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IL-4 attenuates myocardial infarction injury by promoting M2 macrophage polarization

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Abstract

IL-4, an immunoregulatory cytokine, plays a role in various cellular pathways and is known to regulate M2 macrophage polarization. Numerous studies have suggested that promoting the polarization of macrophages toward the M2 phenotype is beneficial for myocardial infarction (MI) recovery. However, whether IL-4 can achieve therapeutic effects in MI by regulating M2 macrophage polarization remains unclear. In this study, the authors observed that IL-4 increased the proportion of M2 macrophages in the ischemic myocardium compared to the PBS group. Additionally, IL-4 reduced the infiltration of inflammatory cells and the expression of proinflammatory-related proteins, while enhancing the expression of genes associated with tissue repair. Furthermore, IL-4 facilitated the recovery of cardiac function and reduced fibrosis in the post-MI phase. Importantly, when macrophages were depleted, the therapeutic benefits of IL-4 mentioned above were attenuated. These findings provide evidence for the effectiveness of IL-4 in treating MI through the regulation of M2 macrophage polarization, thereby encouraging further development of this therapeutic approach.

Keywords: IL-4, macrophage polarization, myocardial infarction

Introduction

Myocardial infarction (MI) continues to be a leading cause of mortality and morbidity worldwide[1]. Recent research has consistently shown that the exacerbation of heart failure following an MI is largely due to a hyperactive inflammatory response[2–5]. Central to this process are macrophages, which are pivotal in both post-MI inflammation and cardiac tissue repair. Exhibiting remarkable phenotypic and functional diversity, macrophages differentiate into two primary phenotypes: the proinflammatory M1 and the reparative anti-inflammatory M2[6–8]. Following MI, the infarcted myocardium is initially populated by proinflammatory M1 macrophages that phagocytose dead cells and release a plethora of inflammatory mediators, instigating the inflammatory response. This is followed by a shift towards anti-inflammatory M2 macrophages, which predominate and aid in dampening inflammation and promoting cardiac repair[9,10]. Contemporary studies propose that driving macrophage differentiation towards the M2 phenotype may represent a viable intervention to mitigate the inflammatory response and enhance myocardial healing[11–13].

Interleukin-4 (IL-4), an anti-inflammatory cytokine secreted by Th2 lymphocytes, basophils, eosinophils, and mast cells, has been recognized for its extensive regulatory roles across various biological activities[14,15]. Consequently, we posited that IL-4 might act as a novel biological agent to modulate inflammation post-MI. Nonetheless, it is imperative to conduct further research to

HIGHLIGHTS

- IL-4 significantly enhances M2 macrophage polarization in ischemic myocardium, suggesting a pivotal role in myocardial infarction (MI) recovery.
- Administration of IL-4 reduces inflammatory cell infiltration and proinflammatory protein expression, while upregulating genes tied to tissue repair, highlighting its dual anti-inflammatory and proreparative actions.
- The therapeutic benefits of IL-4, including improved cardiac function and reduced fibrosis post-MI, are diminished with macrophage depletion, underscoring the essential role of macrophages in IL-4's mechanism of action.

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ascertain IL-4's influence on macrophage polarization and myocardial repair efficacy. In our investigation, we explored the impact of IL-4 on MI in murine models. The findings indicated that IL-4 aggravates MI injury by modulating M2 macrophage polarization.

Material and methods

Procedures of MI and echocardiography

The Institutional Ethics Committee of the Hubei provincial hospital of traditional Chinese medicine granted approval for all procedures. Male C57BL/6 mice, aged 8 weeks, were utilized in this research and were categorically allocated into three groups: Sham, PBS, and IL-4. The establishment of MI followed the methodology previously described[16,17]. Mice were anesthetized with an intraperitoneal dose of pentobarbital sodium at 80 mg/kg. Subsequent to the induction of anesthesia, thoracotomy was performed at the fourth and fifth intercostal spaces to reveal the cardiac structure. The left anterior descending coronary artery was ligatured with a 6-0 polyester suture proximal to the left atrium and adjacent to the pulmonary artery outflow tract (showed in Fig. 1). In the immediate aftermath of MI induction, the IL-4 group received an injection of 3 μg of IL-4 (sourced from Invitrogen), solubilized in 25 μl of PBS, distributed equidistantly around the infarct border. The PBS group was administered an equivalent volume of PBS alone. For the Sham group, left anterior descending ligation was not executed. To achieve macrophage depletion, 3 μl/g of clodronate liposomes (Cl_2MDP, Liposoma) was administered intraperitoneally one day prior to and following MI[13]. Cardiac function assessment was conducted via echocardiographic analysis utilizing a Vevo 2100 apparatus (Visual Sonics).

