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To cite this article: Ye Yang, Lei Huang, Chongchong Tian & Bingjun Qian (2022) Magnesium isoglycyrrhizinate alleviate airway inflammatory responses in ovalbumin-induced mouse model of allergic asthma, *Immunopharmacology and Immunotoxicology*, 44:4, 525-533, DOI: [10.1080/08923973.2022.2055567](https://doi.org/10.1080/08923973.2022.2055567)

To link to this article: <https://doi.org/10.1080/08923973.2022.2055567>



Published online: 29 Mar 2022.



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ORIGINAL ARTICLE



Magnesium isoglycyrrhizinate alleviate airway inflammatory responses in ovalbumin-induced mouse model of allergic asthma

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ABSTRACT

Objective: Asthma is a common chronic airway inflammatory disease, lacking effective therapeutic approaches. Magnesium isoglycyrrhizinate (MgIG) is an anti-inflammatory drug for treating chronic inflammation. However, it is still ambiguous whether MgIG can function in allergy induced asthma. In this study, we investigated the anti-inflammation effect of MgIG in mice with allergy induced asthma and explored the underlying mechanisms.

Methods: Mouse asthma model was established with ovalbumin (OVA) sensitization and challenge. Subsequently, mice sensitized with OVA were randomly assigned into four groups: asthma model group (MDL), dexamethasone group (DXM), MgIG group (MgIG), and normal mice were used as normal control (CON). The mice in MgIG, MDL were given 0.2 mg/mL MgIG solution by atomization inhalation for 30 min before 1% (w/v) OVA challenge. At the completion of model establishment and drug treatment, cells in bronchoalveolar lavage fluid were classified, inflammatory factors in serum were determined, histopathological analysis was performed by H&E staining, and expression of MUC5AC, NLRP3, and cleaved caspase-1 in the lung tissue was also determined by immunohistochemistry and western blotting, respectively.

Key findings: In comparison to MDL group, MgIG treatment could significantly inhibit the recruitment of white blood cells, neutrophils, and eosinophils in BALF, reduced the production of IL-6, TNF- α , and IgE in serum, and reduced mucus secretion and the infiltration of inflammatory cells. Also, an increase of NLRP3 and Caspase-1 protein levels were suppressed by MgIG treatment.

Conclusion: Our study findings support that nebulizer inhalation of MgIG as an effective therapy in treating the allergy induced asthma.

ARTICLE HISTORY

Received 28 September 2021
Accepted 12 March 2022

KEYWORDS

MgIG; inflammation;
asthma; OVA; IgE; NLRP3

Introduction

Bronchial asthma is a chronic airway inflammation involving a variety of cells and cellular components. This inflammation usually causes an increase in airway hyperresponsiveness, contributing to the patients experiencing recurrent wheezing, shortness of breath, chest tightness, or coughing [1,2]. At night or early morning, these symptoms are often accompanied with extensive and variable airflow obstruction. The pathogenesis of asthma remains unclear. In addition to genetic factors, it is also well-accepted that asthma can be induced by airborne pollutants, such as cigarette smoke and traffic/industrial pollution, which exerts a negative effect on the quality of life and exacerbates related symptoms [3–5]. In the past few decades, the prevalence of asthma has rapidly increased to epidemic levels. There are currently an estimated 300 million patients worldwide, and this total is predicted to increase dramatically in the next 15–20 years [6].

Chronic airway inflammation is one of the main characteristics of persistent asthma. Airway chronic inflammatory response is the result of the joint participation and interaction of a variety of inflammatory cells [7,8]. Many cells, especially mast cells, eosinophils, and T lymphocytes, have

been considered to play a key role in the pathogenesis of asthma [9]. Moreover, high serum immunoglobulin E (IgE) levels, airway cell infiltration of eosinophils, and T helper cell 2 (Th2) cytokines also play an important role in the pathological development of asthma [10,11].

The nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3), associated with a series of chronic inflammatory diseases, is a key mediator to regulate airway inflammatory response in asthma [12,13]. NLRP3 inflammasomes can recruit and activate proinflammatory protease caspase-1 through recognizing pathogen-associated molecular patterns (PAMPs). The activated caspase-1 can further cleave IL-1 β , IL-18, and IL-33 precursor, resulting in an increase of IL-1 β and IL-18 secretion to cause inflammation, which was attributed to the combination of IL-1 β and IL-1R complexes to further activate nuclear factor-kappaB (NF- κ B) and mitogen-activated protein kinase (MAPK) pathways resulted in increase of proinflammatory factors, such as IL-6 and TNF [14–16]. IL-6 and TNF play an important role in inflammatory regulation in the pathogenesis of asthma [17]. Additionally, the activated inflammasomes can also induce cell inflammatory necrosis. The resulted inflammatory infiltration alter the

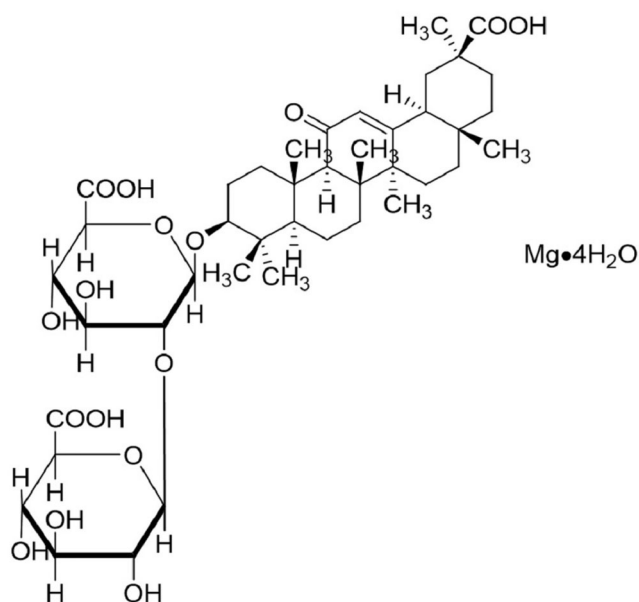


Figure 1. Chemical structure of MglG. Systematic name, (18 α , 20 β)-carboxy-11-oxo-oleanane-12-en-3 β -yl-2-O- β -D-glucopyranosiduronyl- α -D-glucopyranosiduronic acid Magnesium Tetrahydrate; formula, $C_{42}H_{60}MgO_{16} \cdot 4H_2O$.

structural integrity of the epithelium and remodeling the airway wall and accelerate inflammatory development to exacerbate asthma.

Asthma can be effectively controlled by currently available drugs, such as corticosteroids and bronchodilators, but these therapies are associated with side effects [18,19]. Some phytochemicals also exhibit anti-inflammatory activity, such as glycyrrhizic acid (also named glycyrrhizin), which is concentrated in the root of a Chinese medicine plant Licorice (*Glycyrrhiza glabra*) used for curing cough and sputum for thousands of years without adverse reactions [20]. Glycyrrhizic acid preparations or derivatives, such as magnesium isoglycyrrhizinate (MglG, Figure 1), have been developed for clinical treatment of inflammatory diseases [21]. The therapeutic effect of MglG has been confirmed on lung injury induced by paraquat poisoning in rats [22]. Presently, it has been recommended as supportive care for COVID-19 infected patients by National Health Commission of People's Republic of China and National Administration of Traditional Chinese Medicine [23]. Nevertheless, the anti-inflammatory activity and protective effect of MglG in allergic asthma is unclear.

In this paper, we aim to investigate the anti-inflammatory effects of MglG in asthmatic mice and explore its underlying mechanisms.

Materials and methods

Preparation of MglG

MglG injection, containing 5 mg/mL MglG ($C_{42}H_{60}MgO_{16}$) dissolved in normal saline, was purchased from Chia Tai Tianqing Pharmaceutical Group Co., Ltd. (Lianyungang, China). All drugs were stored at 4 °C prior to use.

