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Signa Vitae

ORIGINAL RESEARCH

Methyl jasmonate reduces the inflammation and apoptosis of HK-2 cells induced by LPS by regulating the NF-κB pathway

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Abstract

Background: Methyl jasmonate is a bioactive oxylipid that participates in the defense-related mechanisms of plants. The anti-inflammatory and anti-oxidative capacities of methyl jasmonate against lipopolysaccharide (LPS) induced arthritis have been widely investigated. However, the role of methyl jasmonate in LPS-induced cell model of tubular-interstitial nephritis (TIN) has not been reported.

Methods: LPS (5 μg/mL) was applied to treat human renal tubular epithelial cell line (HK-2) for the establishment of TIN cell model. LPS-induced HK-2 was incubated with 10 or 20 μM methyl jasmonate, cell viability and apoptosis were assessed by MTT and flow cytometry. ELISA and qRT-PCR were performed to determine the levels of interleukin (IL)-1 beta (IL-1β), IL-6, IL-8 and tumor necrosis factor-α (TNF-α). The downstream pathway was investigated by western blot.

Results: LPS induced cytotoxicity in HK-2 cell accompanied by decrease of cell viability and increase of cell apoptosis. Methyl jasmonate dosage dependently enhanced the cell viability and reduced cell apoptosis to ameliorate the cytotoxicity. LPS also induced inflammatory response in HK-2 cell with increased IL-1β, IL-6, IL-8 and TNF-α. Methyl jasmonate attenuated LPS-induced inflammation in HK-2 cell. Protein expression of IκBα was down-regulated, p65 and IκBα phosphorylation were up-regulated in LPS-induced HK-2. Methyl jasmonate attenuated LPS-induced decrease of IκBα and increase of p65 and IκBα phosphorylation in HK-2 cell.

Conclusion: Methyl jasmonate demonstrated anti-apoptotic and anti-inflammatory effects on LPS-induced HK-2 cell through suppression of NF-κB activation.

Keywords

Methyl jasmonate; LPS; Ochratoxin A; Apoptosis; Inflammation; NF-κB

1. Introduction

Tubulointerstitial nephritis (TIN), an inflammatory disease in interstitium and tubules, is one of the most common kidney diseases that leads to acute kidney injury and even renal failure [1]. Idiopathic, infectious (viral, bacterial, parasitic or fungal), immune-mediated or drug-induced nephritis are widely regarded as the leading causes of TIN [2]. Renal inflammatory lesions and tubular cell damage are the main characteristics of tubulointerstitial nephritis (TIN) [3]. Therefore, amelioration of renal inflammatory lesions and tubular cell damage are considered as effective therapeutic strategies for the prevention of TIN [1].

Lipopolysaccharide (LPS), a component of membrane of Gram-negative bacteria, has been shown to stimulate oxidative stress and inflammation [4]. LPS could induce secretion of monocyte chemoattractant protein-1 at the site of kidney injury to recruit macrophages, thus stimulating progressive tubulointerstitial lesions [5]. Therefore, a cell model of TIN was widely established by LPS induction [6].

Methyl jasmonate is a natural cyclopentanone lipid widely distributed in plant kingdom, and was originally isolated from jasmine flower, which was traditionally used to relieve stress, depression, irritability and memory loss [7]. Methyl jasmonate was widely known to suppress tumor cell proliferation and growth, promote cell apoptosis and reactive oxygen species mediated responses [8]. Moreover, methyl jasmonate protected mice against rotenone-induced parkinsonian-like symptoms, such as reducing of cognitive and depressive-like disorders, postural instability and motor activity, through repression of oxidative stress and inflammation [9]. Adjuvant-induced arthritis in Holtzman rats with enhanced reactive oxygen species and inflammatory response could be attenuated by methyl jasmonate [7], and methyl jasmonate diminished the increase in hepatic reactive oxygen species and retarded the systemic inflammation in arthritic rats [10]. LPS induced

arthritis in rats with reduced hepatic antioxidant enzymatic activity and enhanced cytokines secretion was also prevented by methyl jasmonate [11]. Therefore, this study aimed to evaluate protective role of methyl jasmonate against TIN in a LPS-induced cell model. Human renal tubular epithelial cell line (HK-2) was incubated with LPS for the establishment of TIN cell model. The protective roles of methyl jasmonate against LPS-induced cell injury and inflammation in HK-2 cell were then determined. The possible downstream signaling pathways were also explored in this study.