Quantitative PCR (qPCR) assay

Heart tissue samples were subjected to total RNA extraction employing TRIzol (Invitrogen), and cDNA synthesis was enacted using a reverse transcription kit (Takara). Quantitative PCR was operationalized with a SYBR qPCR Mix Kit (Takara) in conjunction with the ABI Step One-Plus Detection system (Applied Biosystems). The relative quantification of mRNA expression levels was ascertained through the $2 - \Delta\Delta CT$ method, with primer sequences delineated in Table 1.

Western blot analysis

Cardiac tissue samples were homogenized in RIPA buffer containing protease inhibitors (Sigma) to isolate total protein, which was subsequently quantified using a bicinchoninic acid (BCA) assay (Beyotime). Proteins in equal concentrations were resolved on a 10% SDS-PAGE (Beyotime) and electrotransferred onto polyvinylidene difluoride (PVDF) membranes (Life Technology). Membranes were blocked with 5% skim milk at ambient temperature for 1 h before overnight incubation at 4°C with primary antibodies (refer to Table 2) at a dilution of 1:1000. Following primary antibody incubation, membranes were washed and incubated with appropriate horseradish peroxidase-conjugated secondary antibodies (1:2000) for 1 h at room temperature. Detection of protein bands was facilitated by enhanced chemiluminescence (ECL) (Vazyme).

Histological and immunofluorescence analyses

Hearts were excised either 3 or 28 days post-MI, fixed in 4% paraformaldehyde overnight, and then paraffin-embedded. For inflammatory cell infiltration quantification, heart tissue sections of 5 μm were stained with hematoxylin and eosin (H&E). Masson's trichrome staining was employed to assess fibrotic regions. Immunofluorescence staining was performed on heart sections to evaluate macrophage polarization or depletion, using antibodies against F4/80, iNOS, or CD206 (refer to Table 3). Staining intensity was quantified using ImageJ software.

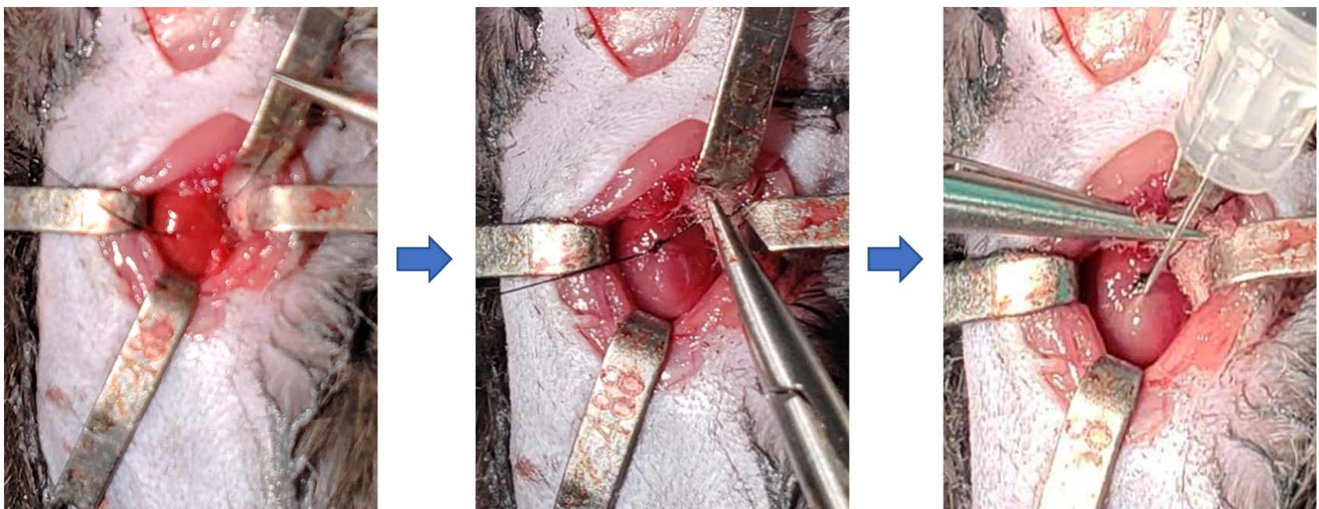

Figure 1. Schematic diagram of myocardial infarction model in mice. The left anterior descending coronary artery was ligatured with a 6-0 polyester suture proximal to the left atrium and adjacent to the pulmonary artery outflow tract, and then injected with 3 μg of IL-4 solubilized in 25 μl of PBS or an equivalent volume of PBS alone.

