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Elevated resistin levels may regulate high mobility group box 1 expression in Guillain-Barré syndrome

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ABSTRACT

Interactions among cytokines have important roles in the inflammatory processes underlying Guillain-Barré syndrome (GBS). Resistin and high mobility group box 1 (HMGB1) are involved in many inflammatory processes. This study examined 51 GBS patients, and found that serum resistin levels were elevated in 51 patients with GBS and correlated with HMGB1 levels. In vitro, resistin induced the release of HMGB1, interleukin (IL)-1β, and IL-6 in THP-1 macrophages. This process was dependent on activation of p38 mitogen-activated protein kinase and NF-κB signaling pathways. These results suggest that signaling between resistin and HMGB1 might be a potential therapeutic target in GBS.

1. Introduction

Guillain-Barré syndrome (GBS) is an immune-mediated, rapidly progressive, and life-threatening polyneuropathy. It is characterized by mostly symmetric limb weakness and/or dysfunction of motor cranial-nerves with a monophasic disease course. About 20% of patients with GBS can suffer from respiratory insufficiency. The mortality rate from GBS is approximately 3–7% (Esposito and Longo, 2017; Goodfellow and Willison, 2016). Although considerable progress in understanding the pathogenesis of GBS was made in recent years, the exact cause and underlying immunologic inflammation mechanisms are poorly understood. Furthermore, existing drugs are insufficient in some patients, especially in the presence of a poor outcome and intolerance. Thus, it is necessary to continue to explore the molecular mechanisms and find new therapeutic targets that attenuate disease severity and further improve outcomes of patients with GBS.

Resistin is a proinflammatory cytokine that is involved in the immune response and inflammatory process in various diseases via production of cytokines (Bokarewa et al., 2005; Nagaev et al., 2016; Zuniga et al., 2017). Resistin is mainly produced by macrophages, inflammatory cells, and leukocytes in humans (Nagaev et al., 2006). There is evidence that resistin is upregulated in patients with inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis, and also is associated with inflammatory markers in several different populations (Santos et al., 2017; Sato et al., 2017). Our previous study found serum resistin levels were elevated in patients with myasthenia gravis (MG) and correlated with disease severity (Zhang et al., 2015). However, serum resistin levels in patients with GBS have not been reported.

High mobility group box 1 (HMGB1) is a DNA-binding protein that elicits proinflammatory properties via inducing the expression of many cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and nitric oxide, and chemokine adhesion molecules such as intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 (Fang and Jiang, 2016; Shah et al., 2018; Sun et al., 2013). HMGB1 is actively secreted extracellularly from stimulated macrophages, and passively released from injured cells. Thus, serum HMGB1 levels are increased in several inflammatory and autoimmune diseases, such as sepsis and MG, suggesting that HMGB1 may play a key role in the pathogenesis of neuroinflammation and immune responses (Andersson et al., 2018; Lan et al., 2017; Uzawa et al., 2015).

Our previous study confirmed that HMGB1 has a significant role in GBS (Zhang et al., 2016). The function of resistin is similar to HMGB1. Therefore, we hypothesized that resistin has a proinflammatory role in

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HMGB1, high mobility group box 1; GBS, Guillain-Barrésyndrome; IL, interleukin; MG, myasthenia gravis; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B; TLR, Toll-like receptor; TNF, tumor necrosis factor

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Table 1
General characteristics of patients with Guillain-Barré syndrome.

Parameters	Patients(n = 51)
Age at disease onset in years (range)	40.7 ± 16.2 (17–75)
Gender (female/male)	24/27
Symptoms preceding infection	27
Diarrhea	10
Upper respiratory tract infection	6
Short-term fever of unexplained origin	11
GBS disability score at 2 weeks after entry	3.37 ± 1.04
WBCs in CSF (10^6/L)	2 (0−10)
Protein in CSF (g/L)	1.03 ± 0.65

Data are expressed as means ± SD. GBS, Guillain-Barré syndrome; WBCs, white blood cells; CSF, cerebrospinal fluid.

GBS and functions cooperatively to HMGB1 in GBS pathogenesis. To investigate this hypothesis, we measured serum resistin levels in 51 patients with GBS. We further analyzed associations between serum resistin levels and HMGB1 in these patients. Considering resistin and HMGB1 are mainly expressed in human macrophages, cooperative mechanisms between resistin and HMGB1 were investigated by detecting HMGB1, IL-1β, IL-6, and TNF-α levels in THP-1 macrophages treated with resistin.

2. Materials and methods

2.1. Subjects and sample collection

We studied 51 patients with GBS from the Neurology Department of Tianjin Medical University General Hospital (Tianjin, China) and 49 healthy sex-, age- and body mass index-matched control subjects. The enrolled patients with GBS fulfilled the Asbury and Cornblath (Asbury and Cornblath, 1990) criteria, and were classified into three subtypes according to Ho's criteria(Ho et al., 1995): 10 patients were classified with acute inflammatory demyelinating polyneuropathy; 33 patients with acute motor axonal neuropathy; and 8 patients were an unclassified subtype. Patients with hypokalemia, hyperkalemia, porphyria, diabetes, ormetabolic, connective tissue, and other neurological disorders were excluded. Clinical and demographic data on the GBS cohort are given in Table 1. Serum samples were collected prior to intravenous immunoglobulin treatment and were stored frozen at −80 °C until use. The ethics committee of Tianjin Medical University General Hospital approved the study, and informed consent was obtained from all patients prior to participation.