2. Materials and methods

2.1 Cell culture and treatment

HK-2 cell line was purchased from FMG-Bio (Sciencell, Shanghai, China) and then cultured in RPMI-1640 medium containing 10% fetal bovine serum (Gibco BRL, Grand Island, NY, USA) in a 37 °C humidified chamber. LPS suspended in phosphate-buffered saline (0, 1, 2, 5 or 10 μg/mL; Sigma-Aldrich, St. Louis, MO, USA) or ochratoxin A (0, 5, 10, 20, 25 μM; Sigma-Aldrich) were incubated with HK-2 cells for 24 hours. For methyl jasmonate treatment, 10 or 20 μM methyl jasmonate (Sigma-Aldrich) was simultaneously added into the culture medium of HK-2 cells with LPS (5 μg/mL) or ochratoxin A (20 μM) for 24 hours.

2.2 Cell viability

HK-2 cells were plated in a 96-well plate and incubated with LPS/ochratoxin A and/or methyl jasmonate for 24 hours, and then incubated with 10 μL MTT solution (5 mg/mL; Sigma-Aldrich) for 4 hours. Following removing of supernatant and incubation with dimethyl sulfoxide (150 μL; Sigma-Aldrich), the absorbance at 570 nm was measured under Spectrometer (Thermo Fisher Scientific, Waltham, MA, USA).

2.2.1 ELISA

HK-2 cells were plated in a 24-well plate and incubated with LPS/ochratoxin A and/or methyl jasmonate for 24 hours. The supernatant of the culture medium was collected and conducted with commercial ELISA kits (Thermo Fisher Scientific) for the determination of IL-1β, IL-6, IL-8 and TNF-α release.

2.2.2 qRT-PCR

RNAs were isolated from HK-2 cells by Trizol (Thermo Fisher Scientific) for 1 hour, and 2 μg of the RNAs were reverse transcribed into cDNAs by MMLV reverse transcriptase (Promega, Madison, WI, USA). The expression levels of IL-1β, IL-6, IL-8, TNF-α and GAPDH were determined by qRT-PCR analysis using SYBR Green real-time PCR Master Mix (Toyobo, Osa, Japan) and the primer sequences were listed below (Table 1).

2.3 Cell apoptosis

HK-2 cells were plated in a 24-well plate and incubated with LPS/ochratoxin A and/or methyl jasmonate for 24 hours. Cells (1×10^6) were then harvested and suspended in 100 μL Annexin V-binding buffer (Thermo Fisher Scientific). Following incubation with 5 μL Annexin V-FITC (Thermo Fisher Scientific) and 2 μL PI solution (2 mg/mL) in Annexin V-binding buffer, Attune™ Flow Cytometer (Thermo Fisher Scientific) was used to evaluate the cell apoptosis rate.

TABLE 1. Primers for qRT-PCR.

