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HDAC5 promotes *Mycoplasma pneumoniae*-induced inflammation in macrophages through NF-κB activation☆

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ABSTRACT

Excessive inflammation is fundamental in the pathophysiology of *Mycoplasma pneumoniae* (MP)-induced respiratory infection in children. Histone deacetylase 5 (HDAC5) is involved in the regulation of inflammation, however, whether it associates with immunity against MP infection is not determined. We report here that HDAC5 expression is decreased in peripheral blood mononuclear cells (PBMCs) from *Mycoplasma pneumoniae* pneumonia (MPP) children as well as in MP-infected peritoneal and THP-1 macrophages. Functionally, HDAC5 overexpression promotes and its depletion inhibits MP-induced proinflammatory cytokine production in THP-1 macrophages. Mechanistically, HDAC5 modulates NF-κB activation in MP-infected THP-1 macrophages, and moreover, inhibition of NF-κB activity *via* pharmacological inhibitor Bay 11-7082 attenuates the promotive effect of HDAC5 on MP-induced proinflammatory cytokine production in THP-1 macrophages, hence suggesting that HDAC5 promotes MP-induced inflammatory response in macrophages through NF-κB activation. Together, this study reveals a novel function of HDAC5 in promoting MP-induced inflammation and implies the possible clinical significance in controlling inflammation that underlies MMP pathophysiology.

1. Introduction

Mycoplasma pneumoniae (MP) is a common atypical bacterium that causes respiratory tract infection and primary pneumonia in human, particularly in children [1]. Sometimes *Mycoplasma pneumoniae* pneumonia (MPP) progresses into refractory MPP (RMPP) or even a life-threatening pneumonia [2,3]. However, to date, the pathophysiological mechanisms that underlie MPP are still largely unknown. Previous observations have shown that multiple types of immune cells are present in pneumonia lesions, such as lymphocytes, neutrophils and macrophages, *etc.*, [4–6]. In addition, the excessive immune response of host against insults from MP infection is deemed to be an important contributor to the pathophysiology of MP infection, including enhanced production of proinflammatory cytokines (*i.e.*, IL-1β, TNF-α and IL-6) and activation of immune cells [7].

Macrophages exert phagocytosis of exogenetic pathogens and antigen presentation, whereby bridging the innate and adaptive immune responses [8]. It has also been demonstrated that the activation of macrophages *via* MyD88-NFκB pathway is critical for the innate immunity against MP infection [5]. Recently, the histone deacetylase 5 (HDAC5), a class II HDACs, was reported to regulate the inflammatory response of macrophages in response to cytokine stimuli [9], and the suppressed expression of HDAC5 by inflammatory cytokines is associated with fibroblast-like synoviocyte activation in patients with rheumatoid arthritis [10]. These findings led us to hypothesize that HDAC5 might be involved in the regulation of inflammatory response of macrophage during MP infection.

In this study, we first compared HDAC5 expression in PBMCs collected from children with or without MPP, and found that HDAC5 expression was decreased in MPP PBMCs. Making use of murine peritoneal macrophages and human macrophage cell line THP-1, we further investigated the functional role and mechanism by which HDAC5 regulates the proinflammatory cytokine production of macrophages induced by MP infection. Our evidence suggests that HDAC5 promotes MP-induced inflammatory response in macrophages, in which NF-κB activation plays an important role.

2. Materials and methods

2.1. Human PBMC specimens

A total of 76 peripheral blood specimens were sampled from

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A

Summary of the demographic and clinical characteristics of control donors and MPP patients.

	Control (n = 34)	MMP (n = 42)	*p* value
Male (%)	21 (61)	24 (57)	0.275
Age (Months)	38.68±26.4	31.17±21.34	0.139
Clinical profiles			
Fever (days)	0	3.83±2.36	< 0.001
Cough (%)	3 (9)	42 (100)	< 0.001
Wheezing (%)	2 (6)	42 (100)	< 0.001
Rhinorrhea (%)	4 (12)	42 (100)	< 0.001
Abnormal lung auscultation (%)	3 (9)	42 (100)	< 0.001
Abnormal chest X-rays (%)	2 (6)	42 (100)	< 0.001
MP positive (%)	0	42 (100)	< 0.001

MMP, *Mycoplasma pneumoniae* pneumonia;
MP, *Mycoplasma pneumoniae*.

