Regenerative Therapy 26 (2024) 33–41

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Original Article

PPARA ameliorates sepsis-induced myocardial injury via promoting macrophage M2 polarization by interacting with DUSP1

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ARTICLE INFO

Article history:
Received 28 February 2024
Received in revised form
29 March 2024
Accepted 25 April 2024

Keywords:
Sepsis
Myocardial injury
PPARA
DUSP1
M2 polarization

ABSTRACT

Background: The morbidity and mortality of sepsis are increasing year by year. Statistically, 40–50% of patients with sepsis have concomitant myocardial injury, and its mortality rate is higher than that of patients with sepsis only. Therefore, it is of great significance to elucidate the mechanism of sepsis-induced myocardial injury.

Methods and results: Human monocytes (THP-1) were used to induce M0 macrophages, followed by treated with lipopolysaccharide (LPS). Cardiomyocytes (AC16) were co-cultured with the conditioned medium of LPS-induced macrophages to induce injury. Quantitative real-time PCR was employed to detect the mRNA levels of peroxisome proliferator-activated receptor α (PPARA) and dual specificity phosphatase 1 (DUSP1). Protein levels of PPARA, macrophage polarization-related markers, apoptosis-related markers, mitochondria-related proteins, and DUSP1 were analyzed by Western blot. Flow cytometry was used to assess M1/M2 cell rates and apoptosis. Low PPARA expression could serve as a biomarker for patients with sepsis. PPARA overexpression enhanced M2 polarization and suppressed M1 polarization in LPS-induced macrophages, and it could alleviate cardiomyocyte injury in co-cultured system. PPARA bound to the DUSP1 promoter region and facilitated its expression. DUSP1 knockdown reversed the effect of PPARA overexpression on M2 polarization and cardiomyocyte injury.

Conclusion: PPARA attenuated cardiomyocyte injury by promoting macrophage M2 polarization through increasing DUSP1 expression, suggesting that PPARA might be a therapy target for sepsis-induced myocardial injury.

1. Introduction

Sepsis can lead to severe systemic inflammatory response syndrome and organ dysfunction [1,2]. The incidence of sepsis has increased at a rate of 8–13% per year, accounting for 11% of all acute and severe diseases [3]. Myocardial injury is one of the serious complications in patients with sepsis, and its mortality rate is approximately up to 90% [4,5]. Although great progress has been made in the treatment of sepsis-induced myocardial injury, the underlying molecular mechanisms still need to be further studied. Studies have shown that macrophage polarization is closely related to the process of myocardial injury in sepsis [6,7]. Therefore, revealing the underlying molecular mechanisms regulating macrophage polarization may provide new strategies for the treatment of sepsis-induced myocardial injury.

Peroxisome proliferator-activated receptors (PPARs), have α, δ (β) and γ isoforms, are a group of nuclear receptor proteins [8,9]. Previous studies have shown that PPARA (PPARα) is involved in regulating the progression of various diseases. It was reported that PPARA activation attenuated iron overload-induced ferroptosis via the Gpx4/TRF axis [10]. Besides, PPARA could inhibit the process of sepsis-associated acute kidney injury, which overexpression alleviated lipopolysaccharide (LPS)-induced kidney cell apoptosis and oxidative stress [11,12]. Importantly, PPARA knockdown exacerbated LPS-induced cardiac dysfunction in mice and promoted mitochondrial dysfunction in LPS-induced cardiomyocytes [13]. Thus, PPARA may be an important regulator for septic

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Peer review under responsibility of the Japanese Society for Regenerative Medicine.

https://doi.org/10.1016/j.reth.2024.04.017

cardiomyopathy. Moreover, the activation of PPARA has been confirmed to promote the M2 polarization of macrophages [14]. However, whether PPARA mediates myocardial injury in sepsis by regulating M2 polarization remains unclear.

Dual specificity phosphatase 1 (DUSP1) is a phosphatase that dephosphorylates the MAP kinase MAPK1/ERK2, leading to its involvement in mediating several cellular processes, including inflammatory responses [15–17]. Recent studies found that DUSP1 was underexpressed in the cardiac tissues of LPS-treated mice, and its overexpression could mitigate LPS-induced myocardial dysfunction by affecting mitochondrial dynamics [18]. Besides, Xin et al. reported that miR-101−3p downregulation attenuated sepsis-induced myocardial injury via enhancing DUSP1 expression [19]. Therefore, DUSP1 may have a protective role against sepsis-induced myocardial injury. Meanwhile, DUSP1 is considered to regulate macrophage polarization to mediate disease progression [20,21]. PPARA has been found to influence gene expression through binding to gene promoter regions [22]. In this, we found that PPARA could bind to the DUSP1 promoter region. However, whether PPARA affects the progression of sepsis-induced myocardial injury via mediating macrophage polarization by regulating DUSP1 expression is unclear.

Here, our study aimed to reveal the role and mechanism of PPARA regulating sepsis-induced myocardial injury through affecting macrophage polarization. In this, we pointed out that PPARA ameliorated sepsis-induced myocardial injury by promoting macrophage M2 polarization through the regulation of DUSP1.

2. Materials and methods

2.1. Serum samples

A total of 29 sepsis patients (10 normal heart function and 19 heart dysfunction) and 29 healthy normal controls from Xinxiang Central Hospital were included for our study. Serum samples were separated from the blood specimens of each participant by centrifugation. All participants signed written informed consent, and this study was approved by the Ethics Committee of Xinxiang Central Hospital.