ID	Sequence(5′-3′)
GAPDH F	AGGTCGGTGTGAACGGATTTG
GAPDH R	TGTAGACCATGTAGTTGAGGTC
IL-1β F	ACGGACCCCAAAAGATGAAG
IL-1β R	TTCTCCACAGCCACAATGAG
IL-6 F	CAAAGCCAGAGTCCTTCAGAG
IL-6 R	GTCCTTAGCCACTCCTTCTG
IL-8 F	CTTGGCAGCCTTCCTGATTT
IL-8 R	TTCTTTAGCACTCCTTGGCAAAA
TNF-α F	CTTCTGTCTACTGAACTTCGGG
TNF-α R	CAGGCTTGTCACTCGAATTTTG

2.4 Western blot

Proteins in HK-2 cells were extracted by incubation with RIPA Lysis and Extraction Buffer (Thermo Fisher Scientific) for 30 minutes on ice, and quantified via acid protein kit (Thermo Fisher Scientific). SDS-PAGE was used to separate the protein samples, and the samples were then electro-transferred onto PVDF membrane (Millipore, Bedford, MA, USA). Bovine serum albumin (5%; Sigma-Aldrich) was used to block the membranes, and specific primary antibodies: anti-cleaved caspase-3 (1 : 2000, Cell Signaling, Beverly, MA, USA), anti-Bax and anti-Bcl-2 (1 : 3000, Cell Signaling), anti-p65 and anti-p-p65 (1 : 3500, Cell Signaling), anti-IκBα, anti-p-IκBα and anti-β-actin (1 : 4000, Cell Signaling) were used to probe the membranes. The membranes were then probed with horseradish peroxidase-labeled secondary antibody (1 : 5000, Cell Signaling), and the immunoreactivities were detected by enhanced chemiluminescence (KeyGen, Nanjin, China). The densitometry of each band was quantified under ImageJ and normalized to β-actin.

2.5 Statistical analysis

Data were expressed as mean $\pm$ SEM, and performed with one-way analysis of variance or student's t test under GraphPad Prism software. The p value < 0.05 was considered as statistically significant.

3. Results

3.1 Methyl jasmonate enhanced cell viability of LPS-induced HK-2 cells

To establish a TIN cell model, HK-2 cells were incubated with 0, 1, 2, 5 or 10 μg/mL LPS for 24 hours. Result showed that LPS induced significantly decrease in cell viability in HK-2 cells in a dose-dependent manner (Fig. 1A). However, simultaneously incubation with methyl jasmonate dosage dependently enhanced the cell viability of LPS (5 μg/mL)-induced HK-2 cells (Fig. 1B), suggesting the protective role of methyl jasmonate in TIN cell model. Moreover, ochratoxin A (0, 5,

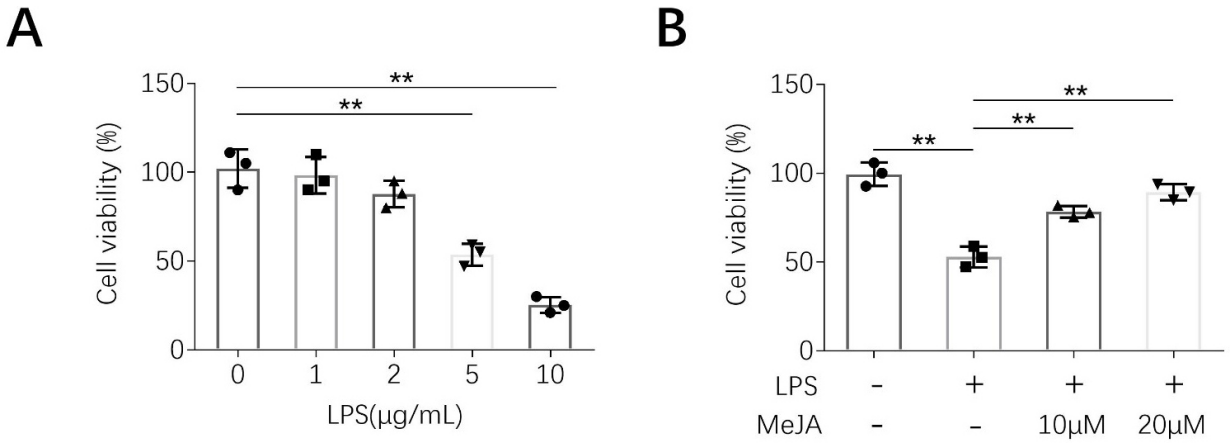

FIGURE 1. Methyl jasmonate enhanced cell viability of LPS-induced HK-2 cells. (A) LPS induced decrease in cell viability in HK-2 in a dosage-dependent manner. (B) Methyl jasmonate attenuated LPS-induced decrease in cell viability in HK-2 cells. ** $p < 0.01$. The experiments were carried out in triplicates.