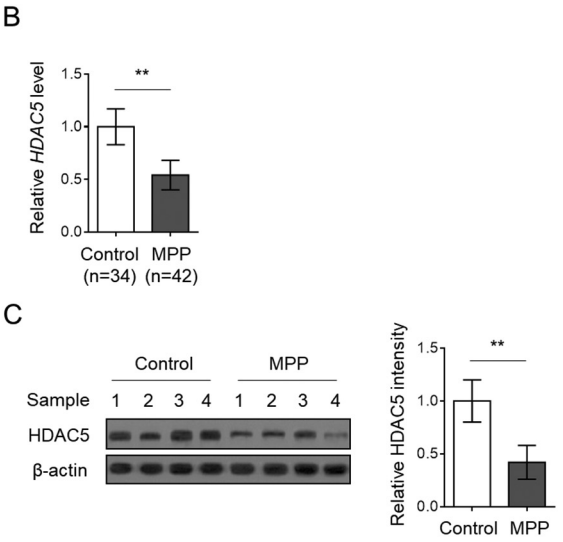

Fig. 1. HDAC5 downregulation in PBMCs from MPP children.
(A) The summary of demographic and clinical characteristics of control donors and MPP patients. P values are also shown. (B) mRNA level of HDAC5 in PBMCs from control individuals (n = 34) and MPP children (n = 42) was determined by qRT-PCR analysis. β-Actin was used as a reference control. Results are expressed as relative to control control. (C) Protein level of HDAC5 in PBMCs from 4 representative control individuals and MPP children was analyzed by immunoblotting. β-Actin was used as a loading control. Relative band intensity analysis of HDAC5 is shown. Data are mean ± s.d. Data were analyzed by Student *t*-test and an analysis of covariance to adjust for clinical characteristics. **, $P < 0.01$.

children without (control donors, n = 34) or with *Mycoplasma pneumoniae* pneumonia (MPP, n = 42) who hospitalized at First Subsidiary Hospital, University of Science and Technology of He'nan. The demographic and clinical characteristics of control donors and MPP patients are summarized in Fig. 1A. The criteria for pneumonia diagnosis conforms to those symptoms and signs such as fever, cough, abnormal lung auscultation and chest X-rays as described previously [11]. MP infection diagnosis was based on the positive indications from serologic testing (MP IgM positive and antibody titer ≥1:160) and MP PCR testing using nasopharyngeal aspirate/swab. Peripheral blood mononuclear cells (PBMCs) were separated from the collected peripheral blood samples by density gradient centrifugation following the well-established protocols [12].

2.2. Peritoneal macrophage isolation and cell culture

Mouse peritoneal macrophages were isolated from 6-week-old C57BL/6 mice as described before [13]. Mice were maintained in a pathogen-free condition throughout this study. All animal experiments were performed according to the protocols approved by First Subsidiary Hospital, University of Science and Technology of He'nan Institutional Animal Care and Use Committee for animal care. In brief, mice were injected intraperitoneally with 3% thioglycollate (Sigma) (1 ml per mouse) and ascites were collected at 4 d following injection. Cell Pellets from ascites were resuspended in red blood cell lysis buffer, and then cells were cultured in DMEM medium supplemented with 10% FBS, 2% HEPES, 1% nonessential amino acids and 1% antibiotic-antimycotic solution. After 4 h, inadherent cells were washed away and the adherent cells were further cultured with fresh culture medium. THP-1 cell line was obtained from ATCC and cultured in RPMI1640 containing 10% FBS and 1% antibiotic-antimycotic solution.

2.3. MP culture, preparation and infection

MP strain M129-B7 was obtained from ATCC and cultured at 37 °C in SP-4 broth containing 5% CO_2. MP were harvested by centrifugation with 10000 × *g* at 4 °C for 20 min. MP pellets were washed and resuspended in PBS (pH 7.4) to yield final titer of 1×10^8 CFU/ml. The cultured peritoneal macrophages and THP-1 cells were infected with 10, 50 or 100 CFU/ml MP for 24 h.

2.4. Cell transfection

For overexpression of HDAC5 in THP-1 cells, lipopolysaccharide-free plasmid DNA (pCMXbased vector encoding for human HDAC5) were transferred (6 μg per well) by electroporation as described previously [14]. For siRNA-mediated knockdown in THP-1 cells, 30 nM HDAC5-specific (siHDAC5) or control siRNA (siCtrl) were transfected using INTERFERin (Polyplus-transfection) according to the manufacturer's instructions. Following 3 or 4 d of transfection, the efficiency of overexpression and knockdown was confirmed by qRT-PCR or immunoblotting analysis. The sequences of siRNAs are listed as follows:

siCtrl 5′-AAUUCUCCGAACGUGUCACGU-3′;
siHDAC5 5′-GGCAGAAGCUAGACAGCAAGA-3′.