2.2. Cell culture, transfection and treatment

Human monocytes (THP-1; Procell, Wuhan, China) were cultured in RPMI-1640 containing 10% FBS, 0.05 mM β-mercaptoethanol and 1% penicillin/streptomycin (Gibco, Carlsbad, CA, USA). For inducing M0 macrophages, THP-1 cells were treated with 100 ng/mL PMA (MedChemExpress, Monmouth Junction, NJ, USA) for 24 h. Besides, M0 macrophages were exposed with 50 ng/mL LPS to induce polarization. In addition, M0 macrophages were transfected with pcDNA PPARA/DUSP1 overexpression vector, siRNA against PPARA (si-PPARA) and negative controls (pcDNA and si-NC) using Lipofectamine 3000 before LPS treatment.

Human cardiomyocytes (AC16; Procell) were grown in DMEM/F12 plus 10% FBS and 1% penicillin/streptomycin. For co-culture system, the medium of LPS-induced macrophages transfected with or without pcDNA/PPARA/DUSP1/si-NC/si-PPARA was collected and centrifuged to obtain conditioned medium, and AC16 cells were cultured with conditioned medium for 24 h to explore the effect of macrophage polarization on cardiomyocyte injury.

2.3. Quantitative real-time PCR (qRT-PCR)

Total RNAs were extracted from the serum samples using TRIzol reagent (Takara, Tokyo, Japan) and then reverse-transcribed into cDNA using cDNA Synthesis Kit (Takara). Target gene was amplified using SYBR Green (Takara) and specific primers (Table 1). Relative expression of PPARA and DUSP1 was normalized to β-actin and calculated using the $2^{-\Delta\Delta CT}$ method.

Table 1
Primer sequences used for qRT-PCR.

Name	Primers for PCR (5′-3′)	
DUSP1	Forward	GGATACGAAGCGTTTTCGGC
	Reverse	CCAGGTACAGAAAGGGCAGG
PPARA	Forward	GCGAACGATTCGACTCAAGC
	Reverse	CATCCCGACAGAAAGGCACT
β-actin	Forward	CTTCGCGGGCGACGAT
	Reverse	CCACATAGGAATCCTTCTGACC

2.4. Western blot (WB)

Total proteins were extracted and quantified by RIPA buffer and BCA Kit (Beyotime, Shanghai, China), respectively. Protein samples (30 μg) were separated on SDS-PAGE gel and transferred to PVDF membranes. After blocking with 5% skim milk, membranes were incubated with antibodies, followed by detecting protein signals using ECL reagent (Beyotime). All antibodies (Abcam, Cambridge, MA, USA) were listed as follows: anti-PPARA (1:1000, ab126285), anti-iNOS (1:1000, ab283655), anti-Arg-1 (1:1000, ab124917), anti-Bcl-2 (1:1000, ab32124), anti-Bax (1:1000, ab32503), anti-DUSP1 (1:500, ab61201), anti-NRF1 (1:1000, ab34682), anti-NRF2 (1:500, ab62352), anti-mtTFA (1:10000, ab176558), anti-β-actin (1:1000, ab8227) and Goat anti-Rabbit IgG (1:50000, ab205718).

2.5. Flow cytometry

After treatment or transfection, macrophages were collected and resuspended in a flow cytometry buffer (BD Biosciences, San Diego, CA, USA). Then, macrophages were stained with anti-CD11b (ab24874) plus anti-iNOS (M1 marker, ab283655) or anti-CD206 (M2 marker, ab270682). The rates of M1 cells (CD11b+ and iNOS+) and M2 cells (CD11b+ and CD206+) were analyzed by flow cytometer and FlowJo software.

For detecting apoptosis rate, co-cultured AC16 cells were collected and suspended with binding buffer, followed by stained with Annexin V-FITC and PI (BD Biosciences). Cell apoptosis rate was assessed under a flow cytometer.

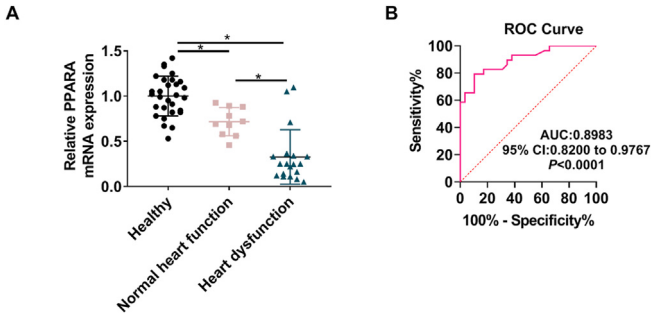

Fig. 1. PPARA expression and diagnosis importance in sepsis patients. (A) PPARA expression in the serum of sepsis patients with normal heart function (n = 10), heart dysfunction (n = 19), and healthy normal controls (n = 29) was analyzed by qRT-PCR. (B) The ROC curve showed the diagnosis importance of PPARA in sepsis patients and healthy normal controls. *$P < 0.05$.

3. ELISA

The levels of TNF-α, IL-1β, IL-6 and IL-4 in the supernatant of macrophages were detected using commercial ELISA Kits (PT518, PI305, PI330, PI618, Beyotime). Besides, the levels of myocardial injury markers (cTnI, CK-MB and LDH) in the supernatant of co-cultured AC16 cells were examined using cTnI ELISA Kit (CSB-E05139h), CK-MB ELISA Kit (CSB-E05140h) and LDH ELISA Kit (CSB-E11720h) (Cusabio, Wuhan, China), respectively. Besides, TNF-α, IL-1β, IL-6, IL-4, cTnI, CK-MB and LDH levels in mice serum samples were determined by corresponding kits (PT512, PI301, PI326, PI612, CSB-E08421 m, CSB-E14404 m and CSB-E11723 m), respectively.

3.1. Cell counting kit 8 (CCK8) assay

Co-cultured AC16 cells were collected and re-seeded into 96-well plates. After 48 h, cells were incubated with CCK8 reagent (Beyotime) for 2 h. Cell viability was assessed by a microplate reader at 450 nm.