Table 1

Primers for qPCR

Gene name	Forward primer	Reverse primer
Mouse *Mrc1*	TTCAGCTATTGGACGCGAGG	GAATCTGACACCCAGCGGAA
Mouse *Nos2*	GGTGAAGGGACTGAGCTGTT	ACGTTCTCCGTTCTCTTGCAG
Mouse *vegf*	TATTCAGCGGACTCACCAGC	AACCAACCTCCTCAAACCGT
Mouse *pdgf*	AAAATGCGGGTTTTGAGCCC	AGCTCCTGAGACCTTCTCCT
Mouse *fgf*	GGCTGCTGGCTTCTAAGTGT	GTCCCGTTTTGGATCCGAGT
Mouse *pigf*	GGGCGGGAGAGTTAGATAGC	TTGTCCACGAAGAAGGACGG
Mouse *nos3*	CCTGAGCAGCACAAGAGCTA	TCGAGCAAAGGCACAGAAGT
Mouse *pecam1*	CTTGAGCCTCACCAAGCTCT	GGTCGACCTTCCGGATCTCA
Mouse *blc2*	GACTGAGTACCTGAACCGGC	AGTTCCACAAAGGCATCCCAG
Mouse *ho1*	GCTAGCCTGGTGCAAGATACT	TGGGGGCCAGTATTGCATTT
Mouse 18S	GTAACCCGTTGAACCCCATT	CCATCCAATCGGTAGTAGCG

Statistical analysis

Data were presented as mean ± SD. Multiple group comparisons were conducted using one-way ANOVA or one-way ANOVA with repeated measures, followed by a Bonferroni post-hoc test when appropriate. Two-group comparisons were executed using Student’s *t*-test. A *P*-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed utilizing GraphPad Prism version 8 software.

Results

IL-4 regulated macrophage polarization after MI

Initially, to ascertain the impact of IL-4 on macrophages, we quantified macrophage counts and subsets within the myocardium postinfarction. Data from immunofluorescence staining revealed a marked increase in infiltrating macrophages ($F4/80^+$) subsequent to myocardial injury. Yet, comparative analysis between the IL-4 and PBS groups showed no significant differences ($P > 0.05$) as depicted in Figure 2A. Contrastingly, the fraction of M2 macrophages ($CD206^+$) exhibited a significant rise in the IL-4 group, while the proportion of M1 macrophages ($iNOS^+$) experienced a decrease ($P < 0.05$), as evidenced by Figure 2B and C. Concordantly, western blot analysis confirmed a substantial upregulation of CD206 (M2 marker) protein levels and a downregulation of iNOS (M1 marker) protein levels in the IL-4 treated group ($P < 0.05$), aligning with the immunofluorescence findings (Fig. 2D). Quantitative PCR results corroborated these trends ($P < 0.05$) (Fig. 2E). Collectively, these outcomes substantiate that IL-4 facilitates a shift in macrophage polarization towards an M2 phenotype following MI.

Table 2

Primary antibodies used for western blotting

Antibody	Company	Host species	Dilution ratio
CD206	Santa Cruz	Mouse	1:1000
iNOS	Abcam	Rabbit	1:1000
NFκB-P65	CST	Rabbit	1:1000
p-P65	CST	Rabbit	1:1000
GAPDH	Abcam	Mouse	1:1000

Table 3

Primary antibodies used for immunofluorescence analyses

Antibody	Company	Host species	Dilution ratio
F4/80	Abcam	Mouse	1:200
CD206	Santa Cruz	Mouse	1:200
iNOS	Abcam	Rabbit	1:200

IL-4 alleviated inflammation and increased expression of repair-related gene after MI

IL-4 plays a critical role in modulating the inflammatory cascade post-MI. At Day 3 post-MI, we assessed cardiac inflammatory markers and observed a significant decrease in inflammatory cell infiltration within the IL-4-treated cohort, as evidenced by hematoxylin and eosin (H&E) staining ($P < 0.05$) (Fig. 3A). Concurrently, there was a notable downregulation in the protein expression levels of proinflammatory mediators, namely NFκB-P65 and phosphorylated P65 ($P < 0.05$) (Fig. 3B). Furthermore, IL-4 treatment was associated with increased expression of genes implicated in anti-inflammatory responses, angiogenesis, and tissue repair processes, including vegf, pdgf, fgf, pigf, nos3, pecam1, bcl2, and ho1 ($P < 0.05$) (Fig. 3C). Collectively, these findings suggest that IL-4 administration mitigates excessive inflammation in the myocardium following MI and promotes reparative gene expression.