Animals

Seven-week-old female BALB/c mice weighing approximately 22 g (SPF grade, production license number: SCXK2008-0016), purchased from Shanghai Super-B&K Laboratory Animal Co., Ltd. (Shanghai, China), were housed in cages, and raised under the specific pathogen-free conditions with room temperature of 21–23 °C, humidity of about 60 $\pm$ 5%, and a 12 h light/dark cycle at Center of Experimental Animal, Jiangsu Vocational College of Medicine. All animals were treated in accordance with the guidelines and regulations for the use and care of animals of the Center for Laboratory Animal Care, Jiangsu Experimental Animal Ethics Committee.

Construction of experimental mouse model of asthma and MglG treatment

The mouse asthma model was established as previously described, with some modifications [24–26]. Briefly, a 0.2 mL mixture containing 50 μ g ovalbumin (OVA), 2 mg aluminum hydroxide ($Al(OH)_3$) and magnesium hydroxide ($Mg(OH)_2$) was injected intraperitoneally into mice on days 1, 8 and 15 for establishing mouse asthma models. The normal control (CON) group was injected intraperitoneally with the same amount of physiological saline.

On the 21st day of the mouse asthma models construction, all the mouse asthma models established were randomly divided into three groups ($n=10$ in each group): asthma model group (MDL), dexamethasone group (DXM), and MglG group (MglG). And they were placed in a 4 L closed container and nebulized with physiological saline containing 1% (w/v) OVA for 30 min/day to trigger asthma and lasted for 7 days. The CON group was sprayed with normal saline with the same method. Additionally, the mice in MglG, MDL, and CON groups were given 20 mL of 0.2 mg/mL MglG solution, same amount of normal saline, and same amount of normal saline, respectively, by atomization inhalation for 30 min before stimulation with 1% (w/v) OVA. But the mice in DXM were intraperitoneally injected with 2 mg/kg dexamethasone 30 min before 1% (w/v) OVA stimulation.

Measurement of body weights

The body weight of mice was measured on days 0, 7, 14, 21, 22, 25, and 28 after initial sensitization with 0.2 mL of 250 μ g/mL OVA.

Cells classification in bronchoalveolar lavage fluid (BALF)

To evaluate airway inflammation, bronchoalveolar lavage fluid (BALF) was collected, and the inflammatory cells in which were determined. After the mice were anesthetized, their lung were exposed. Subsequently, the trachea was intubated and immediately lavaged with 1 mL of Hank's balanced salt solution (calcium and magnesium free) three times [27]. The lavage fluid was collected and placed on ice, followed by a centrifugation at 400 g for 10 min at 4 °C. The

supernatant was removed carefully, and the cell pellet was resuspended in 1 mL of Hank's balanced salt solution for counting with a standard hemocytometer. Smears were prepared and stained with Liu's staining solution (PS0290, Beijing Jin Ming Biotechnology Co., Ltd. China) for cell classification. Approximately 200 cells/slide were differentiated and counted according to the standard morphological criteria, and classified as white blood cells, neutrophils, and eosinophils.

Detection of TNF- α , IL-6, and total IgE in serum

To investigate the level of tumor necrosis factor (TNF)- α , interleukin (IL)-6, and total IgE in serum of mice with/without treatment, blood was collected from the mice orbital sinus. After a centrifugation at 1000 g for 15 min, the supernatant and serum were collected for standby. The levels of TNF- α , IL-6, and total IgE were determined with ELISA kits (Beyotime, Shanghai, China) as per the manufacturer's recommendation.

Histopathological analysis

To evaluate the effect of MglG treatment on OVA-induced allergic asthma, The left upper lobe of the mouse lung in each group was removed for histopathological examinations after anesthetization on the 28th day of treatment. The removed lung tissues were rinsed with ice-cold normal saline and fixed in 10% formalin (Shanghai Jianxin Chemical Co., Ltd., Shanghai, China). Then, the fixed tissues were dehydrated and embedded in paraffin (Shanghai Yongye Biological Technology Co., Ltd., Shanghai, China), followed by slicing into 2–4 μ m-thick sections with a Leica RM 2135 microtome (Leica Microsystems GmbH, Wetzlar, Germany).