2.2. Cell culture and reagents

The human monocytic leukemia cell line, THP-1, was obtained from the Stem Cell Bank, Chinese Academy of Sciences (Shanghai, China). Cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (Thermo Fisher Scientific, Waltham, MA, USA) and 0.05 mM 2-mercaptoethanol (Invitrogen, Carlsbad, CA, USA) in a humidified atmosphere of 5% CO_2at 37 °C.THP-1 cells were induced to differentiate from monocytes to macrophages by treatment with 0.1 μM phorbol 12-myristate 13-acetate (Sigma-Aldrich, St. Louis, MO, USA) for 72 h. THP-1 macrophages were plated on 6-well plates at 5×10^5 cells/mL for 6 h in culture medium without fetal bovine serum, then recombinant resistin protein (PeproTech, Rocky Hill, NJ, USA) (25,50, 100 ng/mL) or lipopolysaccharide (LPS) (100 ng/mL) were added. After incubation for 24 h, the culture medium was collected for detection of cytokines. Cells were washed twice with phosphate-buffered saline, and then total protein was extracted.

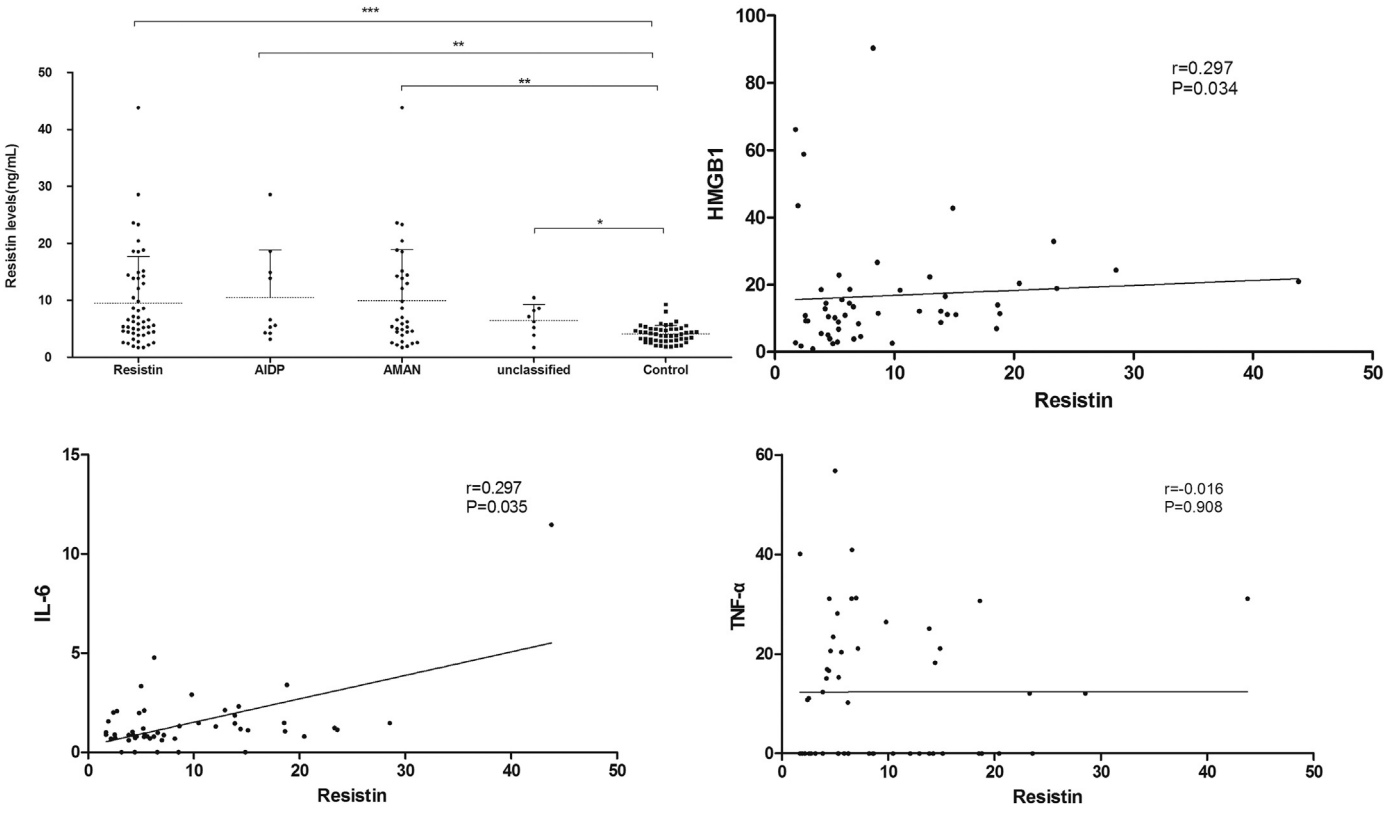

Fig. 1. Serum resistin levels and the relationships among resistin, high mobility group box 1 (HMGB1), interleukin (IL)-6, and tumor necrosis factor (TNF)-α in 51 patients with Guillain-Barré syndrome (GBS), including 10 acute inflammatory demyelinating polyneuropathy (AIDP), 33 acute motor axonal neuropathy (AMAN) and 8 unclassified cases. (A) Serum resistin levels in patients with GBS. Correlations between serum resistin and (B) HMGB1, (C) IL-6, and (D) TNF-α levels in patients with GBS. ***p < .001;**p < .01; *p < .05 vs. control group.

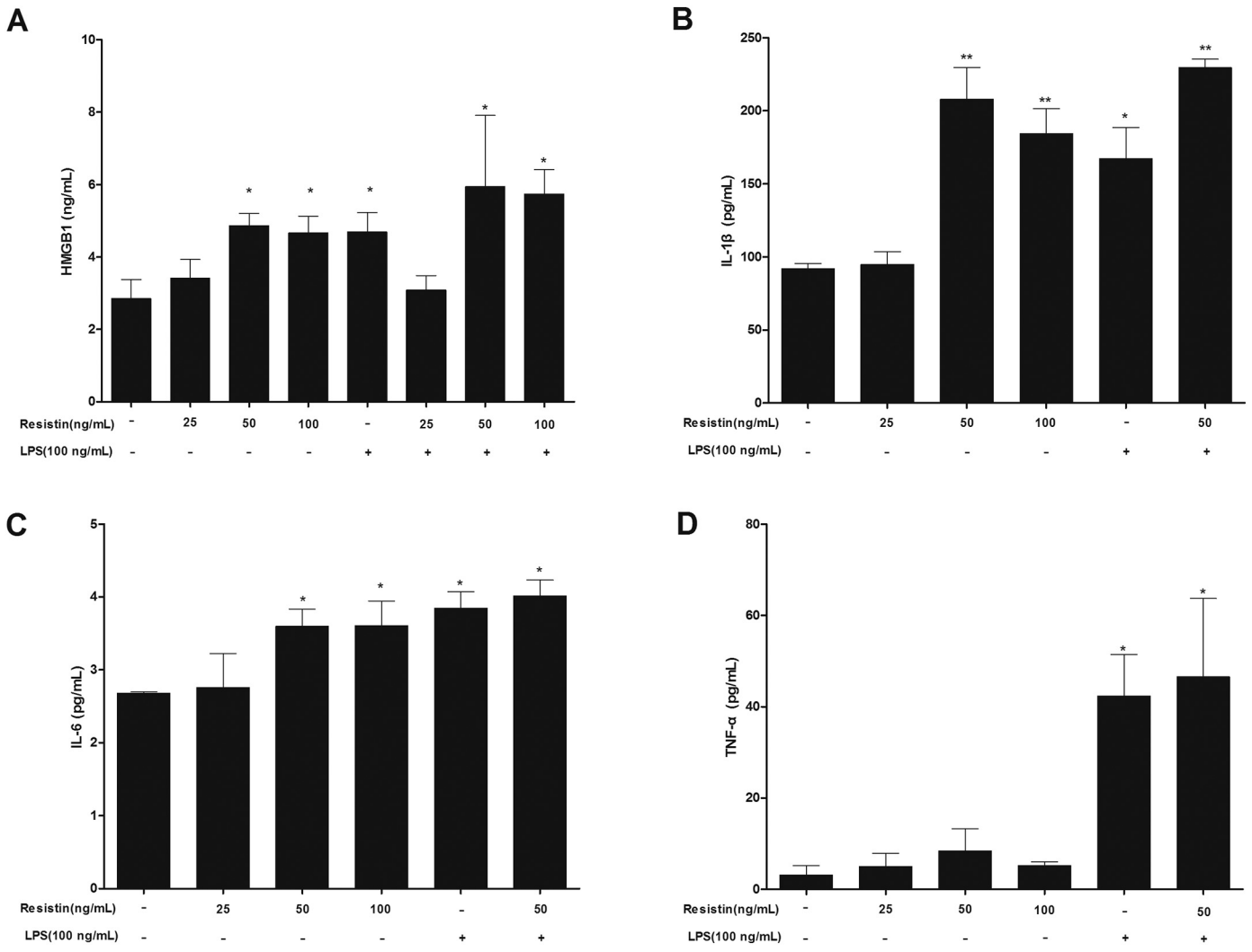

Fig. 2. Levels of (A) high mobility group box 1 (HMGB1), (B) interleukin (IL)-1β, (C) IL-6, and (D) tumor necrosis factor (TNF)-α in the culture medium of THP-1 cells treated with resistin or lipopolysaccharide (LPS). Data are expressed as means ± SD. *p < .05; **p < .01.