IL-4 effectively preserved cardiac function after MI

Subsequent to MI, cardiac function was assessed via echocardiography in murine models. Initial observations at Day 3 post-MI did not reveal substantial differences in left ventricular function between IL-4 treated mice and the PBS group ($P > 0.05$). Notably, at the 14-day and 28-day marks, there was a statistically significant improvement in cardiac function in the IL-4 cohort ($P < 0.05$) (Fig. 4A). Additionally, a considerable reduction in the size of MI was observed at Day 28 in the IL-4 treated group ($P < 0.05$) (Fig. 4B). Collectively, these findings suggest that IL-4 administration may facilitate the recovery of cardiac function following MI.

Depletion of macrophages with Cl_2MDP reduced the effects of IL-4 after MI

The above data have demonstrated that IL-4 mitigates the inflammatory response while enhancing myocardial repair post-MI. However, whether these benefits working by acting on macrophages remains to be confirmed. As previously described, we administered Cl_2MDP to induce macrophage depletion in murine models. Immunofluorescence staining results indicated a substantial diminution of cardiac macrophages ($F4/80^+$) post-Cl_2MDP administration ($P < 0.05$) (Fig. 5A). Cardiac function assessment revealed that the IL-4 + Cl_2MDP cohort exhibited no significant improvement in heart function relative to the PBS + Cl_2MDP group ($P > 0.05$) (Fig. 5B). Furthermore, comparative analysis of fibrosis did not yield statistical significance between the groups ($P < 0.05$, Fig. 5C), suggesting that the cardioprotective effects of IL-4 are compromised upon macrophage depletion. Collectively, these findings underscore macrophages as primary targets through which IL-4 exerts cardioprotective actions.