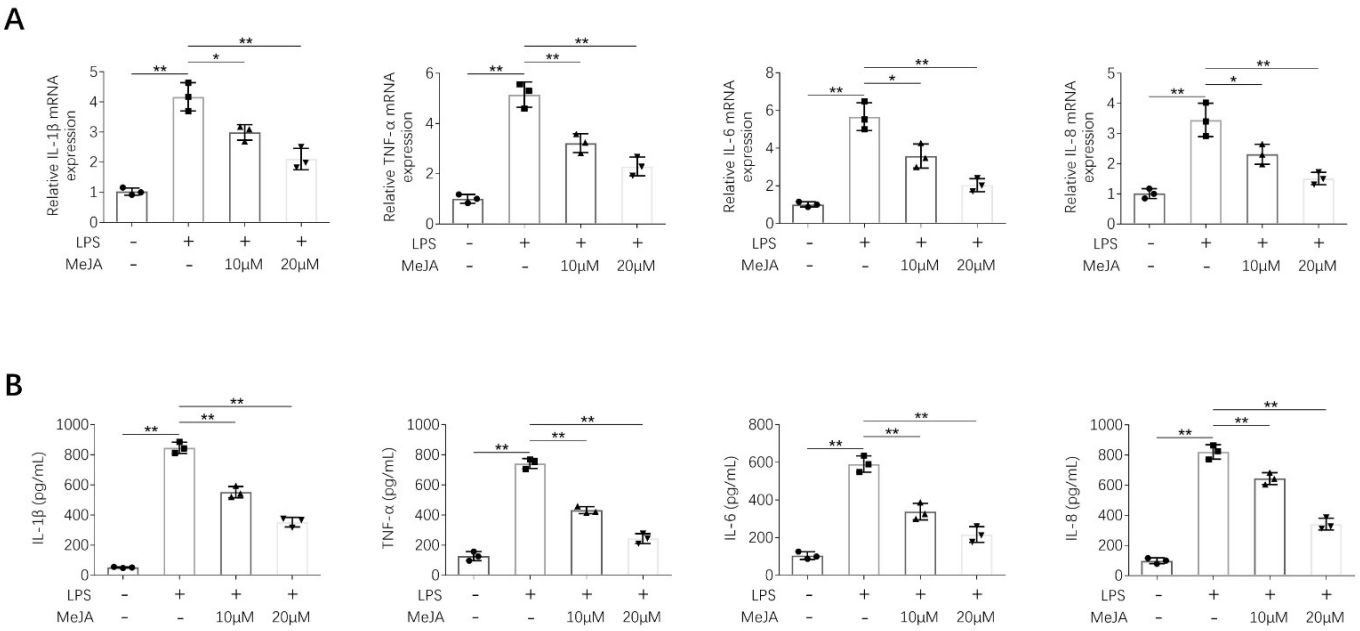

FIGURE 2. Methyl jasmonate suppressed inflammation in LPS-induced HK-2 cells. (A) Methyl jasmonate attenuated LPS-induced increase in IL-1β, IL-6, IL-8 and TNF-α mRNA expression in HK-2 cells. (B) Methyl jasmonate attenuated LPS-induced increase in IL-1β, IL-6, IL-8 and TNF-α secretion in HK-2 cells. * $p < 0.05$, ** $p < 0.01$. The experiments were carried out in triplicates.