The p38 mitogen-activated protein kinase (MAPK) inhibitor, SB203580, was purchased from Cell Signaling Technology (Danvers, MA, USA). The nuclear factor (NF)-κB inhibitor, Bay11–7085, was purchased from Sigma-Aldrich.

2.3. Measurements of resistin, HMGB1, TNF-α, IL-1β, and IL-6 levels

Serum levels of resistin were detected using a human resistin enzyme-linked immunosorbent assay (ELISA) kit (eBioscience, San Diego, CA, USA) according to the manufacturer's instructions. The levels of HMGB1 (Shino-Test Corporation, Tokyo, Japan), TNF-α, IL-1β, and IL-6 (eBioscience) in the culture medium were measured using commercially available ELISA kits according to the manufacturers' instructions. If the level was less than the limit of detection, we considered it to be zero.

2.4. Western blotting

Cells were lysed with radioimmunoprecipitation assay buffer to extract proteins. Total protein concentrations were measured using the bicinchoninic acid assay (BioTeke, Beijing, China). Proteins were separated by electrophoresis on 10% polyacrylamide gels, then transferred to polyvinylidene difluoride membranes (EMD Millipore, Bedford, MA, USA). We used 5% (w/v) non-fat dry milk to block the membranes for 2 h which were then incubated at 4 °C overnight with the following primary antibodies from Cell Signaling Technology: anti-HMGB1 (1:1000; #3935), p38MAPK (1:1000; #8690),phospho-p38MAPK (1:1000; #4511) , NF-κBp65 (1:1000; #8242), phospho-NF-κBp65(1:1000; #3033),rabbit anti-actin (1:1000; #4970) and anti TLR4 antibody (1:200 ; sc-293,072) from Santa Cruz biotechnology. The membranes were then incubated with horseradish peroxidase-linked secondary antibodies and bands were visualized using a chemiluminescence detection kit (Bio-Rad, Hercules, CA, USA). Quantitation was performed by luminal chemiluminescence using a ChemiDocXRS system (Bio-Rad).

2.5. Statistical analyses

The unpaired *t*-test was used to analyze statistical differences between two groups, and one-way analysis of variance was used to analyze statistical differences among more than two groups by PRISM 5.0 software (GraphPad Software, San Diego, CA, USA). We also analyzed the relationship between serum resistin and serum HMGB1 levels using Spearman's rank correlation. P values < .05 were considered significant.

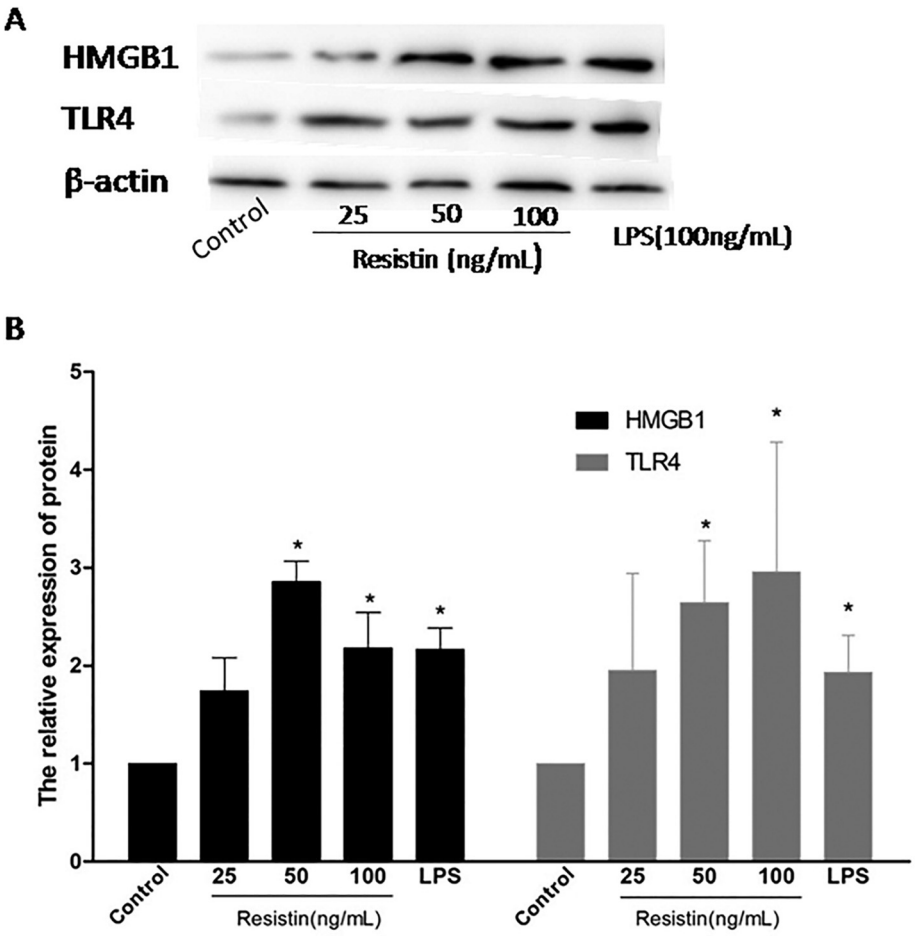

Fig. 3. Levels of high mobility group box 1 (HMGB1) and Toll-like receptor (TLR) 4 in THP-1 cells treated with resistin or lipopolysaccharide (LPS). (A) The protein expression levels of HMGB1 and TLR4 in THP-1 cells were detected by western blot; (B) Quantitation analysis using Quantity One software. Data are expressed as means ± SEM. *$p < .05$.