3.2. ChIP assay

Cells transfected with pcDNA DUSP1 binding site 1 (from −497 to −480 bp)/2 (from −872 to −855 bp) were fixed with formaldehyde, and sonicated nuclear lysates were processed for the immunoprecipitation with anti-PPARA or anti-IgG using EZ-ChIP Kit (Millipore, Billerica, MA, USA). Then, the precipitated DNA was collected for qRT-PCR with specific ChIP primers.

3.3. Dual-luciferase reporter assay

The wild-type and mutant-type sequences of DUSP1 promoter containing PPARA binding sites and mutated sites were introduced into the pGL3-basic vector to generate WT-DUSP1 and MUT-DUSP1 vectors. 293T cells were co-transfected with si-NC/si-PPARA/pcDNA/PPARA and WT/MUT-DUSP1 vectors. Luciferase activity was analyzed by Dual-Luciferase Reporter Assay Kit (Beyotime) after 48 h.

3.4. Cecal ligation and puncture (CLP) mice models

C57BL/6 mice (Vital River, Beijing, China) was anesthetized by 5.0% isoflurane and then exposed abdominal cavity. The cecum was ligated with 4-0 silk and punctured twice by a 25-gauge needle. After squeezed the feces from the formed holes, the peritoneum and skin were sutured in turn. The sham surgery was performed as the control group. The mice in CLP + PPARA and CLP + sh-PPARA groups were administered with lentiviral particles containing PPARA or sh-PPARA through tail veins. After 48 h, the myocardial tissues and blood samples were collected for further investigation. All animal experiments were approved by the Ethics Committee of Xinxiang Central Hospital.

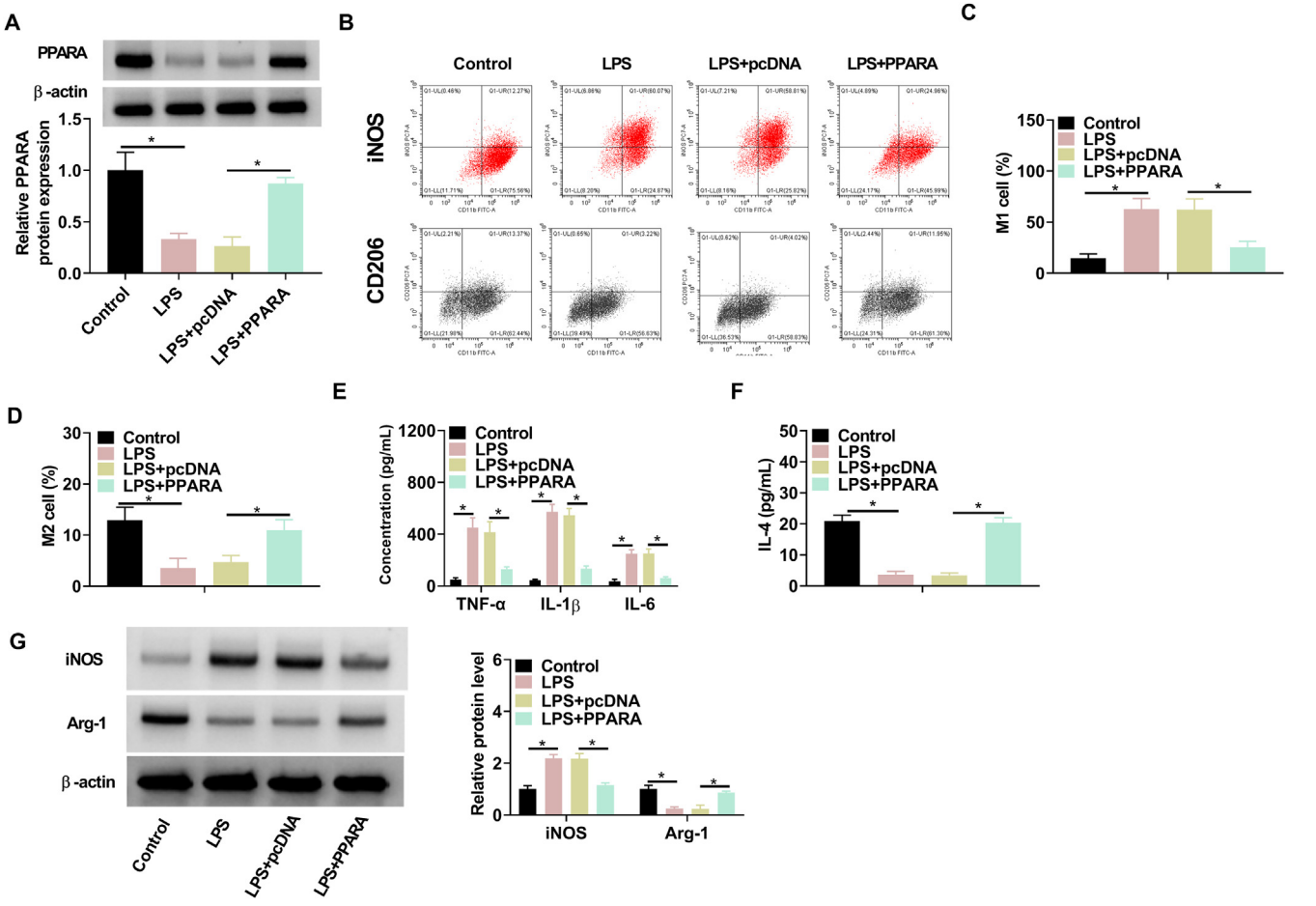

Fig. 2. Effect of PPARA on M2 and M1 polarization in LPS-induced macrophages. M0 macrophages were transfected with pcDNA/PPARA overexpression vector and induced with LPS. (A) PPARA protein expression was analyzed by WB. (B–D) Flow cytometry was used to analyze iNOS and CD206 positive cells to assess M1 and M2 cell rates. (E–F) ELISA was performed to assess TNF-α, IL-1β, IL-6 and IL-4 levels. (G) Protein levels of iNOS and Arg-1 were analyzed by WB. *$P < 0.05$.