10, 20, 25 μM) also decreased cell viability of HK-2 cells in a dose-dependent manner (Supplemental Fig. S1A), and methyl jasmonate incubation enhanced the cell viability of ochratoxin A (20 μM)-induced HK-2 cells (Supplemental Fig. S1B), also suggesting the protective role of methyl jasmonate in TIN cell model.

3.2 Methyl jasmonate suppressed inflammation in LPS-induced HK-2 cells

Inflammation in LPS/ochratoxin A-induced HK-2 cells was investigated by determination of cytokines production, including IL-1β, IL-6, IL-8 and TNF-α. qRT-PCR analysis indicated that LPS increased the expression of IL-1β, IL-6, IL-8 and TNF-α expression in HK-2 cells (Fig. 2A), while incubation with methyl jasmonate dosage dependently reduced the expression of IL-1β, IL-6, IL-8 and TNF-α (Fig. 2A). Moreover, methyl jasmonate also dosage dependently attenuated LPS (Fig. 2B) or ochratoxin A (Supplemental Fig. S1E)-induced increase in IL-1β, IL-6, IL-8 and TNF-α secretion in HK-2, suggesting the anti-inflammatory role of methyl jasmonate against LPS-induced HK-2.

3.3 Methyl jasmonate suppressed apoptosis in LPS-induced HK-2 cells

In addition to the anti-inflammatory role, the effect of methyl jasmonate on apoptosis of LPS/ochratoxin A-induced HK-2 cells was then evaluated. Result showed that methyl jasmonate dosage dependently attenuated LPS (Fig. 3A) or ochratoxin A