3. Results

3.1. Increased serum resistin levels and the positive relationship between serum resistin, and HMGB1 and IL-6 levels in patients with GBS

To investigate the role of resistin in GBS, we determined serum resistin levels in patients with this disorder. A significant increase in serum resistin levels was found in GBS patients compared to healthy controls($p < 0.001$, Fig. 1A). Across the three different GBS subtypes, resistin levels were significantly higher in all subtypes than in control subjects ($p < .05$ for each subtype, Fig. 1A). However, no difference in serum resistin levels was found among the GBS subtypes ($p > .05$, Fig. 1A). In addition, there was no obvious correlation between resistin levels and the GBS disability score assessed at two weeks after entry ($r = 0.151$; $p = .289$).

To investigate the relationship between serum resistin levels and HMGB1 in GBS patients, we determined their correlation. There was a significant positive correlation between serum resistin levels and HMGB1in patients with GBS ($r = 0.297$, $p = .034$; Fig. 1B). We also found that serum resistin levels were positively correlated with IL-6 levels in GBS patients ($r = 0.297$, $p = .035$, Fig. 1C). No significant correlation was found between serum resistin levels and TNF-α($r = -0.016$; $p = .908$, Fig. 1D).

3.2. Resistin increased HMGB1, IL-1β, and IL-6 levels in THP-1 macrophages

Previous studies found that LPS induced the secretion of HMGB1 (Rao et al., 2018).Thus, we used LPS as the positive control group. To investigate cooperative effects between resistin and HMGB1, we used an ELISA to detect HMGB1 levels in the culture medium of THP-1 macrophages treated with resistin and/or LPS for 24 h. The results showed that the secretion of HMGB1was increased significantly following treatment with 50 or 100 ng/mL, but not 25 ng/mL, resistin ($p < .05$, Fig. 2A).There was little difference in HMGB1 levels when resistin plus LPS or LPS alone was added (Fig.2A). The levels of IL-1β and IL-6 were significantly higher in the different resistin treatment groups compared to the blank control group ($p < .05$, Fig. 2B, C). There was no difference in the TNF-α level between the resistin and blank control groups (Fig. 2D). We also found that there were no cooperative effects between resistin and LPS for the secretion of TNF-α, IL-1β, and IL-6 (Fig. 2B–D).

The expression of HMGB1 protein in THP-1cells was determined by western blotting assays. The results showed that HMGB1 protein levels were increased following treatment with 50 or 100 ng/mL, but not 25 ng/mL, resistin ($p < .05$, Fig. 3A, B). Based on these results, we chose a resistin concentration of 50 ng/mL for subsequent experiments.