3.5. Statistical analysis

Data were assessed by GraphPad Prism 7.0 software and shown as mean ± SD. Differences were compared by Student's *t*-test or ANOVA. $P < 0.05$ was considered significantly different.

4. Results

4.1. Low PPARA expression could be used as a diagnostic index for sepsis patients

PPARA expression in sepsis patients with normal heart function and heart dysfunction was lower than that in healthy normal controls, and it was significantly reduced in sepsis patients with heart dysfunction compared to patients with heart function (Fig. 1A). The diagnostic importance of PPARA in sepsis patients was evaluated by ROC curve analysis, and the results showed that the AUC value of PPARA was 0.8983 (Fig. 1B), revealing that the population of sepsis patients and healthy normal controls could be distinguished according to PPARA expression.

4.2. PPARA promoted M2 polarization in LPS-induced macrophages

To reveal the effect of PPARA on the polarization of macrophages, M0 macrophages were transfected with PPARA overexpression vector and then induced with LPS. LPS treatment markedly reduced PPARA protein expression, and the transfection of PPARA overexpression vector abolished this effect (Fig. 2A). Through analyzing the positive cells of M1 phenotype marker iNOS and M2 phenotype marker CD206, we confirmed that LPS treatment enhanced M1 cell rate and reduced M2 cell rate, while PPARA overexpression reversed these effects (Fig. 2B–D). Also, PPARA overexpression reduced the levels of pro-inflammation factors (TNF-α, IL-1β and IL-6) and promoted the level of anti-inflammation factor (IL-4) in LPS-induced macrophages (Fig. 2E and F). Upregulation of PPARA decreased the protein expression of M1 polarization marker iNOS and increased M2 polarization marker Arg-1 in LPS-induced macrophages (Fig. 2G). These data showed that PPARA promoted M2 polarization and suppressed M1 polarization in LPS-induced macrophages.

4.3. PPARA alleviated cardiomyocyte injury by promoting M2 polarization

To explore whether PPARA regulated M2 macrophage polarization to mediate sepsis-induced myocardial injury, AC16 cells were co-cultured with the conditioned medium from LPS-induced macrophages. Through detecting the contents of myocardial injury markers (cTnI, CK-MB and LDH), we confirmed that LPS-induced macrophages accelerated AC16 cell injury, and PPARA overexpression reversed this effect (Fig. 3A–C). Also, upregulation PPARA in LPS-induced macrophages promoted AC16 cell viability and Bcl-2 protein level, while reduced apoptosis rate and Bax protein level (Fig. 3D–F). Moreover, PPARA overexpression enhanced the levels of mitochondria-related proteins (NRF1, NRF2 and mtTFA) (Fig. 3G). Above all, PPARA promoted M2 polarization to inhibit cardiomyocyte injury.