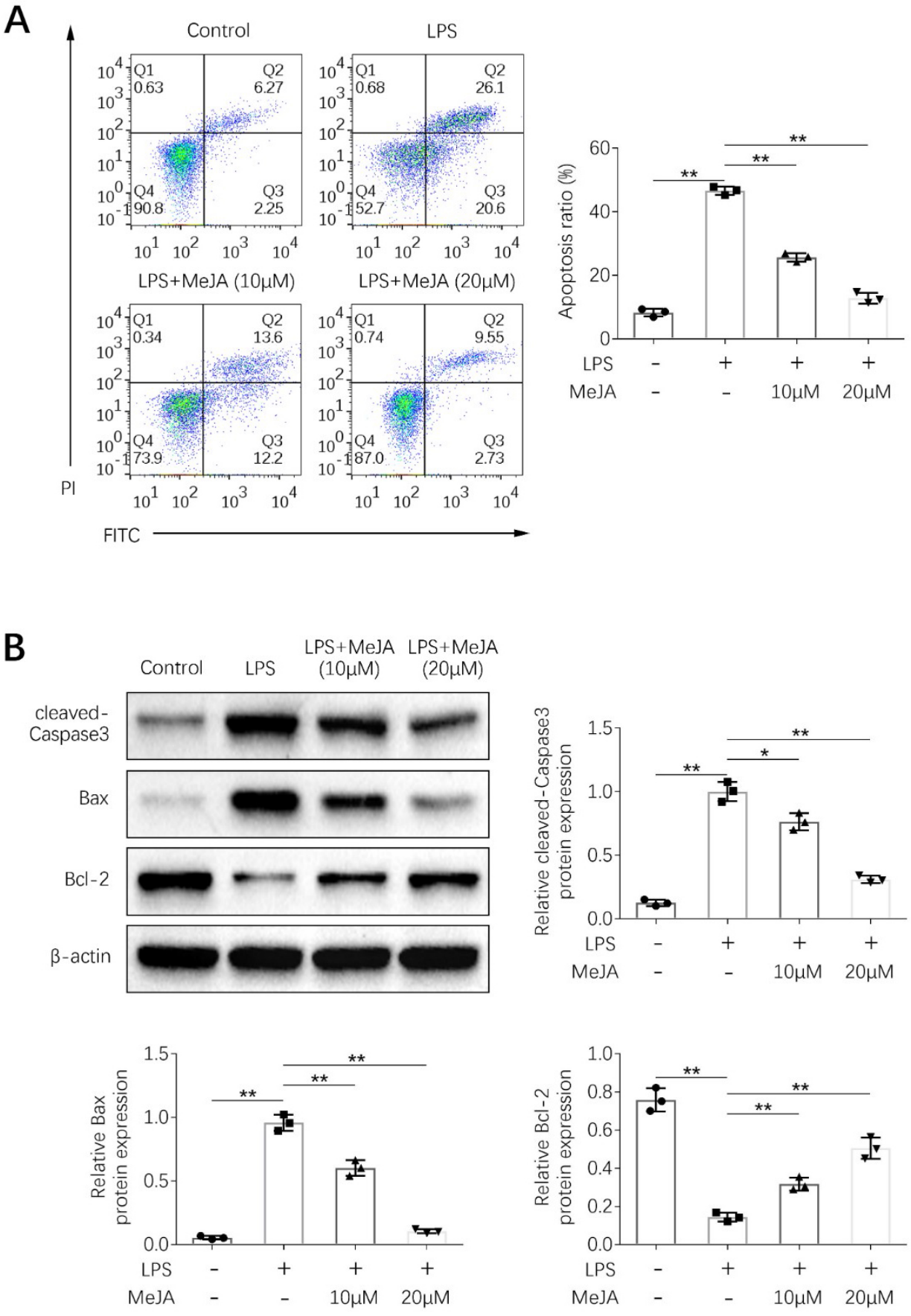

FIGURE 3. Methyl jasmonate suppressed apoptosis in LPS-induced HK-2 cells. (A) Methyl jasmonate attenuated LPS-induced increase in cell apoptosis in HK-2. (B) Methyl jasmonate attenuated LPS-induced decrease in Bcl-2 and increase in Bax and cleaved caspase-3 protein expression in HK-2. * $p < 0.05$, ** $p < 0.01$. The experiments were carried out in triplicates.