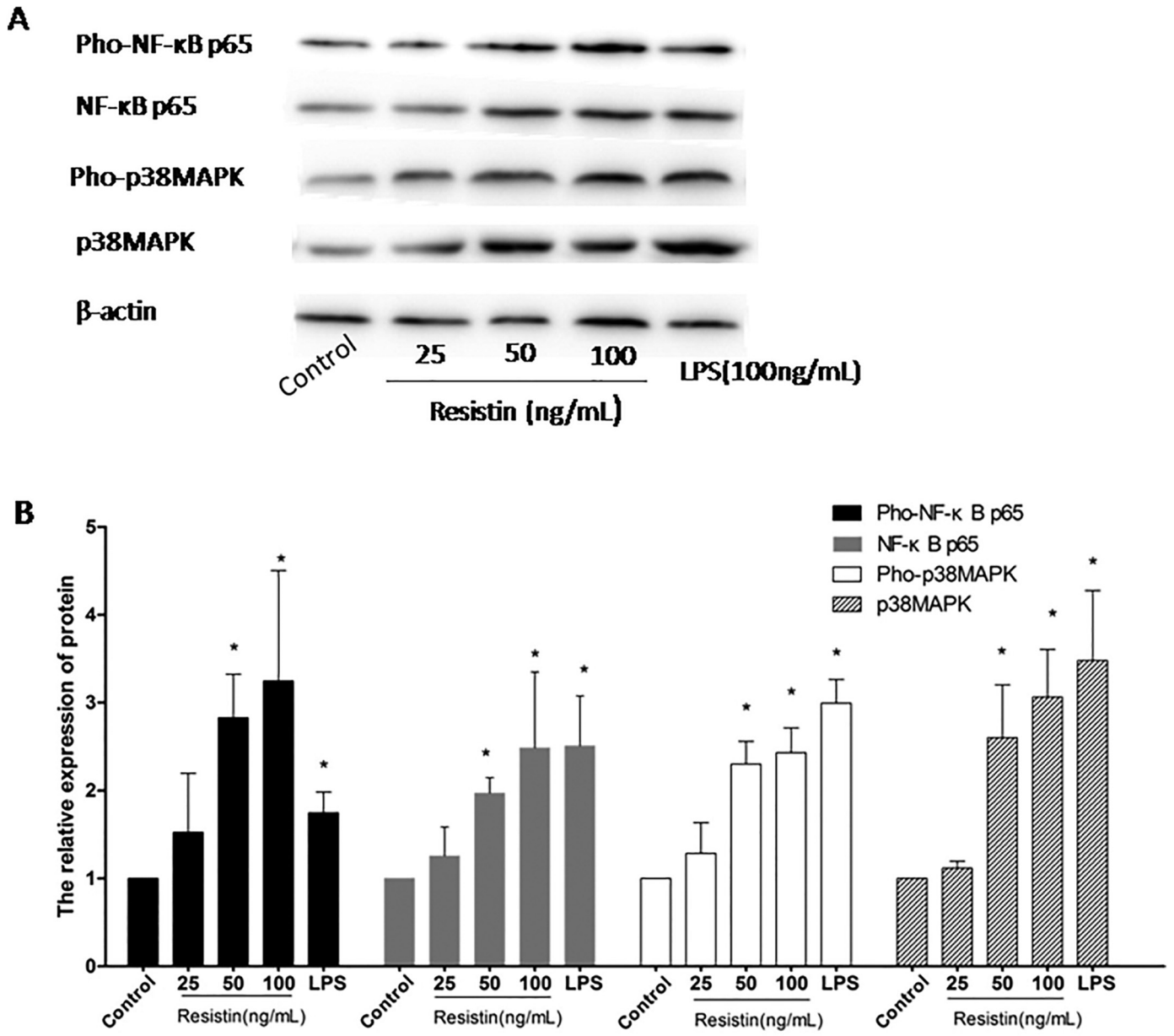

Fig. 4. Levels of p38 mitogen-activated protein kinase (MAPK) and NF-κB in THP-1 cells treated with resistin or LPS. (A) The protein expression levels in THP-1 cells were detected by western blot; (B) Quantitation analysis using Quantity One software. Data are expressed as means ± SEM.*p < .05.

3.3. Resistin increased HMGB1, IL-1β, and IL-6 levels in THP-1 macrophages by activating p38MAPK and NF-κB

Previous studies demonstrated that resistin promoted the synthesis of proinflammatory cytokines by binding to TLR4 (Li et al., 2018). We analyzed expression of the TLR4 protein in THP-1cells by western blotting. The results showed that TLR4 protein levels were increased following treatment with resistin ($p < .05$, Fig. 3A, B). Resistin binding to TLR4 can activate the p38MAPK and NF-κB signaling pathways. To explore the mechanism by which resistin enhanced the expression of HMGB1, we studied whether p38MAPK and/or NF-κB were involved in its synthesis. Compared to the blank control group, THP-1 cells treated with resistin exhibited significant increases in the expression of p38MAPK and NF-κB ($p < .05$, Fig. 4A, B). Inhibitors of p38MAPK (SB203580) and NF-κB (Bay11–7085) significantly decreased the secretion of HMGB1, TNF-α, IL-1β, and IL-6 into the culture medium ($p < .05$, Fig. 5).Western blotting revealed that expression of the HMGB1 protein was also decreased by these inhibitors ($p < .05$, Fig. 6). These results suggest that the p38MAPK and NF-κB signaling pathways play important roles in resistin-induced HMGB1 expression.

4. Discussion

A wide variety of cytokines and mediators participating in inflammation and immune responses contribute to the pathophysiology of GBS (Winer, 2011). Our previous studies showed that resistin played crucial roles in inflammatory processes in MG and neuromyelitis optica (Qi et al., 2016; Zhang et al., 2015). However, there are few studies on the role of resistin in GBS. In the current study, we found that serum resistin levels were increased in patients with GBS, indicating that it may be involved in GBS pathophysiology. Resistin promoted the expression of inflammatory cytokines such as TNF-α and IL-6, which play important roles in B-cell activation and T-cell development. Our previous study found that serum TNF-α and IL-6 levels were also elevated in patients with GBS (Zhang et al., 2016). Moreover, some inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, can induce