2.5. RNA isolation and qRT-PCR analysis

Total RNA was extracted from cells using TRIzol reagent (Invitrogen). Real-time qRT-PCR was performed with cDNA template synthetized from RNA and SYBR Green PCR reagent and the 7500 Fast Real-Time PCR System (Applied Biosystems). The primers used for amplifying human and mouse target genes *HDAC5* and *ACTB* are listed as follows: Human *HDAC5* sense 5′-CCCAACCAGTTCAGCCTCTA-3′, Human *HDAC5* anti-sense 5′-GGCAGCCAGGAATAGAGGAT-3′; Mouse *Hdac5* sense 5′-GGAGGAGACAGAAGAGGAGC-3′, Mouse *Hdac5* anti-sense 5′-CTCTCGCCATCCTCATCCTT-3′; Human *ACTB* sense 5′-CATCC GCAAAGACCTGTACG-3′, Human *ACTB* anti-sense 5′-CCTGCTTGCTG ATCCACATC-3′; Mouse *Actb* sense 5′-TAGGCGGACTGTTACTGAGC-3′, Mouse *Actb* anti-sense 5′-GCCTTCACCGTTCCAGTTTT-3′;

2.6. Immunoblotting

PBMCs, mouse peritoneal macrophages and THP-1 cells were lysed in RIPA lysis buffer. The procedures of immunoblotting were conducted as previously described [15]. Human and mouse HDAC5 was detected by antibodies against HDAC5 obtained from Abcam. Antibodies against p-NF-κB p65 and NF-κB p65 were obtained from Cell Signaling. β-Actin

(Santa Cruz) was used as a loading control. After further probing with secondary antibodies (Santa Cruz), protein bands were identified by chemiluminescence (ThermoFisher Scientific). The analysis of band intensity was performed with ImageJ software.

2.7. ELISA assay

A number of 5×10^5 THP-1 cells were seeded into each well of 24-well plates containing 0.5 ml medium. After treatment and infection, the concentrations of proinflammatory cytokines IL-6, IL-1β and TNF-α in the culture supernatants were evaluated with ELISA kits (eBioscience) according to the manufacturer's protocols.

2.8. Statistical analysis

All data from at least 3 independent experiments are expressed as mean ± SD. The significance of difference between two groups was calculated by two-tailed Student's *t*-test. The comparisons among multiple groups were analyzed by one-way ANOVA or two-way ANOVA followed by Tukey's post-hoc test. P values < 0.05 were considered to be statistically significant.

3. Results

3.1. HDAC5 expression is decreased in PBMCs from MPP children

To seek the possibility HDAC5 may participate in regulating the host immune response against MP infection, we initially compared its transcript level in peripheral blood mononuclear cells (PBMCs) collected from 42 case of *Mycoplasma pneumoniae* pneumonia (MPP) children and 34 control donors (Fig. 1A). As shown by qRT-PCR analysis, HDAC5 transcript level was significantly downregulated in PMBCs from MMP children as compared with counterparts from control donors (Fig. 1B). To ascertain the expression change of HDAC5, we determined its protein level by immunoblotting assay. We found that similar to the downregulation of its transcript level, the protein expression of HDAC5 was also decreased in PMBCs from MMP group (Fig. 1C). These results suggest that HDAC5 expression in PMBCs from host is downregulated when infected with MP, and also imply a possible association between HDAC5 and immune response to MP infection.

3.2. HDAC5 expression is decreased in MP-infected peritoneal and THP-1 macrophages

In order to confirm the expression change of HDAC5 in response to MP infection, we employed mouse primary peritoneal macrophages and THP-1 macrophage cell line to analyze HDAC5 expression after MP infection under culture condition *in vitro*. Similar to HDAC5 downregulation in PMBCs from MMP children, HDAC5 expression was decreased in mouse peritoneal macrophages infected with MP in dose-dependent manner at both transcript level (Fig. 2A) and protein level (Fig. 2B). Moreover, similar results were obtained when THP-1 macrophages were infected with MP (Fig. 2C–D), together strengthening the downregulation of HDAC5 in response to MP infection and suggesting that HDAC5 may have a regulatory role in macrophage-associated immune response against MP infection.