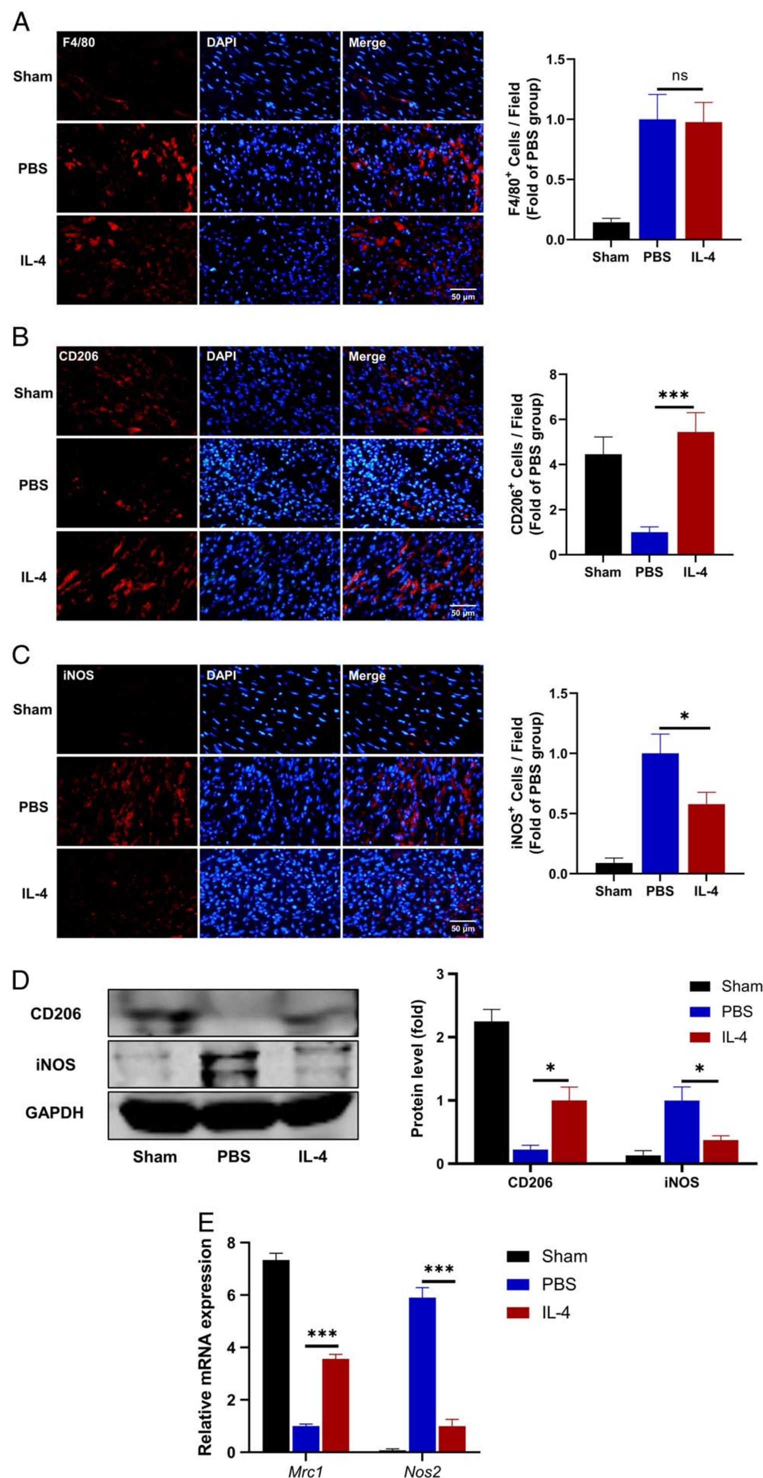

Figure 2. IL-4 regulated macrophage polarization at 3 days after MI. (A) Immunofluorescence analysis of F4/80$^+$ cells with corresponding quantitative statistics. Scale bar: 50 μm. (B) Immunofluorescence analysis of CD206$^+$ cells with corresponding quantitative statistics. Scale bar: 50 μm. (C) Immunofluorescence analysis of iNOS$^+$ cells with corresponding quantitative statistics. Scale bar: 50 μm. (D) Western blot analysis for CD206 and iNOS proteins with relative quantification. (E) mRNA levels of the M2 marker (Mrc1) and the M1 marker (Nos2). Sample size ($n = 4$). Data are presented as mean ± SD. Statistical differences at a single time point were determined using one-way ANOVA. $^{ns}P > 0.05$. $^*P < 0.05$. $^{***}P < 0.001$.