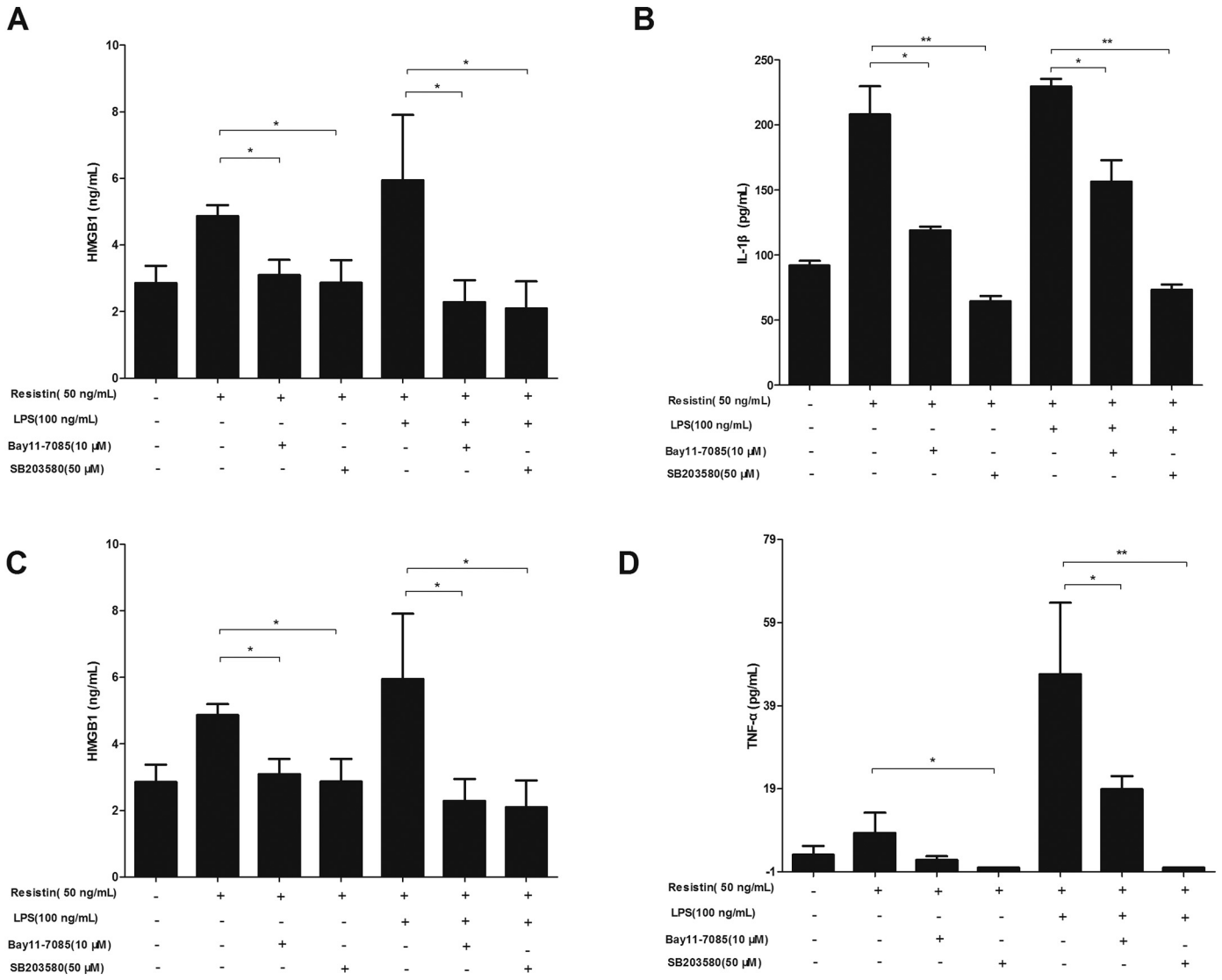

Fig. 5. Levels of (A) high mobility group box 1 (HMGB1), (B) interleukin (IL)-1β, (C) IL-6, and (D) tumor necrosis factor (TNF)-α in the culture medium of THP-1 cells treated with p38 mitogen-activated protein kinase (MAPK) and NF-κB inhibitors. Data are expressed as means ± SD. *p < .05; **p < .01.

resistin expression.

Based on the known interactions among resistin, IL-6, and TNF-α, we analyzed the association between resistin levels, and IL-6 and TNF-α in patients with GBS. The results showed that serum resistin levels were positively correlated with IL-6 levels. Resistin is a proinflammatory cytokine that is involved in the immune response and inflammatory process in various diseases via production of numerous cytokines, such as IL-6 and TNF-α. These cytokines can promote immunoglobulin synthesis by B lymphocytes and are associated with autoantibody production, which may be related to the pathogenesis of peripheral nerve damage (Adornetto et al., 2019; Buyukakilli et al., 2014; Maimone et al., 1993). Taken together, these findings indicate that resistin may be involved in the pathogenesis of GBS through cytokine interactions, despite the lack of a correlation between serum resistin levels and disability, perhaps due to the limited number of enrolled patients and complex interactions among cytokines. In addition, resistin exerts chemotactic activity on CD4-positive lymphocytes which may contribute to the progression of GBS (Walcher et al., 2010).

HMGB1 is a proinflammatory molecule that is involved in the pathogenesis of various inflammatory diseases. During inflammatory reactions, activated monocytes/macrophages are the main source of HMGB1. When the production of exogenous bacterial endotoxins such as LPS, or endogenous inflammatory cytokines, is stimulated, HMGB1, which is mainly concentrated in the nucleus, is released from activated monocytes/macrophages. Our previous study (Zhang et al., 2016) found high levels of HMGB1 in patients with GBS, suggesting that it has an important role in this disorder and is involved in the inflammation processes of GBS.

Interestingly, the functions of resistin are similar to HMGB1. However, an association between resistin and HMGB1was not previously investigated in patients with GBS. The current study found a positive relationship between resistin and HMGB1, suggesting that resistin may regulate the expression of HMGB1 in GBS to enhance inflammatory immune responses.