3.3. HDAC5 overexpression promotes MP-induced proinflammatory cytokine production in THP-1 macrophages

The production of proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α, is a fundamental event through which macrophages launch the host immune response against MP infection [16–18]. To examine whether HDAC5 regulates immune response in macrophages infected with MP, we overexpressed HDAC5 in THP-1 macrophages with or without MP infection (Fig. 3A). The production of proinflammatory cytokines was determined by ELISA assay using the supernatants of culture medium. The results showed that the production of IL-1β (Fig. 3B), IL-6 (Fig. 3C) and TNF-α (Fig. 3D) was all induced in THP-1 macrophages when infected with MP, suggesting an immune response was triggered in these cells. Importantly, HDAC5 overexpression markedly elevated the production of these proinflammatory cytokines in MP-infected THP-1 macrophages, however in non-infected THP-1 macrophages, HDAC5 overexpression did not affect their production (Fig. 3B–D). These results suggest that HDAC5 overexpression only promotes MP-induced proinflammatory cytokine production in THP-1 macrophages.

3.4. HDAC5 silencing inhibits MP-induced proinflammatory cytokine production in THP-1 macrophages

To further corroborate the function of HDAC5 involved in macrophage immune response against MP infection, we depleted its expression through small-interfering RNA (siRNA) technique. Although MP infection already decreased HDAC5 expression, the transfection of specific siRNA further resulted in an undetectable level of HDAC5 (Fig. 4A), indicating the efficacy of siRNA-mediated depletion. Along with the drastic decrease of HDAC5 by siRNA transfection, the MP-induced production of IL-1β (Fig. 4B), IL-6 (Fig. 4C) and TNF-α (Fig. 4D) was all minimized, which is in agreement with the above results obtained in experiments applying HDAC5 overexpression (Fig. 3). Collectively, these findings illustrate that HDAC5 functions as a positive regulator in modulating macrophage immune response against MP infection, at least under these *in vitro* conditions using THP-1 macrophages.

3.5. Inhibition of NF-κB activity attenuates the promotive effect of HDAC5 on MP-induced proinflammatory cytokine production in THP-1 macrophages

Previous studies have demonstrated that NF-κB pathway activation and the following transcriptional induction of target genes involved in inflammation are crucial elements for immune response elicited by macrophages [9,19]. To gain mechanistic insight into the regulation of HDAC5 in macrophage immune response against MP infection, we first monitored whether HDAC5 affects NF-κB pathway status. As shown, MP infection caused an elevated level of phosphorylation of NF-κB p65 in THP-1 macrophages, which was further enhanced by HDAC5 overexpression (Fig. 5A). Moreover, adversely, HDAC5 depletion attenuated the increased phosphorylation of NF-κB p65 in MP-infected THP-1 macrophages (Fig. 5B). These results suggest that HDAC5 promotes NF-κB pathway activation induced by MP infection. At last, to analyze the functional role of NF-κB pathway in influencing HDAC5 effect on macrophage immune response against MP infection, this pathway was inhibited by using the Bay 11-7082, an inhibitor of NF-κB pathway [20], in THP-1 macrophages infected with MP (Fig. 5C). As results, in the presence of Bay 11-7082, the promoted production of IL-1β (Fig. 5D), IL-6 (Fig. 5E) and TNF-α (Fig. 5F) by HDAC5 overexpression was largely diminished, suggesting that NF-κB pathway activation contributes to the positive regulatory role of HDAC5 in modulating macrophage immune response against MP infection.

In summary, this study identifies HDAC5 as a novel regulator of immune response against MP infection in macrophages, together with the finding that its expression is downregulated in PBMCs from MMP children, whereby pointing to a potential clinical relevance to MMP pathophysiology.

4. Discussion

Mycoplasma pneumoniae infection is one of the leading causes of pneumonia (MPP) inflicting children and young adults. Despite of its benign and self-limited clinical features, it has been reported that a