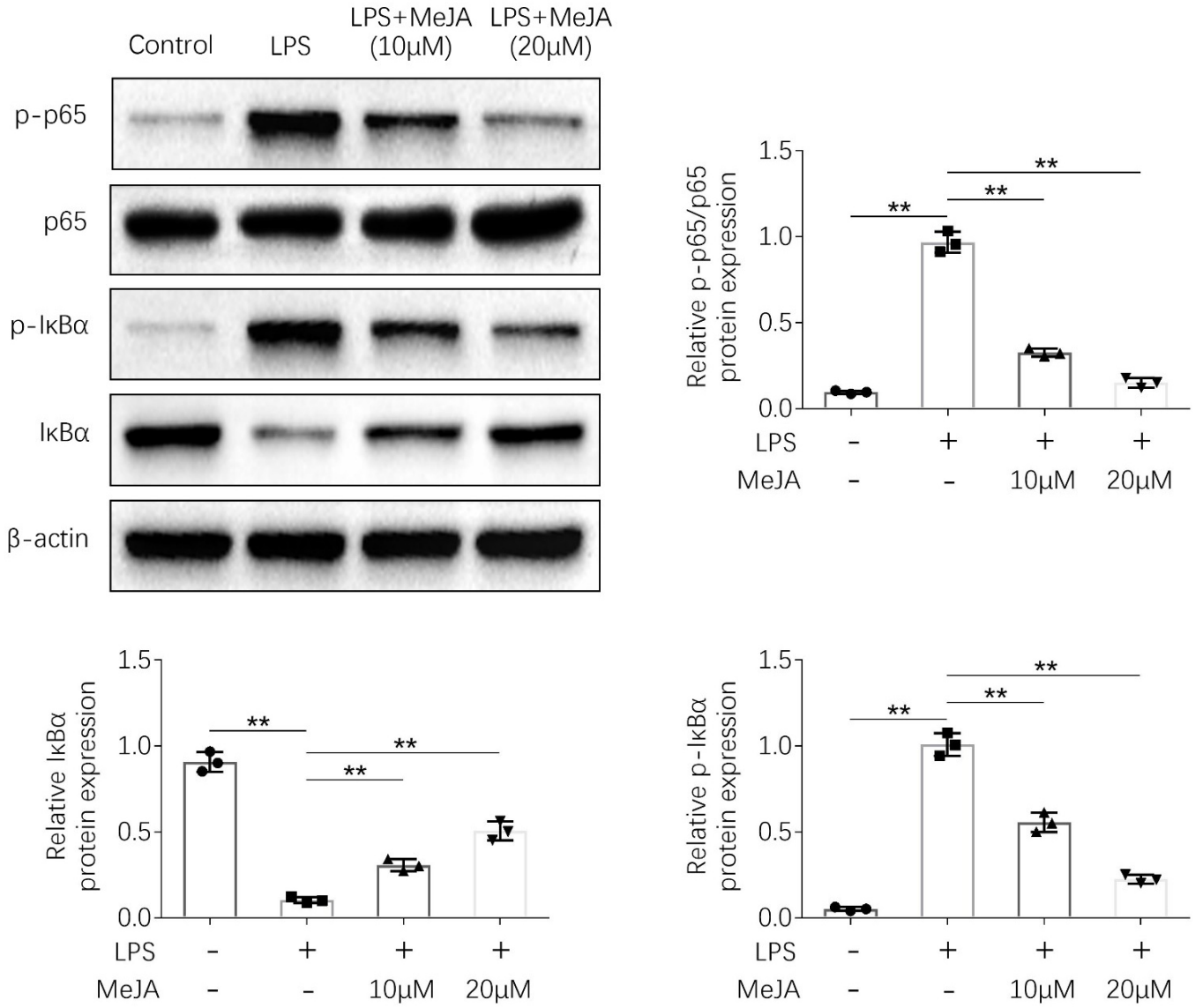

FIGURE 4. Methyl jasmonate suppressed NF-κB activation in LPS-induced HK-2 cells. Methyl jasmonate attenuated LPS-induced decrease of IκBα and increase of p65 and IκBα phosphorylation protein expression in HK-2. ** $p < 0.01$. The experiments were carried out in triplicates.

(Supplemental Fig. S1C,D)-induced increase in cell apoptosis in HK-2 cells. Moreover, LPS-induced decrease in Bcl-2 and increase in Bax and cleaved caspase-3 protein expression in HK-2 cells were also reversed by incubation with methyl jasmonate (Fig. 3B), suggesting the anti-apoptotic role of methyl jasmonate against LPS-induced HK-2 cells.

3.4 Methyl jasmonate suppressed NF-κB activation in LPS-induced HK-2 cells

Protein expression of IκBα was reduced in LPS-induced HK-2, while p65 and IκBα phosphorylation were enhanced (Fig. 4), indicating that LPS induced activation of NF-κB pathway in HK-2 cells. However, methyl jasmonate dosage dependently reversed the effects of LPS on protein expression of IκBα, p65 and IκBα phosphorylation (Fig. 4). These results demonstrated that methyl jasmonate suppressed NF-κB activation in LPS-induced HK-2 cells.

4. Discussion

Natural herbal medicine, such as ginseng, ginger, garlic, pomegranate and saffron, are widely used in the prevention of acute kidney injury [12]. The anti-inflammatory activity of methyl jasmonate has been widely investigated in disease related to inflammation [13]. Therefore, the role of methyl jasmonate on TIN, inflammatory disease in interstitium and tubules, was assessed in this study.

Kidney is usually exposed to toxins and drugs, and infection, drugs, hereditary, immune-mediated, metabolic or hematologic disorders could stimulate inflammation in the kidney, causing the recruitment and infiltration of inflammatory cells, extracellular matrix accumulation in the interstitium and the secretion of pro-inflammatory factors [14]. The inflammatory responses, such as tubular dilation and atrophy, extracellular matrix proteins accumulation, leukocyte infiltration or interstitial edema in the tubulointerstitial compartment, have been reported to be implicated in the pathogenesis of TIN [14].