The sections were deparaffinized with xylene and stained with hematoxylin and eosin (H&E) for evaluating the infiltration of cells. The evaluation was finished independently by three pathologists in a blinded manner. Cell infiltration was scored as follows: 0, no cells; 1, a few cells; 2, a ring of cells and 1 cell deep; 3, a ring of cells and 2–4 cells deep; and 4, a ring of cells and >4 cells deep. Goblet cell hyperplasia in the airway epithelium was quantified based on a five-point system: 0, without goblet cells; 1 point, <25% of the epithelium; 2 points, 25–50% of the epithelium; 3 points, 50–75% of the epithelium; and 4 points, >75% of the epithelium. The final score for each group was calculated as mean of scores from ten mice in each group.

Immunohistochemistry

The deparaffinized sections were rehydrated and soaked in sodium citrate buffer to expose antigen. The treated sections were immersed in 3% hydrogen peroxide for 10 min to inactive endogenous peroxidase, and subsequently blocked with 5% bovine serum albumin (BSA) for 30 min to remove the background noise. Then, Sections were incubated with MUC5AC antibody (ab3649, Abcam, Cambridge, UK) in 1:500 dilution of original antibody dilution buffer (beotim,

Shanghai, China) for 12 h at 4°C. After washing with phosphate buffered saline (PBS) three times, the sections were incubated with horseradish peroxidase (HRP) conjugated rabbit anti-mouse secondary antibodies for 1 h at room temperature. Secondary antibody was detected with SignalStain (R) DAB Substrate Kit (Cell Signaling Technology, Beverly, MA, United States). Slides were counterstained with hematoxylin (Leagene, Beijing, China) and mounted. To evaluate protein expression, Image was generated with the DM6B positive fluorescence microscope (Leica, Frankfurt, Germany), and Image-Pro Plus 6.0 software was used to measure the average optical density (IOD) using semi-quantitative image analysis.

Western blotting

To investigate the underlying mechanism of MglG on allergic asthma, the levels of NLRP3 and cleaved caspase-1 in the lung tissues of mice in each group were determined by western blotting. The the lung tissue were homogenized in lysis buffer (Beyotime, Shanghai, China), containing 1 nM phenylmethanesulfonyl fluoride (PMSF) (Beyotime, Shanghai, China). After a centrifugation (8000 g, 10 min), the supernatant was collected, and its protein concentration was determined using a BCA protein assay kit (Beyotime, Shanghai, China). The equal amounts of proteins were then