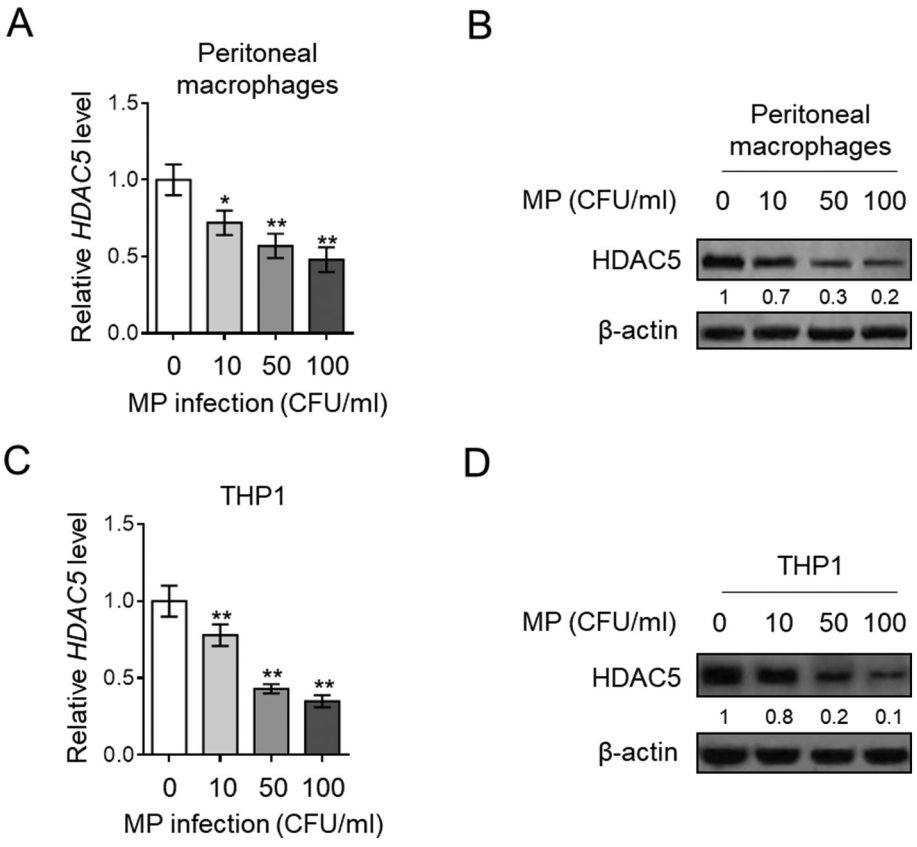

Fig. 2. HDAC5 downregulation in MP-infected peritoneal and THP-1 macrophages.
(A) Mouse peritoneal macrophages were infected with different concentrations of MP as indicated for 24 h. mRNA level of HDAC5 was determined by qRT-PCR analysis. β-Actin was used as a reference control. Results are expressed as relative to group without infection. (B) Mouse peritoneal macrophages were treated as in (A). Protein level of HDAC5 was detected by immunoblotting. β-Actin was used as a loading control. (C–D) THP-1 cells were treated as in (A). mRNA (C) and protein (D) expression of HDAC5 was determined as in (A–B). The fold change of HDAC5 expression is shown below the blots. Data are mean ± s.d. Data were analyzed by one-way ANOVA followed by Tukey's post-hoc test. **, $P < 0.01$; *, $P < 0.05$.