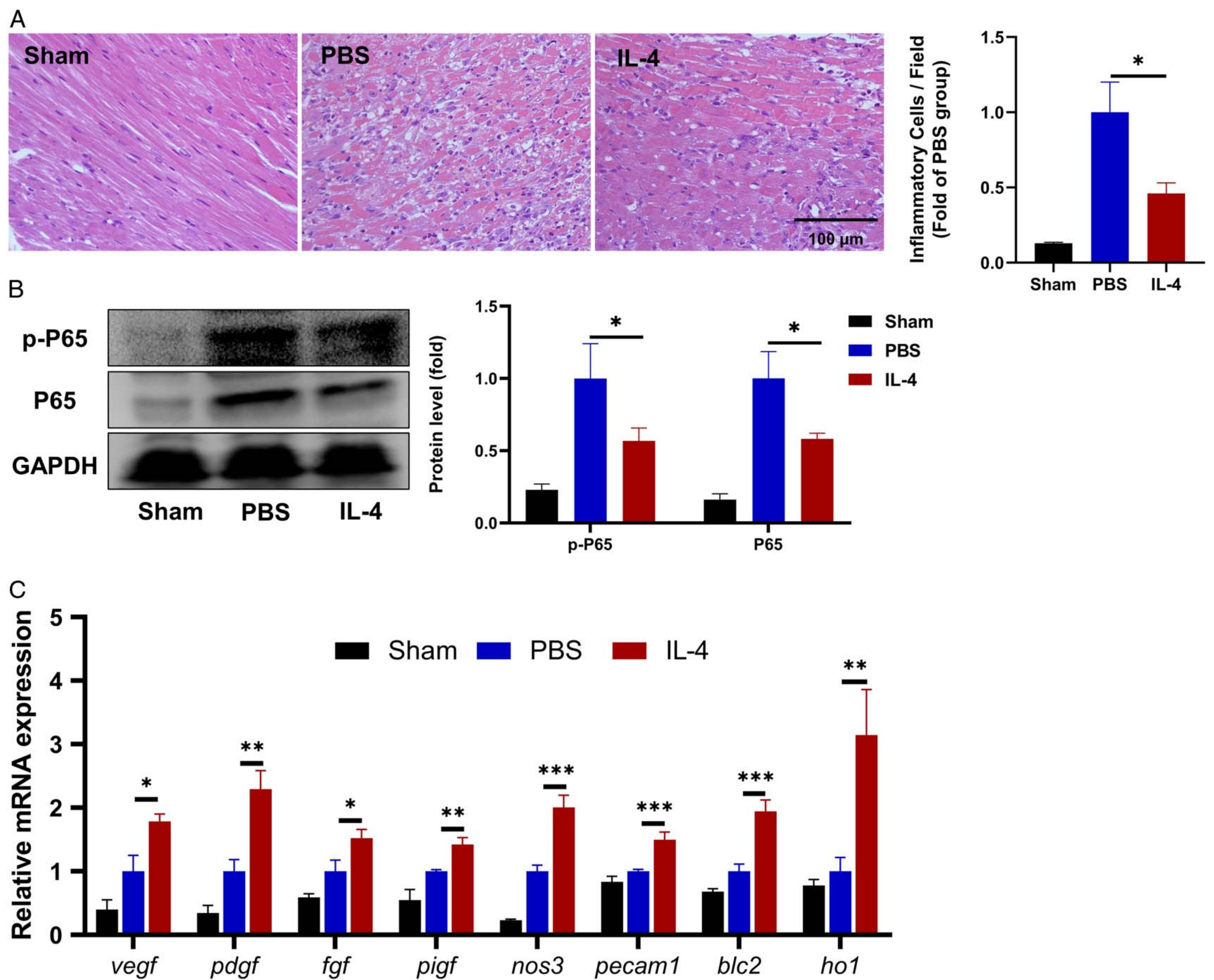

Figure 3. IL-4 alleviated inflammation and increased expression of repair-related gene at 3 days after MI. (A) HE staining depicts inflammatory cell infiltration (scale bar: 100 μm), accompanied by quantification of the infiltrates. (B) Western blot analysis of p-P65 and P65 proteins with corresponding quantification. (C) Expression profile of the genes vegf, pdgf, fgf, pigf, nos3, pecam1, bcl2, and ho1. Statistical sample size ($n = 4$). Data are presented as mean ± SD. Single time point multiple comparisons were conducted using one-way ANOVA. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Discussion

In the present study, we have successfully elucidated that IL-4 exerts a significant influence on promoting M2 macrophage polarization, thereby enhancing the reparative capacity of myocardial tissue following MI. This effect is achieved via the upregulation of a spectrum of anti-inflammatory and tissue repair-related genes, namely *vegf*, *pdgf*, *fgf*, *pigf*, *nos3*, *pecam1*, *blc2* and *ho1*, culminating in enhanced cardiac function and reduced pathological remodeling in the myocardium. To precisely elucidate the role of IL-4 in cardiac repair via the promotion of M2 macrophage polarization, we conducted a 'macrophage depletion' study employing Cl_2MDP. Notably, the group treated with IL-4 in conjunction with Cl_2MDP displayed functional and fibrotic profiles in the damaged cardiac tissue that were analogous to those observed in the PBS + Cl_2MDP group. These findings offer robust evidence of the critical role that macrophage polarization plays in the IL-4-mediated repair process following myocardial injury.

While M1 macrophages are typically recognized for their robust antibacterial and antitumoral functions, they can also induce tissue damage, provoke oxidative stress responses, and impede tissue regeneration and wound healing. In contrast, M2 macrophages are characterized by their anti-inflammatory properties and ability to promote repair[18,19], suggesting that modulation of macrophage phenotypic shift may accelerate the repair of tissue damage[20]. Although the intricate molecular mechanisms driving macrophage polarization remain to be fully deciphered, this domain emerges as an innovative and promising therapeutic target to rejuvenate damaged tissues and organs. As with other tissues, modulation of macrophage polarization may indeed be advantageous for recovery post-MI[9]. Postischemic cardiac injury elicits an inflammatory cascade characterized by an initial surge of M1 macrophages within the early days post-MI. These cells peak in prevalence ~3 days subsequent to the infarct,