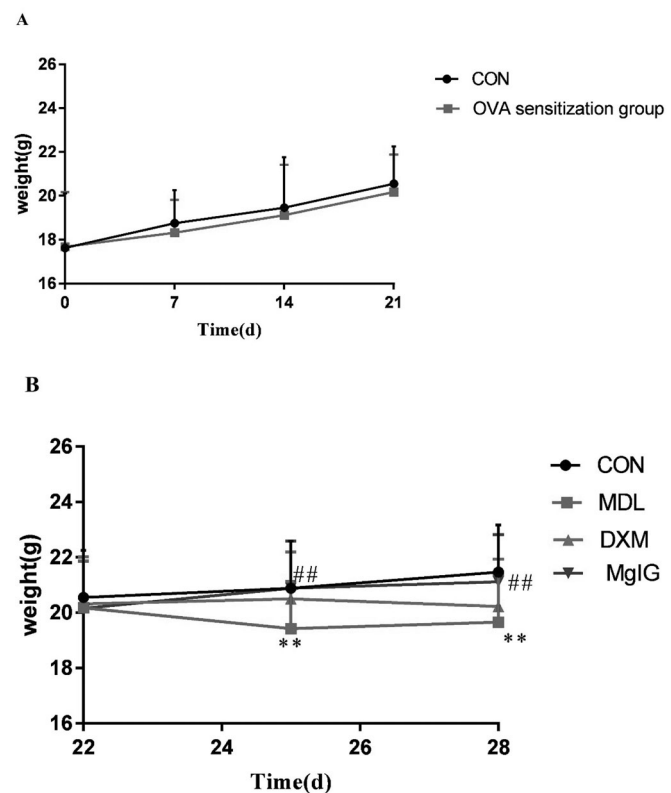


Figure 2. Changes of body weight of in control and OVA-sensitized and challenged mice with or without MglG or dexamethasone treatment. (A) Changes of body weight of mice during 21-day asthmatic model establishment. All data were presented as means $\pm$ SD ($n = 10$ in CON group, $n = 30$ in OVA sensitization group); (B) changes of body weight of mice from CON, MDL, MglG, and DXM group during the asthma challenge period. All data were presented as means $\pm$ SD ($n = 10$ per group). Statistical significance of differences were determined by one-way ANOVA. ** $p < 0.01$ compared to CON group. ## $p < 0.01$ compared to MDL group.

separated using 10% SDS-PAGE and transferred to PVDF membranes, which were probed with corresponding primary antibody anti-NLRP3 (EPR23073-1, 1:1000 Abcam, Cambridge, United Kingdom) and anti-caspase 1 (ab138483, 1:1000, Abcam, Cambridge, United Kingdom) followed by HRP-conjugated (1:10,000 dilution in TBST containing 5% skimmed milk) secondary antibody. The bands were visualized using a western blot detection kit (Beyotime, Shanghai, China). The blot was scanned and analyzed using UN-SCAN-IT version 5.1 software to measure the band intensity.

Statistical analysis

All data were presented as the mean $\pm$ standard deviation, and statistical analysis were performed with Graphpad Prism 8 software. Comparisons between experimental groups were conducted using Tukey's after ANOVA for group to group comparison. Values of $p < 0.05$ were considered significant.

Results

Effect of MglG on body weight in OVA-induced asthma model mice

All the mice were alive. During the experimental sensitization period from 0 to 21 days, the weight of mice remained a

steady increase, and no significant difference was observed among the groups (Figure 2(A)). However, during subsequent 7 days of stimulation with 1% OVA, the weight of mice in MDL group decreased significantly ($p < 0.01$) compared with that in CON and MglG group (Figure 2(B)). And, MglG treatment exhibited a better recovery effect than dexamethasone treatment ($p < 0.01$, Figure 2(B)).

MglG decreased inflammatory cell numbers in BALF

The inflammatory cells in BALF from OVA induced asthmatic mice were mainly classified into white blood cell, neutrophils, and eosinophils. Compared with mice in CON group, the number of all inflammatory cells in BALF from mice in MDL, DXM, MglG group increased significantly after sensitization and challenge with OVA. However, MglG and dexamethasone treatment resulted in a significantly lower number of all inflammatory cells in BALF than in the MDL group ($p < 0.01$, Figure 3(A–C)).

MglG ameliorated lung inflammation, bronchial wall thickening and MUC5AC production in asthmatic mice

Histological analysis were performed to identify whether the mouse asthma model was built successfully and measure the