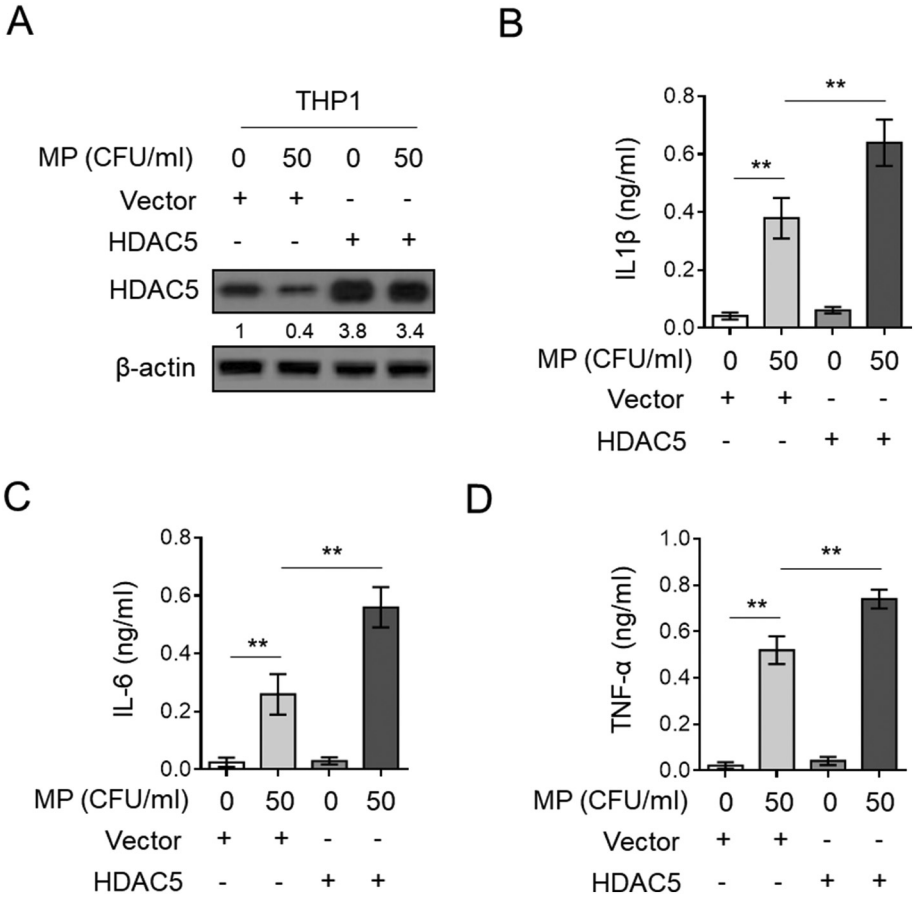

Fig. 3. HDAC5 overexpression promotes MP-induced inflammatory response in THP-1 macrophages.
(A) THP-1 cells were transfected with plasmid overexpressing vector control or HDAC5, 2 d later, THP-1 cells were further infected with or without 50 CFU/cell MP for 24 h. Protein level of HDAC5 was analyzed by immunoblotting. β-Actin was used as a loading control. The fold change of HDAC5 expression is shown below the blots. (B–D) THP-1 cells were treated as in (A). Production of IL-1β (B), IL-6 (C) and TNF-α (D) was measured by ELISA assay. Data are mean ± s.d. Data were analyzed by two-way ANOVA followed by Tukey's post-hoc test. **, $P < 0.01$.

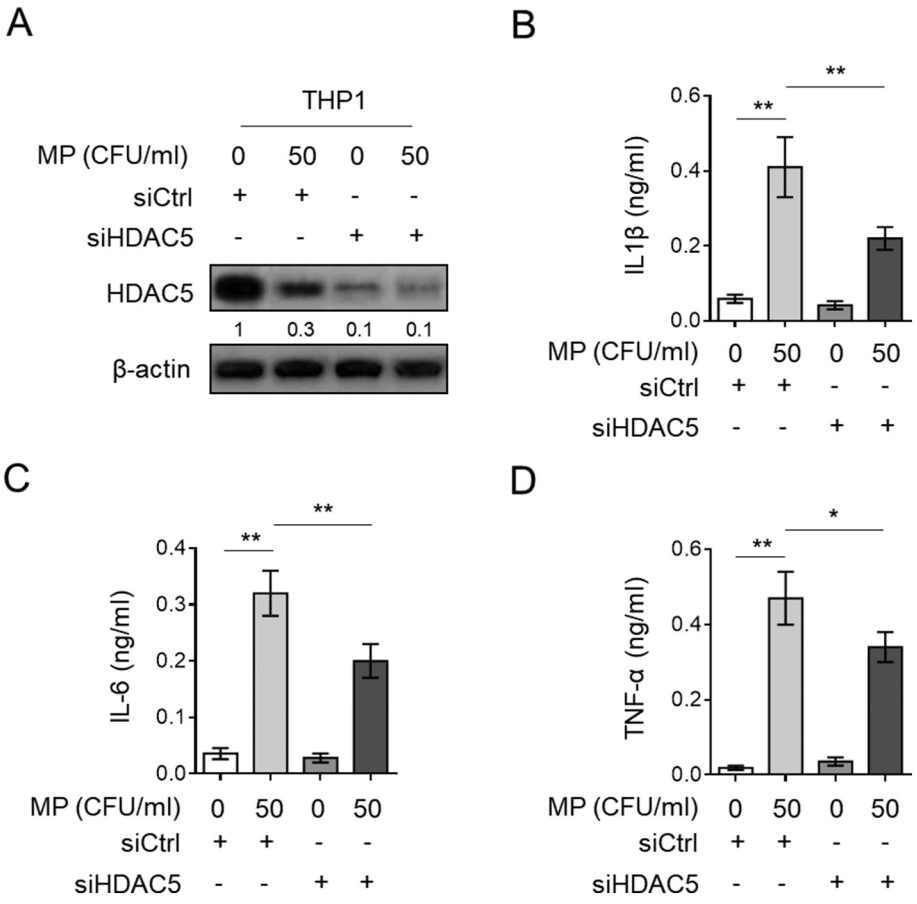

Fig. 4. HDAC5 silencing inhibits MP-induced inflammatory response in THP-1 macrophages.
(A) THP-1 cells were transfected with siRNA targeting luciferase (siCtrl) or HDAC5 (siHDAC5), 2 d later, THP-1 cells were further infected with or without 50 CFU/cell MP for 24 h. Protein level of HDAC5 was analyzed by immunoblotting. β-Actin was used as a loading control. The fold change of HDAC5 expression is shown below the blots. (B–D) THP-1 cells were treated as in (A). Production of IL-1β (B), IL-6 (C) and TNF-α (D) was measured by ELISA assay. Data are mean ± s.d. Data were analyzed by two-way ANOVA followed by Tukey's post-hoc test. **, $P < 0.01$; *, $P < 0.05$.