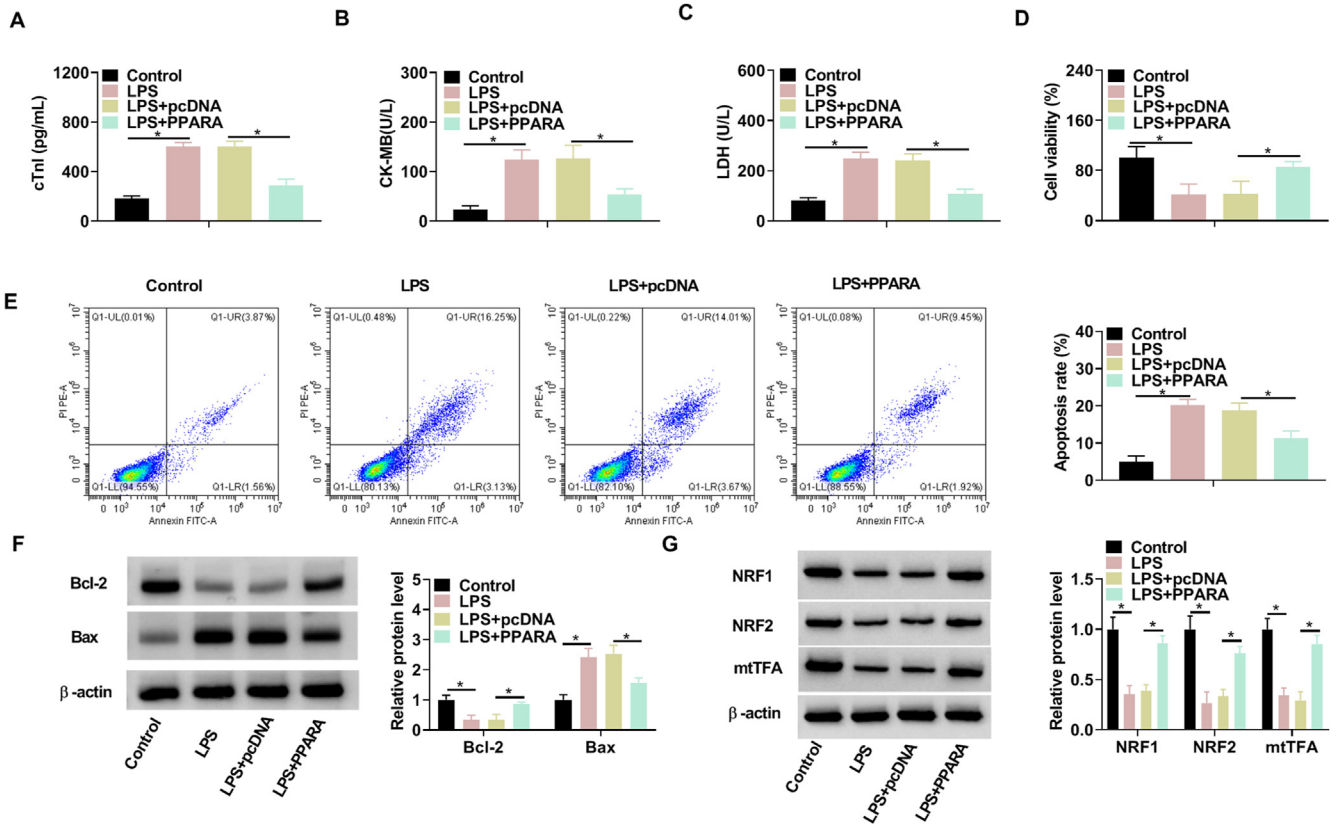

Fig. 3. Effect of LPS-induced macrophages overexpressed PPARA on cardiomyocyte injury. AC16 cells were co-cultured with conditioned medium from LPS-induced macrophages transfected with pcDNA/PPARA overexpression vector. (A–C) ELISA was employed to detect the contents of cTnI, CK-MB and LDH. CCK8 assay (D) and flow cytometry (E) were used to measure cell viability and apoptosis. (F–G) Protein levels of Bcl-2, Bax, NRF1, NRF2 and mtTFA were tested by WB. *$P < 0.05$.

4.4. DUSP1 expression was positively correlated with PPARA expression in sepsis patients

DUSP1 was downregulated in sepsis patients with normal heart function and heart dysfunction compared to healthy normal controls, and was lower expressed in sepsis patients with heart dysfunction than that in patients with heart function (Fig. 4A). DUSP1 had diagnostic importance for sepsis patients (AUC value was 0.8639) (Fig. 4B). Also, DUSP1 had decreased protein expression in LPS-induced macrophages (Fig. 4C). Pearson correlation analysis suggested that there had a positively correlation between DUSP1 and PPARA mRNA levels in the serum of sepsis patients (Fig. 4D).

4.5. PPARA interacted with DUSP1

Jaspar software predicted that PPARA had 2 targeted binding region to the DUSP1 promoter (Fig. 5A). Furthermore, ChIP assay suggested that immunoprecipitated DUSP1 promoter site 2 fragments (from −872 to −855 bp) were significantly enriched by anti-PPARA (Fig. 5B). Moreover, the luciferase activity of WT-DUSP1 vector could be reduced by PPARA knockdown and enhanced by PPARA overexpression, while that of the MUT-DUSP1 vector was not affected (Fig. 5C and D). These data confirmed the interaction between PPARA and DUSP1 promoter. Besides, PPARA knockdown could decrease DUSP1 protein expression, and PPARA overexpression had an opposite effect (Fig. 5E). Thus, PPARA bound to DUSP1 promoter region to positively regulate its expression.

4.6. PPARA regulated M2 polarization in LPS-induced macrophages by mediating DUSP1 expression

To explore DUSP1 roles in macrophage polarization and whether PPARA regulated DUSP1 to mediate macrophage polarization, M0 macrophages were co-transfected with PPARA overexpression vector and si-DUSP1 followed by induced with LPS. The transfection of PPARA overexpression vector significantly increased DUSP1 protein expression, and si-DUSP1 abolished this effect (Fig. 6A). DUSP1 knockdown reversed PPARA-mediated the reduced M1 cell rate and promoted M2 cell rate (Fig. 6B and C). Meanwhile, the regulation of PPARA on the levels of inflammation factors could be reversed by DUSP1 knockdown (Fig. 6D and E). Also, DUSP1 silencing overturned the decreasing effect of PPARA overexpression on iNOS protein level and the increasing on Arg-1 protein level (Fig. 6F). These data showed that PPARA increased DUSP1 expression to promote M2 polarization in LPS-induced macrophages.

4.7. PPARA regulated DUSP1 to alleviate cardiomyocyte injury

After co-cultured with the conditioned medium, we assessed the functions of AC16 cells. PPARA overexpression in LPS-induced macrophages reduced the contents of cTnI, CK-MB and LDH in AC16 cells after co-culture, while this effect was abolished by DUSP1 knockdown (Fig. 7A–C). DUSP1 knockdown also eliminated the promoting effect of PPARA overexpression on cell viability and Bcl-2 protein level, as well as the repressing effect on