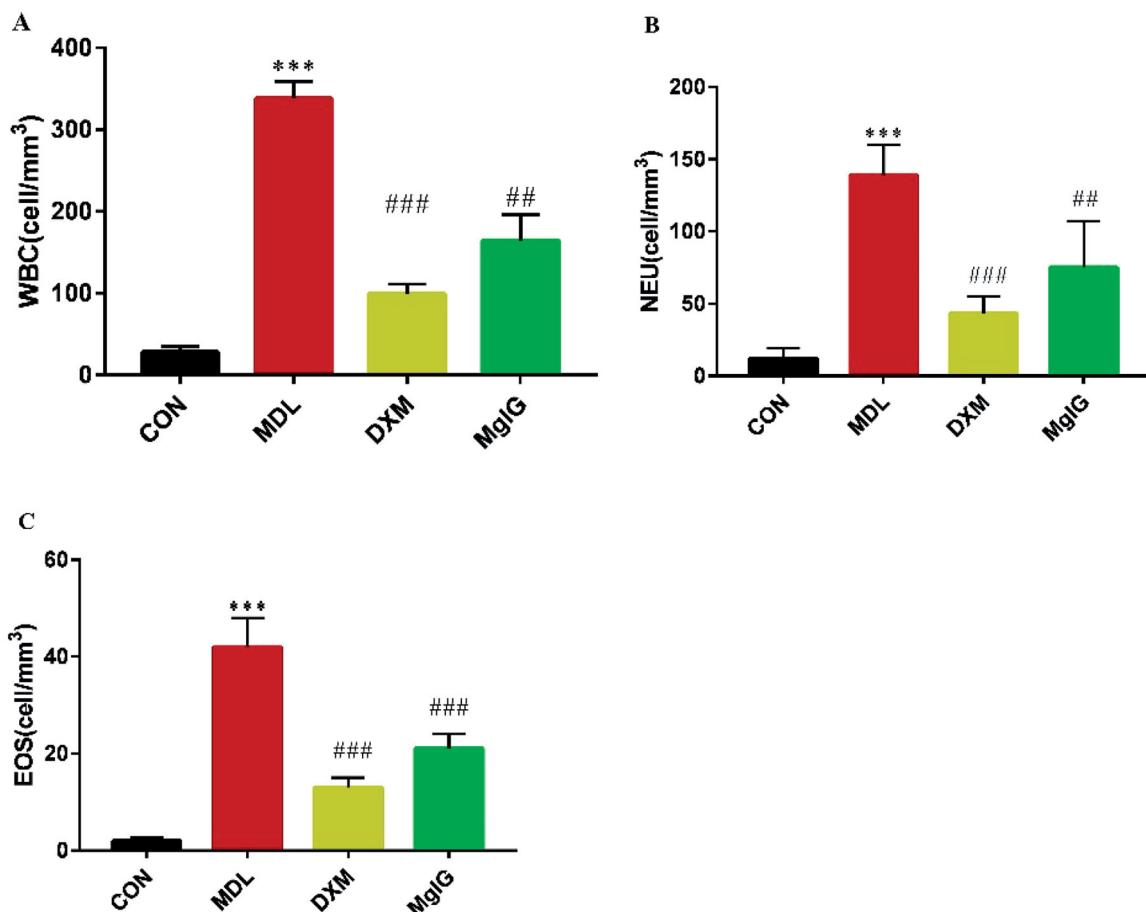


Figure 3. The inflammatory cells proliferation of control and OVA-sensitized and challenged mice with or without MglG or dexamethasone treatment. (A) Number of white blood cells in the BALF of mice after 7-day different treatment; (B) Number of neutrophils in BALF of mice after 7-day different treatment; (C) Number of lymphocytes in BALF mice after 7-day different treatment. All data were presented as means $\pm$ SD ($n = 10$ per group). Statistical significance of differences were determined by one-way ANOVA. *** $p < 0.001$ compared to CON group. ### $p < 0.001$, ## $p < 0.01$ and # $p < 0.05$ compared to MDL group.