growing proportion of MPP cases progress into severe RMPP or even a life-threatening pneumonia at one week or extended time period after macrolide therapy [2,21]. Observations from clinical and experimental studies have also suggested that the cell-mediated immunity elicited by the host is tightly associated with MP-induced pneumonia [22]. However, the detailed immunopathogenesis underlying MP infection in humans is still poorly understood. Among the involved immune mediators, macrophages are crucial components that launch host immune response against pathogen infection, including MP [23,24]. HDAC5, one member of histone deacetylases that function to modify chromatin structure and also interact with non-histone proteins [25], has recently been implicated in the regulation of immune response of macrophages [9]. This knowledge prompted us to examine whether HDAC5 has connection with MPP. Focusing on macrophages, we subsequently investigated the role and mechanism of HDAC5 in MP infection-induced inflammatory response.

First, we established a clinical relevance of HDAC5 to MPP through comparing the expression level of HDAC5 in PMBCs collected from children with or without MMP. The decreased HDAC5 expression in MMP group implies its possible association with clinical features of MMP in pediatric patients. Second, by making use of MP infection in mouse peritoneal and THP-1 macrophages cultured *in vitro*, a similar decreased expression change in HDAC5 was detected, which phenocopies the comparison results observed in clinical samples of PMBCs. These lines of *in vivo* and *in vitro* evidence suggest that the down-regulation of HDAC5 in response to MP infection might be a common phenomenon taking place in immune-associated cells. Third, functionally, gain-and loss-of-function studies discovered that HDAC5 played a positive role in MP-induced proinflammatory cytokine production in THP-1 macrophages. Fourth, we found that NF-κB activity was induced by MP infection in THP-1 macrophages and that HDAC5 expression was positively associated with NF-κB activation. The positive regulation of NF-κB activity by HDAC5 is an important mechanism by which HDAC5 affects MP-induced inflammation in THP-1 macrophages, since NF-κB inhibition through the pharmacologic inhibitor Bay 11-7082 attenuates HDAC5 effect on MP-induced proinflammatory cytokine production in THP-1 macrophages. Thus, our study identifies HDAC5 as a novel positive regulator of macrophage immune response against MP infection, together with the finding that HDAC5 is downregulated in PMBCs from MPP children, suggesting that MP infection-mediated HDAC5 reduction is possibly one of the strategies through which MP antagonizes the host immune response and evades the fiery immune attack. Therefore, we propose that in an opposite direction, restoration of HDAC5 expression or activity may be of therapeutic benefit in the intervention of MP-infection induced MPP or even RMPP.

We show that HDAC5 expression is decreased in PMBCs from MMP patients, as well as in MP-infected peritoneal and THP-1 macrophages at both mRNA and protein levels. These observations imply that the transcription of HDAC5 may be suppressed in macrophages when infected with MP. Previous studies have reported that the mRNA and protein expression of HDAC5 could be downregulated by inflammatory stimuli in macrophages, such as bacterial LPS [26] and inflammatory cytokines IL-1β and TNFα [10]. According to these clues, we suspect that the MP infection-induced production of inflammatory cytokines, either from macrophages or other immune cells, may be responsible for its suppressed expression. If this is the case, a negative feed-back regulation between HDAC5 and intensity of immune response induced by MP infection may exist, in which HDAC5 promotes the production of inflammatory cytokines in MP-infected macrophages, which in turn suppress HDAC5 expression. Nevertheless, further investigations are needed to provide solid evidence to demonstrate whether the down-regulation of HDAC5 expression is indeed caused by the stimulation of inflammatory cytokines and elucidate how HDAC5 expression is molecularly regulated in macrophages in response to MP infection.