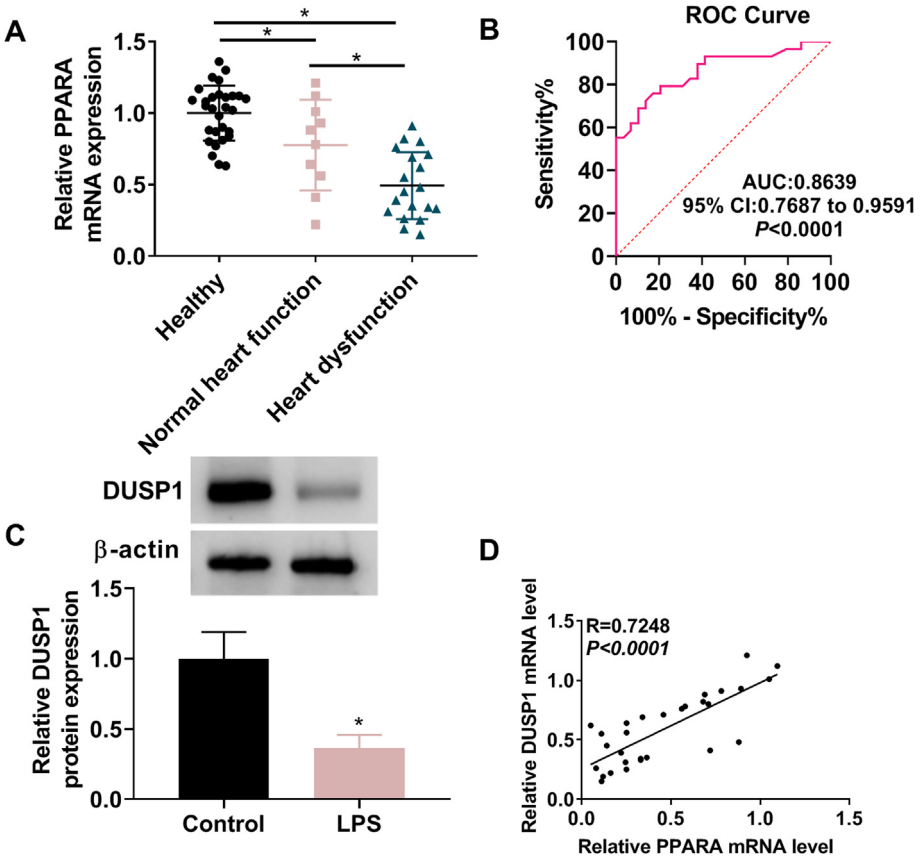

Fig. 4. DUSP1 expression in sepsis patients and LPS-induced macrophages. (A) DUSP1 expression was examined by qRT-PCR in the serum of sepsis patients with normal heart function (n = 10), heart dysfunction (n = 19), and healthy normal controls (n = 29). (B) The ROC curve showed the diagnosis importance of DUSP1 in sepsis patients and healthy normal controls. (C) DUSP1 protein expression in macrophages treated with or without LPS was examined by WB. (D) Pearson correlation analysis was used to detect the correlation between DUSP1 and PPARA expression. *$P < 0.05$.

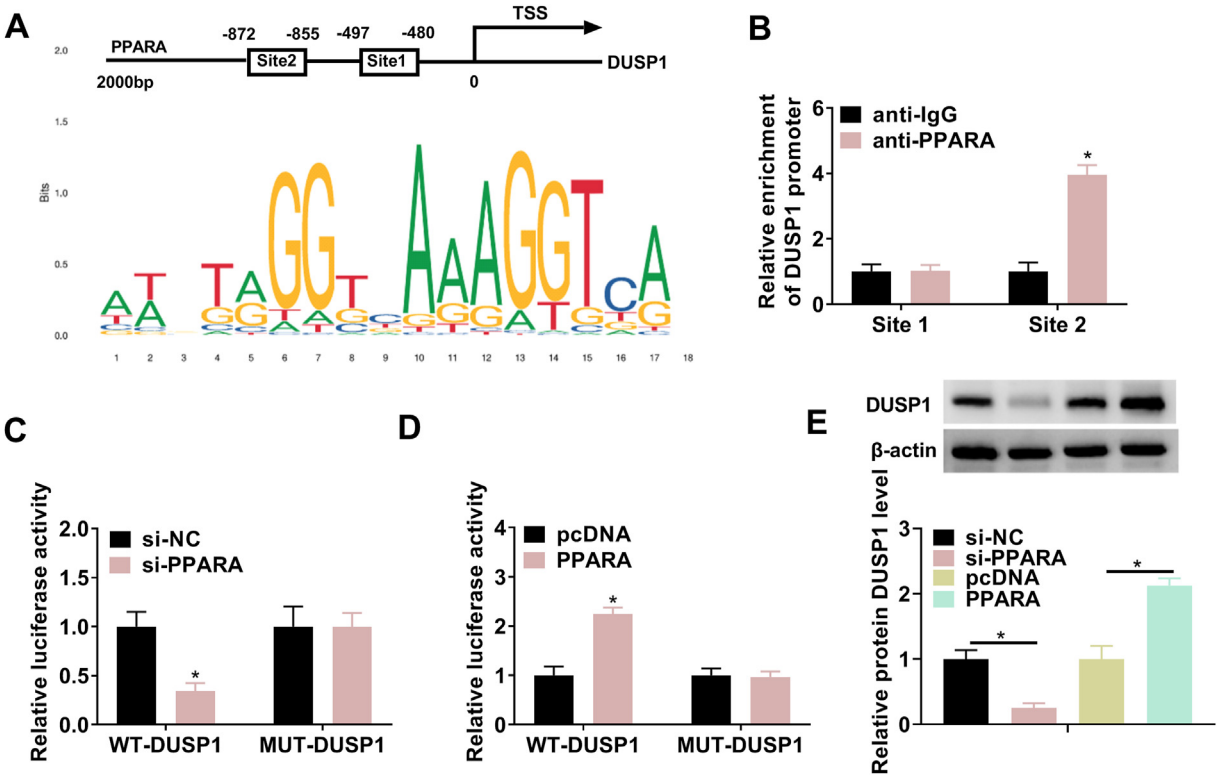

Fig. 5. PPARA interacted with DUSP1. (A) Jaspar software predicted the binding region of PPARA in the DUSP1 promoter. ChIP assay (B) and dual-luciferase reporter assay (C–D) were used to confirm the interaction between PPARA and DUSP1 promoter. (E) DUSP1 protein expression was analyzed by WB in macrophages transfected with si-NC/si-PPARA/pcDNA/PPARA. *$P < 0.05$.

apoptosis rate and Bax protein level in AC16 cells after co-culture (Fig. 7D–F). Furthermore, the facilitation effect of PPARA on the levels of NRF1, NRF2 and mtTFA were abolished by DUSP1 downregulation (Fig. 7G). Therefore, PPARA restrained cardiomyocyte injury via promoting M2 polarization by increasing DUSP1 expression.