Production of pro-inflammatory cytokines, such as IL-1β and TNF-α, could escalate the inflammatory process and aggravate the kidney injury [14]. LPS-induced release of IL-1β, IL-6, and TNF-α in HK-2 cells has been reported before, and the reduction of cytokines release ameliorated LPS-induced renal tubular epithelial cell injury [15]. The present study identified that LPS could induce inflammation of HK-2 cell by increasing the levels of IL-1β, IL-6, IL-8 and TNF-α. Methyl jasmonate showed anti-inflammatory properties by reducing the secretion of IL-1β, IL-6, IL-8 and TNF-α in LPS-induced HK-2 cells.

Excessive secretion of pro-inflammatory cytokines damages the mitochondrial function of renal tubular cells, thereby inducing cell apoptosis and necrosis during the development of TIN [16]. Suppression of renal tubular cell apoptosis has been shown to alleviate renal tubulointerstitial fibrosis in obstructive nephropathy [17]. This study showed that methyl jasmonate attenuated LPS-induced cytotoxicity in HK-2 cell by enhancing cell viability and reducing cell apoptosis. Since hepatocellular carcinoma cell necrosis and apoptosis were stimulated by methyl jasmonate through inhibition of glycolysis [18], the pathway involved in methyl jasmonate-suppressed apoptosis in LPS-induced HK-2 cells should be investigated in the further investigation.

Stimulation with inflammatory signals (TNFα or LPS) leads to phosphorylation-dependent degradation of IκBα, translocate NF-κB into nucleus, and NF-κB functions as a transcription factor to regulate inflammatory cytokines expression [19]. NF-κB was activated in renal tubular cells with decrease in IκBα and increase in p65 and IκBα phosphorylation, and activation of NF-κB plays a major role in tubulointerstitial inflammatory lesions in lupus nephritis [20]. Suppression of NF-κB activation facilitated for amelioration of TIN [21]. Expressions of NF-κB was down-regulated by methyl jasmonate in rotenone-induced mice [9]. This study revealed that LPS-induced decrease in IκBα and increase in p65 and IκBα phosphorylation in HK-2 were reversed by methyl jasmonate incubation, suggesting that methyl jasmonate might demonstrate anti-inflammatory effect against TIN through inactivation of NF-κB pathway. Methyl jasmonate showed cytotoxic effect against cancer cells through stimulation of MAPKs pathway [22]. However, methyl jasmonate protected against LPS-induced cytotoxic effect in HK-2 through inactivation of NF-κB pathway. Moreover, oxidative stress and apoptosis have been considered to be the main mechanisms for the pathogenesis of TIN [14], and enhanced oxidative stress was found in patients with TIN through up-regulation of IL-6, IL-10 and TNF-α [23]. Methyl jasmonate was shown to alter antioxidative defense system and lipid peroxidation in soybean under drought [24], and demonstrated anti-oxidant effect in β-amyloid-induced microglial cells [25]. Additionally, methyl jasmonate ameliorated oxidative stress [26] and reduced the oxidative stress in arthritic rats [27]. Therefore, methyl jasmonate might also exert anti-xidant effect to protect against TIN.

5. Conclusions

In summary, this study verified that methyl jasmonate alleviated LPS-induced apoptosis and inflammatory injuries in HK-2 cells by suppressing NF-κB pathway. These results might provide a theoretical basis for the clinical use of methyl jasmonate for the treatment of TIN. However, the *in vivo* protective effect of methyl jasmonate against TIN needs further investigation.

AUTHOR CONTRIBUTIONS

FHC and WW designed the study, supervised the data collection. XGC analyzed the data, interpreted the data. HSY, XJZ, CSQ, LLL and ZCS prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://??.

AVAILABILITY OF DATA AND MATERIALS

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

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