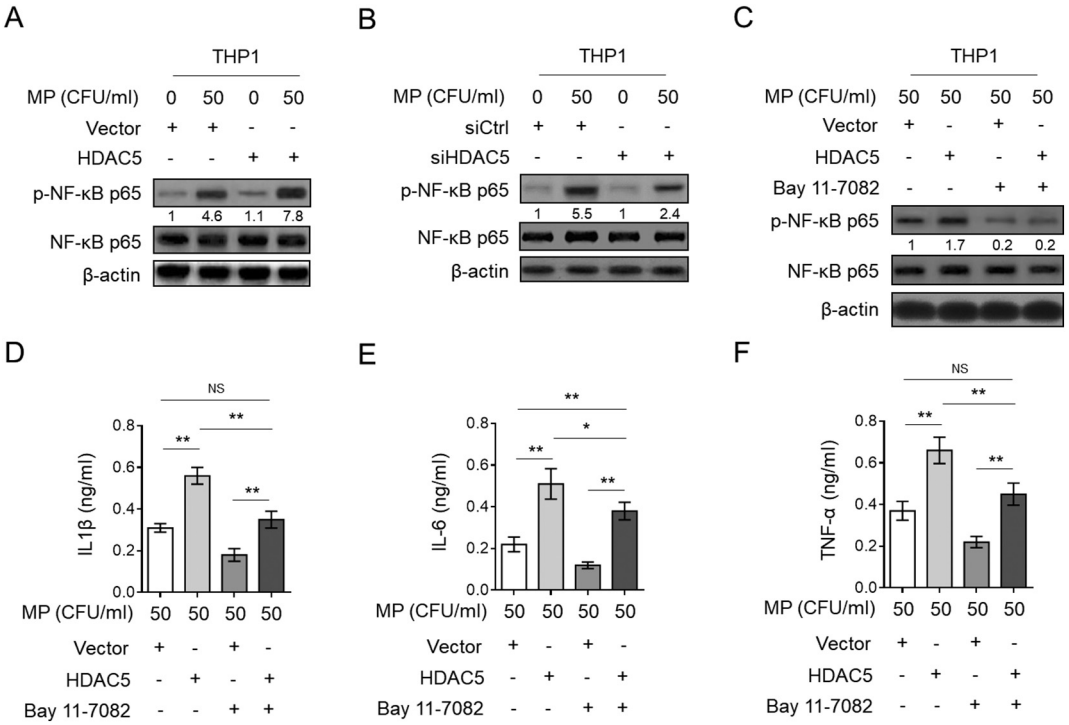

Fig. 5. NF-κB activation contributes to HDAC5 effect on MP-induced inflammatory response in THP-1 macrophages.
(A) THP-1 cells were transfected with plasmid overexpressing vector control or HDAC5, 2 d later, THP-1 cells were further infected with or without 50 CFU/cell MP for 24 h. Protein level of p-NF-κB p65 and basal NF-κB p65 was analyzed by immunoblotting. β-Actin was used as a loading control. The fold change of p-NF-κB p65/NF-κB p65 is shown below the blots. (B) THP-1 cells were transfected with siCtrl or siHDAC5, 2 d later, THP-1 cells were further infected with or without 50 CFU/cell MP for 24 h. Protein level of p-NF-κB p65 and basal NF-κB p65 was analyzed as in (A). (C) THP-1 cells were transfected with plasmid overexpressing vector control or HDAC5, 2 d later, THP-1 cells were further infected with 50 CFU/cell MP for 24 h in the presence or absence of 20 μM Bay 11-7082. Protein level of p-NF-κB p65 and basal NF-κB p65 was analyzed as in (A). (D–F) THP-1 cells were treated as in (C). Production of IL-1β (D), IL-6 (E) and TNF-α (F) was measured by ELISA assay. Data were analyzed by two-way ANOVA followed by Tukey's post-hoc test. **, $P < 0.01$; *, $P < 0.05$; NS, not significant.

Mechanistically, we prove that the function of HDAC5 in regulating macrophage immune response against MP infection is related to the altered activity of NF-κB. The inhibition of HDAC was previously shown to prevent NF-κB activation by stabilizing IκBα *via* the inhibition of proteasome activity [27]. Whether this mechanism can also be applied to explain HDAC5-regulated NF-κB activity under our experimental conditions remains to be addressed in the future. Besides, it has long been known that HDAC inhibition displays a broad anti-inflammatory effect in animal models of chronic inflammation diseases, like rheumatoid arthritis [28], hepatitis [29] and colitis [30]. Furthermore, under the stimulation with bacterial LPS and cytokines, HDAC5 was found to act as a positive regulator in the pro-inflammatory response in macrophages [9], which at least partly coincides with the functional role of HDAC5 we observed in macrophages during MP infection. We doubt that the regulation of NF-κB activity by HDAC5 may be ubiquitously present in other pathological conditions associated with inflammation. Addressing this hypothesis may help to shade new light on the physiological function of HDAC5 involved in the pathogenesis of inflammation diseases in which NF-κB plays an important role.

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