4.8. PPARA alleviated myocardial injury in CLP mice models

To further confirm our results, we constructed a septic CLP model. PPARA protein was upregulated in CLP + PPARA group and downregulated in CLP + sh-PPARA group (Supplementary Fig. 1A). PPARA overexpression could inhibit the levels of pro-inflammatory

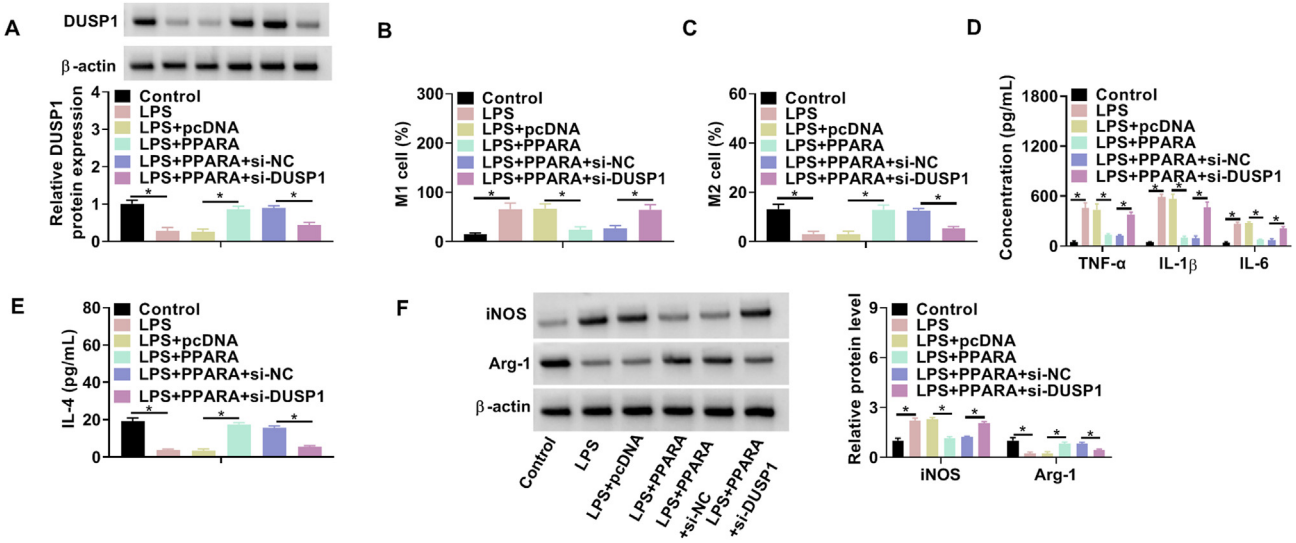

Fig. 6. Effect of PPARA and si-DUSP1 on M1 and M2 polarization in LPS-induced macrophages. M0 macrophages were transfected with pcDNA/PPARA/si-NC/si-DUSP1 and induced with LPS. (A) WB was used for detecting DUSP1 protein expression. (B–C) iNOS and CD206 positive cells were analyzed by flow cytometry to assess M1 and M2 cell rates. (D–E) TNF-α, IL-1β, IL-6 and IL-4 levels were examined by ELISA. (F–G) Protein levels of iNOS and Arg-1 were examined using WB. *$P < 0.05$.

