and exogenous CTRP6 intervention experiments, this study demonstrates that CTRP6 exerts cardioprotective effects in MI via a novel mechanism that suppresses cardiomyocyte pyroptosis, thereby ameliorating myocardial fibrosis and restoring cardiac function. These findings not only substantiate the previously hypothesized protective role of CTRP6 in ischemic myocardial injury but also offer novel therapeutic avenues by identifying the pyroptosis-fibrosis axis as a potential target for myocardial repair strategies. Specifically, the therapeutic benefits of CTRP6 were: (1) recovery of cardiac function: LVEF was improved by subcutaneous injection of 0.2 mg/kg/ day (28 days) in MI rats; (2) Anti-fibrosis: reduced collagen deposition and blocked the TGF-β1 pathway.

In the present study, we initially observed significantly decreased CTRP6 protein levels in the myocardial tissue of MI model rats (Fig. 1), suggesting CTRP6's potential role in MI development and progression. This finding supports the findings of Tabatabaei SA et al., who reported a similar reduction in CTRP6 in patients with coronary artery disease [11]. The subsequent administration of exogenous CTRP6 effectively restored CTRP6 levels and yielded two clinically relevant outcomes: a significant reduction in fibrotic markers (Collagen III, α-SMA, and TGF-β1) and improved cardiac function parameters (LVEF and LVFS) (Figs. 2-3). These linked effects provide preliminary evidence for CTRP6's therapeutic potential in the treatment of MI. By analyzing our data systematically and integrating it with existing literature, we identified two complementary mechanisms through which CTRP6 likely exerts its cardioprotective effects: (1) Modulation of inflammation leading to reduced fibrosis: Our results clearly show that CTRP6 treatment causes a significant change in cytokine profiles, characterized by decreased levels of pro-inflammatory mediators (IL-1β, TNF-α, IL-6, and IL-8) and increased levels of the anti-inflammatory cytokine IL-10 (Fig. 4). These findings extend previous research [12] suggesting that CTRP6 may regulate inflammatory responses by inhibiting the NF-κB signaling pathway, ultimately preventing NLRP3 inflammasome activation. This mechanism would decrease pro-inflammatory cytokine release and reduce inflammation in the myocardial environment. (2) Direct inhibition of fibrotic pathways: Our study further confirms the work of Yan et al. [13], showing that CTRP6 suppresses the TGF-β1/Smad3 pathway, preventing the transformation of fibroblasts into myofibroblasts. This is supported by our observed reductions in TGF-β1 and α-SMA protein levels, as well as notably less collagen deposition (particularly Collagen III) in rats treated with CTRP6. Notably, our findings highlight the connection between CTRP6's anti-fibrotic effects and its ability to inhibit pyroptosis [14]. This connection is evident because IL-1β and IL-18, produced during pyroptosis, are potent activators of fibroblasts and promote excessive extracellular matrix (ECM) production [15]. Therefore, we propose that CTRP6 coordinates a multi-faceted anti-fibrotic approach by sequentially blocking "pyroptosis → cytokine release → fibroblast activation". In addition, our study presents the first experimental evidence that CTRP6 suppresses cardiomyocyte pyroptosis by modulating the NLRP3/caspase-1/GSDMD signaling pathway. The underlying mechanisms may involve the following aspects: Upstream regulation: CTRP6 likely initiates its protective effects through activation of the AMPKα pathway, which subsequently attenuates reactive oxygen species (ROS)-mediated NLRP3 inflammasome assembly [16]. Diminished ROS production reduces NLRP3 oligomerization, suppresses caspase-1 self-cleavage (as evidenced by decreased cl-caspase-1 expression), and ultimately prevents GSDMD proteolytic activation (manifested as reduced NT-GSDMD fragments) (Fig. 4). Downstream effects: By inhibiting the pyrop-

tosis executioner protein GSDMD, CTRP6 diminishes plasma membrane pore formation, thereby preventing the release of IL-1β and IL-18 and consequently disrupting the vicious cycle of "pyroptosis-inflammation-fibrosis" (Fig. 4). While the current literature offers limited precedents for CTRP6's role in pyroptosis regulation, our findings align with established clinical evidence that identifies lipid peroxidation and membrane disruption as fundamental prerequisites for pyroptotic cell death [17,18]. Given that CTRP6 functions as a lipid metabolism regulator, it may enhance cellular resistance to pyroptosis by maintaining membrane phospholipid homeostasis, such as by increasing sphingomyelin levels [19]. This intriguing hypothesis warrants further investigation through comprehensive lipidomic profiling in future studies.

Furthermore, this study is the first to establish the "CTRP6-pyroptosis-fibrosis" regulatory axis, elucidating the molecular mechanism by which CTRP6 attenuates post-MI fibrosis via targeting the NLRP3/caspase-1/GSDMD pathway. Using a well-established MI rat model, we demonstrated that intravenous administration of exogenous CTRP6 improves cardiac function. These findings provide crucial experimental evidence supporting the development of CTRP6-based therapeutic approaches, including both gene therapy and protein replacement strategies. Our research suggests several promising clinical applications that warrant further investigation: First, regular monitoring of serum CTRP6 levels could potentially serve as a valuable biomarker for evaluating the risk of fibrosis development in MI patients. Second, combinatorial regimens pairing CTRP6 with established pyroptosis inhibitors (such as MCC950) may produce enhanced anti-fibrotic effects through synergistic mechanisms. Third, the dual protective properties of CTRP6—targeting both metabolic and cardiovascular systems—may be particularly beneficial for the management of diabetic patients with MI, potentially yielding superior therapeutic outcomes in this high-risk population.

While our study provides important insights, several limitations must be considered. First, the precise molecular mechanism remains unclear—we cannot determine whether CTRP6 exerts its anti-pyroptotic effects through direct interaction with NLRP3 or via indirect modulation of upstream regulatory kinases, such as ASK1. Second, our experimental design did not incorporate sex-based analyses, despite existing evidence suggesting estrogen may influence CTRP6 expression patterns [20]. Third, the absence of clinical specimen data prevents validation of the observed relationship between CTRP6 levels and pyroptosis markers.

As a conclusion, CTRP6 ameliorates myocardial fibrosis and enhances cardiac function by inhibiting NLRP3/caspase-1/GSDMD-mediated cardiomyocyte pyroptosis, thereby reducing pro-inflammatory cytokine release and fibroblast activation in an MI animal model. These findings not only expand our understanding of CTRP6's role in cardiovascular diseases but also provide novel strategies for precision medicine in the treatment of MI.

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Ethical approval

The study protocol was approved by the Ethics Committee of The Second People's Hospital of Changzhou (Approval number:20210301002).

Conflict of interest

The authors had no separate personal, financial, commercial, or academic conflicts of interest.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

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Study conception and design: ZGC, QZ; Data collection: XC; Data analysis and interpretation: HP; Drafting of the article: QZ. Critical revision of the article: All authors.

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