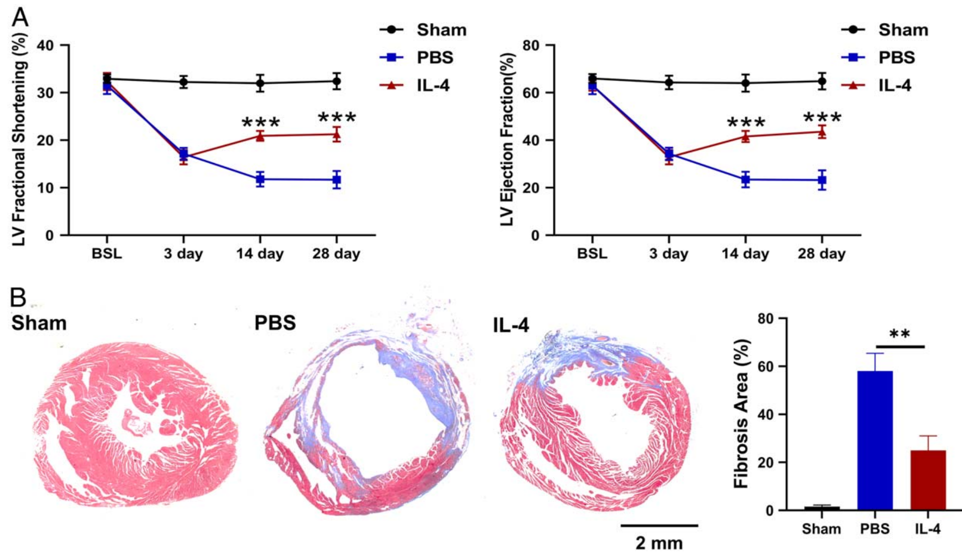

Figure 4. IL-4 effectively preserved cardiac function after MI. (A) Quantitative analysis of left ventricular (LV) ejection fraction and LV fractional shortening at different time points following MI ($n = 5$). (B) Assessment of myocardial fibrosis via Masson's trichrome staining at Day 28 post-MI (scale bar: 2 mm), accompanied by relative quantification of fibrotic tissue ($n = 4$). Data are expressed as mean ± SD. Statistical analyses included one-way ANOVA for multiple comparisons at individual time points and two-way ANOVA for sequential measurements across different time points. $^{**}P < 0.01$, $^{***}P < 0.001$. BSL, baseline.