To study the relationship between resistin and HMGB1, and the underlying mechanisms in GBS, we used THP-1 macrophages treated with different concentrations of resistin. The resulting high HMGB1 levels in the culture medium and cells suggested that resistin promoted the expression of HMGB1.

Some studies demonstrated that HMGB1 can be up-regulated by stimulation with proinflammatory cytokines such as IL-1β, IL-6, and TNF-α (Andersson et al., 2018).We found a positive correlation between serum resistin and IL-6 levels in patients with GBS. Taken together, these findings indicate that resistin may promote the release of

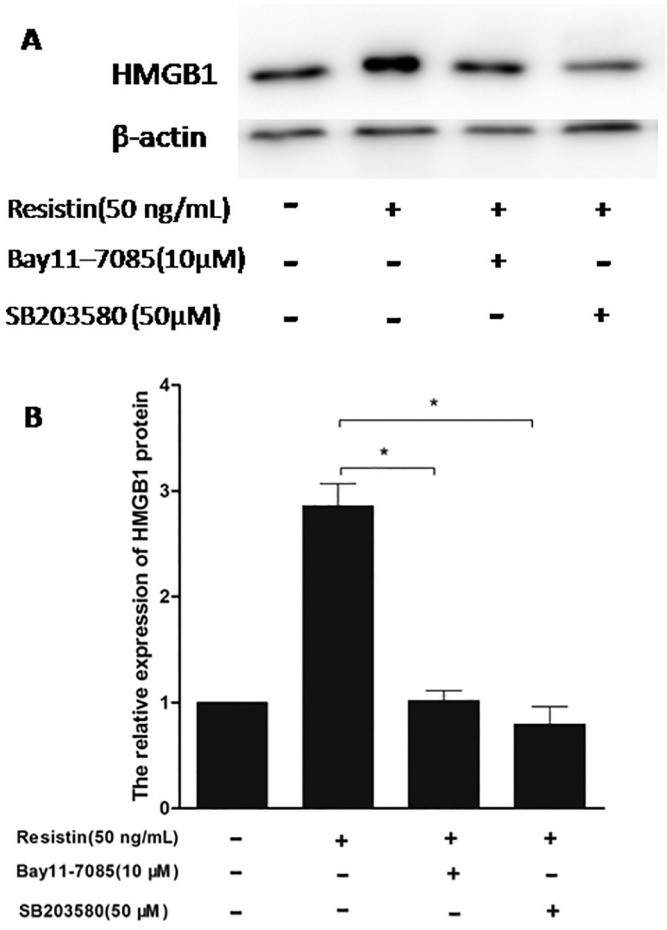

Fig. 6. Levels of high mobility group box 1 (HMGB1) protein in THP-1 cells treated with p38 MAPK and NF-κB inhibitors. (A) The protein expression levels in THP-1 cells were detected by western blot (B) Quantitation analysis using Quantity One software. Data are expressed as means ± SEM. *p < .05.

IL-6 and IL-1β. These proinflammatory cytokines then induce the expression and release of HMGB1 and promote inflammation. The results of our study also show that the release of HMGB1, IL-6, TNF-α, and IL-1β is significantly increased after treatment of THP-1 cells with LPS.

The mechanism of resistin-enhanced HMGB1expression is unknown. Resistin is known to enhance the expression of proinflammatory cytokines through TLR4 (Li et al., 2018).The findings reported here indicated that the expression of TLR4 was significantly higher in THP-1 macrophages treated with resistin. The activation of TLR4 relays cell surface signals to various intracellular pathways, including the NF-κB and MAPK pathways (Hsieh et al., 2014; Li et al., 2017).To evaluate the role of these pathways in the resistin-induced release of HMGB1, inhibitors of NF-κB (Bay11-7085) and p38MAPK (SB203580) were added to THP-1 cells. The results showed that the resistin-induced release of HMGB1, IL-6, and IL-1β was significantly decreased by both inhibitors. Simultaneously, treatment with resistin significantly increased the levels of NF-κB and p38MAPK proteins. Moreover, the addition of NF-κB and p38MAPK inhibitors decreased expression of the HMGB1 protein. Although the signaling pathway is complicated, these findings still indicate that activation of p38 MAPK and NF-κB plays an important role in the synthesis of HMGB1initiated by resistin in THP-1 macrophages.

5. Conclusions

In summary, our study found that elevated serum resistin levels correlate with HMGB1 levels in patients with GBS, and resistin can induce the release of HMGB1, IL-1β, and IL-6, and promotes the synthesis of HMGB1 through TLR4 by activating the NF-κB/MAPK signaling pathway in THP-1 macrophages. This indicates that resistin may be involved in the pathogenesis of GBS through the signaling pathway between resistin and HMGB1, despite the limitation that the in vitro experiments were not conducted using GBS samples. Importantly, these results suggest that the signaling pathway between resistin and HMGB1 might become a potential therapeutic target in GBS.

Conflict of interest statement

All authors report that there are no conflicts of interests.

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