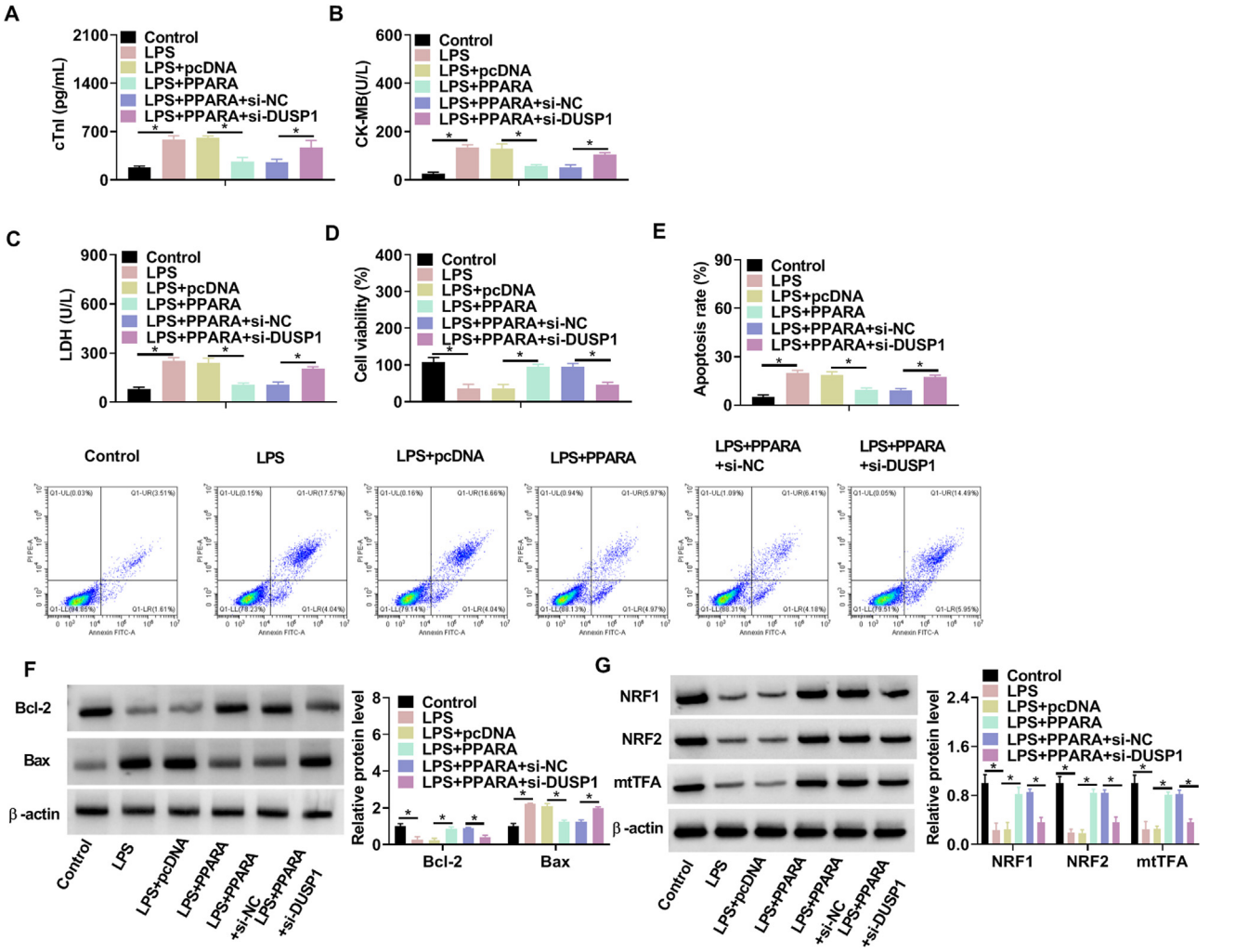

Fig. 7. Effect of LPS-induced macrophages overexpressed PPARA and silenced DUSP1 on cardiomyocyte injury. AC16 cells were co-cultured with conditioned medium from LPS-induced macrophages transfected with pcDNA/PPARA/si-NC/si-DUSP1. (A–C) The contents of cTnI, CK-MB and LDH were evaluated by ELISA. Cell viability and apoptosis were examined by CCK8 assay (D) and flow cytometry (E). (F–G) Bcl-2, Bax, NRF1, NRF2 mtTFA protein levels were tested using WB. *$P < 0.05$.

factors (TNF-α, IL-1β and IL-6), promote anti-inflammatory factor IL-4 level, decrease the contents of myocardial injury markers (cTnI, CK-MB and LDH), reduce the M1 polarization marker iNOS expression, increase the M2 polarization marker Arg-1 expression, and enhance the expression of mitochondria-related proteins (NRF1, NRF2 and mtTFA). However, sh-PPARA had the opposite effect (Supplementary Fig. 1B-H). The information suggested that PPARA promoted M2 polarization, inhibited M1 polarization and improved mitochondrial function to alleviate sepsis-related myocardial injury.

5. Discussion

Sepsis remains a serious public health problem worldwide [23]. Although the treatment of sepsis has achieved great clinical success, the mortality rate of patients is still increasing due to its secondary complications, among which septic cardiomyopathy is regarded as an important cause of death in patients [24,25]. Macrophages are one of the important components of innate and adaptive immunity, and their polarization process plays an important role in regulating inflammatory response and cell injury [26,27]. Macrophage polarization is associated with sepsis-induced myocardial injury [28–30]. Therefore, exploring the potential molecular targets that regulate macrophage polarization is expected to provide new ideas for treating sepsis-induced myocardial injury.

PPARA, a nuclear transcription factor that regulates gene expression, is a key mediator of lipid metabolism and inflammation. Su et al. demonstrated that abnormally expression of PPARA was related to sepsis-induced acute kidney injury [11]. It had been revealed that etinoic acid improved the cardiac function of LPS-treated mice by increasing PPARA expression [31]. Also, PPARA deficiency in cardiomyocytes led to an exacerbation of LPS-induced cardiac dysfunction [13]. In regulating macrophage polarization, PPARA knockdown promoted M1 polarization and suppressed M2 polarization in bone marrow-derived macrophages [32]. Besides, PPARA enhanced M2 macrophage polarization to mediate secondary bacterial infection [14]. The above information confirmed the protective effect of PPARA on sepsis-induced myocardial injury, as well as the promoting effect on M2 polarization. Consistent with above evidences, we found that PPARA overexpression repressed M1 polarization and accelerated M2 polarization in LPS-induced macrophages. After AC16 cells were co-cultured with the conditioned medium of LPS-induced macrophages, we confirmed that PPARA overexpression facilitated AC16 cell viability and alleviated apoptosis, suggesting that PPARA enhanced M2 polarization to suppress cardiomyocyte injury. In addition, PPARA was lowly

expressed in sepsis patients and had significant diagnostic significance, revealing that PPARA might be a potential biomarker for sepsis.

There is growing evidence that DUSP1 plays an important role in septic myocardial injury. Zhu et al. reported that DUSP1 overexpression ameliorated inflammation and apoptosis in LPS-induced cardiomyocytes [18]. Besides, overexpression of DUSP1 relieved apoptosis and inflammation in sepsis-induced cardiomyopathy [19]. Previous study showed that DUSP1 overexpression inhibited M1 polarization and promoted M2 polarization, thus alleviating inflammation and injury in lung [20]. Moreover, DUSP1 (also named as MKP-1) is able to shift macrophage activation from a proinflammatory (M1) phenotype to an anti-inflammatory (M2) phenotype [21]. Here, we found that DUSP1 was downregulated in sepsis patients and could serve as a biomarker for sepsis diagnosis. Activated PPARA has been found to positively/negatively regulate the expression of target genes [33]. Through analysis and validation, we revealed that PPARA positively regulated DUSP1 expression by binding to its promoter region. In functional experiments, PPARA overexpression enhanced M2 polarization and alleviated cardiomyocyte injury, while these effects could be abolished by DUSP1 knockdown. These data further confirmed the conclusion that PPARA interacted with DUSP1 to alleviate cardiomyocyte injury via increasing M2 polarization.

In conclusion, our study suggests a novel mechanism for regulating sepsis-induced myocardial injury. This study revealed that PPARA and DUSP1 might be potential biomarkers for the diagnosis of sepsis. PPARA inhibited cardiomyocyte injury by promoting M2 polarization through increasing DUSP1 expression. These results provide potential molecular targets for the treatment of sepsis-induced myocardial injury.

Ethics approval and consent to participate

Written informed consents were obtained from all participants and this study was permitted by the Ethics Committee of Xinxiang Central Hospital.

Consent for publication

Not applicable.

Funding

None.

Authors' contributions

Li Cheng designed and performed the research; Dezhi Liu, Shanglan Gao analyzed the data; Li Cheng wrote the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2024.04.017.

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