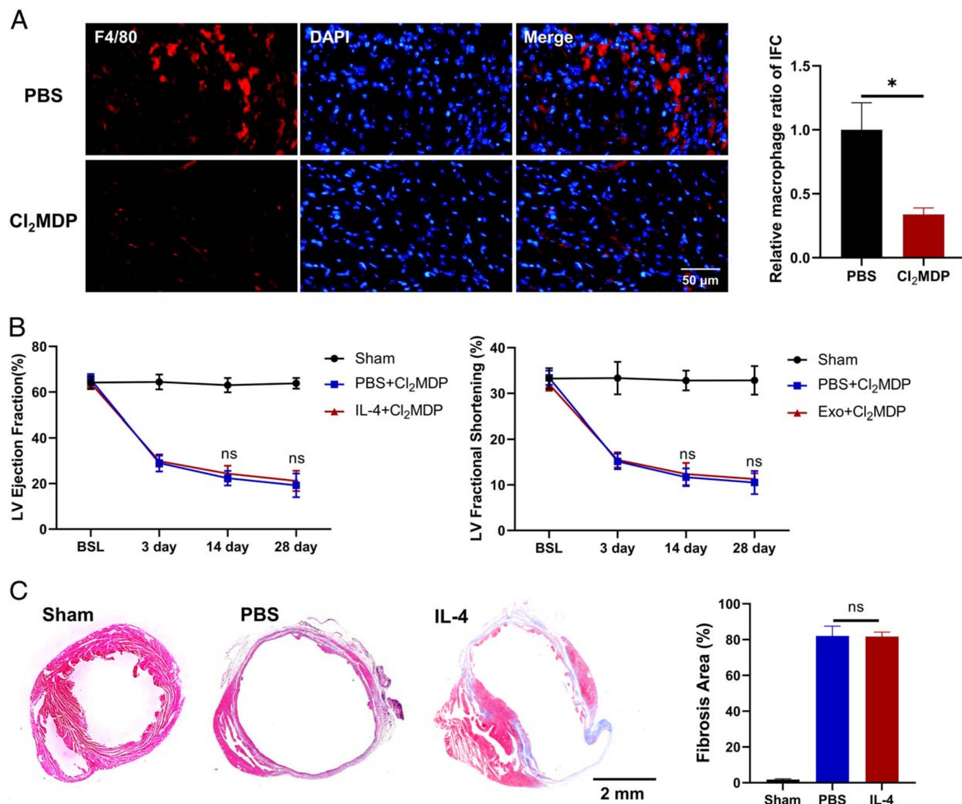

Figure 5. Macrophage depletion with Cl_2MDP diminishes IL-4 efficacy post-MI. (A) Cardiac macrophage quantification via F4/80 immunofluorescence staining ($n = 4$). Scale bar: 50 μm. (B) Statistical analysis of left ventricular ejection fraction and fractional shortening post-MI at different time points ($n = 5$). (C) Masson's trichrome staining depicts fibrotic regions 28 days post-MI (scale bar: 2 mm), accompanied by fibrosis quantification ($n = 4$). Data are presented as mean ± SD. One-way ANOVA was utilized for multiple comparisons at a single time point, whereas two-way ANOVA was employed for sequential time point measurements. $^{ns}P > 0.05$, $^{*}P < 0.05$.

thereby intensifying the inflammatory milieu[21]. In the ensuing period, the infarcted myocardium witnesses a progressive rise in M2 macrophages, which serve to mitigate inflammation and spearhead processes such as extracellular matrix reconstitution and angiogenesis[12,22,23]. Accordingly, the early post-MI phase benefits from a transition of macrophages from the M1 proinflammatory phenotype to the M2 reparative phenotype, attenuating the hyperactive inflammatory response, diminishing ischemic myocardial damage, and enhancing myocardial repair which collectively contribute to the amelioration of cardiac function. The selection of day 3 for the analysis of macrophage polarization in this study is informed by prior investigations[21,23]. Nevertheless, it is imperative to recognize that macrophage polarization is a dynamic process, hence, subsequent studies should incorporate a broader spectrum of temporal checkpoints. IL-4 is pivotal in orchestrating macrophage functional diversity, predominantly driving the induction of the M2 phenotype[24]. Our data demonstrate that IL-4 administration post-MI augments the M2 macrophage contingent within the murine myocardium. Crucially, IL-4 therapy correlates with a marked diminution in pathological fibrosis within ischemic territories, conservation of myocardial integrity, and considerable enhancements in cardiac performance. The therapeutic efficacy of IL-4 was significantly diminished with the depletion of macrophages, highlighting the pivotal role these cells play in the cardioprotective mechanism of IL-4 treatment. Notably, the administration of 3 μg of IL-4 led to favorable results in managing MI, prompting the necessity for additional research to ascertain the ideal dosage, administration route, and timing for IL-4 therapy. IL-4 is known to exhibit a range of biological activities, which may exert a direct effect on various cell types within the myocardium, including myocytes, fibroblasts, endothelial cells, and various inflammatory cells, contributing to an overarching cardioprotective response[25–29]. The current study sheds light on the potential pathway through which IL-4 mediates myocardial protection via macrophage polarization, yet the exact molecular mechanisms remain to be delineated through future research.

Conclusion

The present study substantiates that IL-4 therapy facilitates the restoration of cardiac function following MI by modulating macrophage polarization, a key process in myocardial repair. These insights underscore the potential of IL-4 as a promising therapeutic candidate for MI, thus encouraging further investigations within the realm of clinical MI management.

Ethical approval

No patients were involved in this study. The present study followed international, national, and institutional guidelines for humane animal treatment and complied with relevant legislation.

Consent

No patients were involved in this study. The present study followed international, national, and institutional guidelines for humane animal treatment and complied with relevant legislation.

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Author contribution

D.L., J.F., and Y.L.: contribute equally in this study; D.L., J.F., and K.Y.: performed the experiments; Y.L.: analyzed the data; F.Z., T.M., and F.Z.: designed the investigation, reviewed, and edited the manuscript. All authors read and approved the manuscript. All authors have read and approved the final version of this manuscript to be published.

Conflicts of interest disclosure

The authors declare that there is no conflicts of interest.

Research registration unique identifying number (UIN)

No patients were involved in this study.

Guarantor

Feng Zhu, as the sponsor of the study and the holder of the fund (named Jiangsu Province Double Innovation Doctoral Talent Project), designed the investigation, reviewed and edited the manuscript, and is the guarantor of the study.

Data availability statement

The datasets supporting the conclusions of this article are included within the article.

Provenance and peer review

The paper was not invited.

Acknowledgement

Not applicable.

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