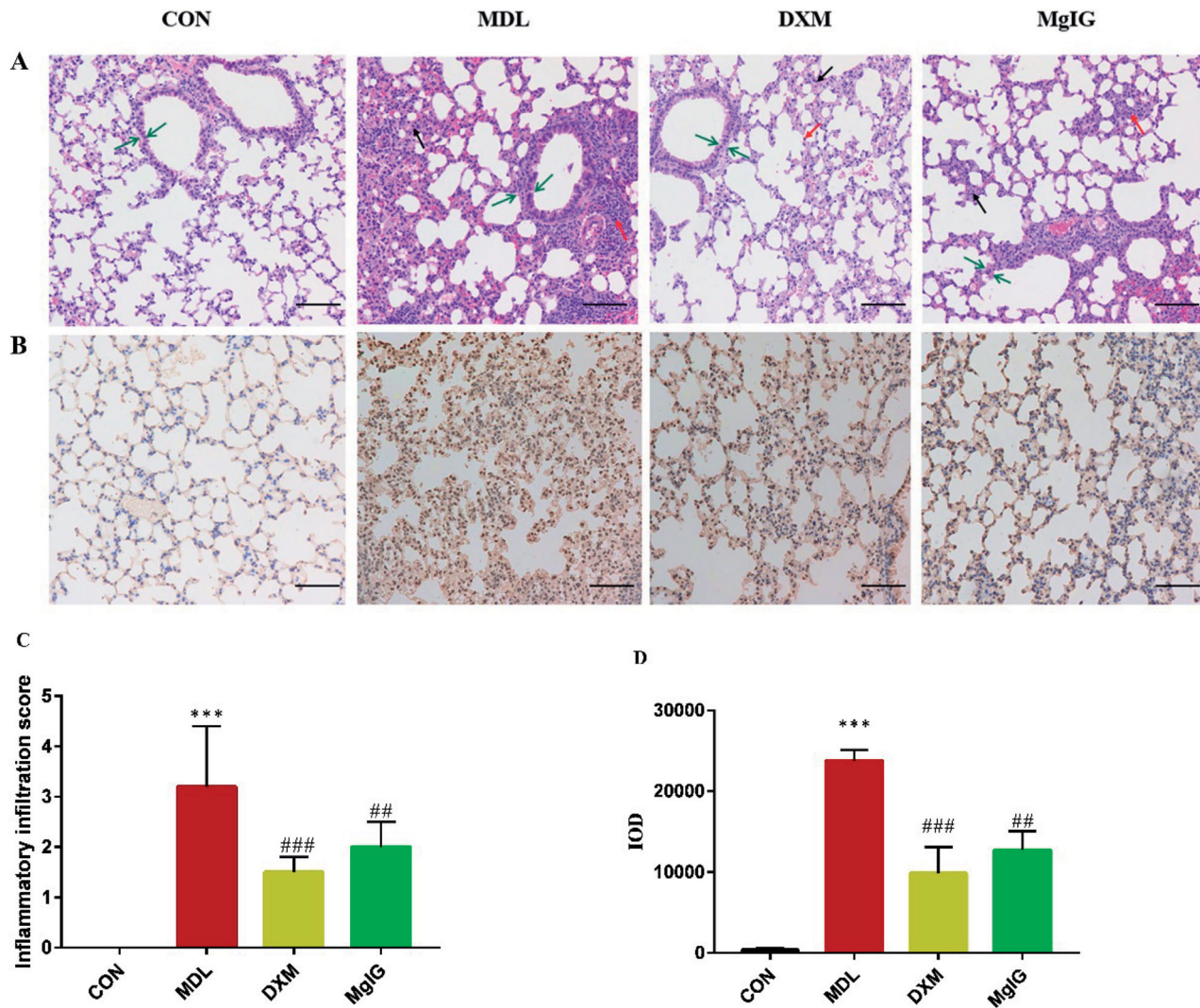


Figure 4. Histopathological changes and MUC5AC expression in control and OVA-sensitized and challenged mice with or without MglG or dexamethasone treatment. (A) The upper lobe of left lungs was collected and the histopathological changes of the lung tissue were observed by H&E staining; (B) Immunohistochemical staining for MUC5AC. (C) Histological scoring of inflammatory cell infiltration; (D) IOD in CON, MDL, MglG, and DXM group. IOD: Integral optical density. All data were presented as means $\pm$ SD ($n = 10$ per group). Statistical significance of differences were determined by one-way ANOVA. *** $p < 0.001$ compared to CON group. ### $p < 0.001$ and ## $p < 0.01$ compared to MDL group. Bar = 100 μ m.

effects of MglG treatment on pathological features of OVA-induced allergic asthma. This showed that the inflammatory response of asthma, induced by OVA, is mainly the infiltration of inflammatory cells, dominated by eosinophils, compared with the CON group (Figure 4(A,C)). Compared with the MDL group, MglG treatment resulted in a significant reduction of the infiltration degree in eosinophils ($p < 0.01$, Figure 4(A,C)). There were obvious corpuscle proliferation and fibroblast proliferation in the lung bronchus of mice in the MDL group as compared to CON group, and MglG treatment significantly attenuated OVA induced proliferation of goblet cells and fibroblasts in bronchial wall epithelium as dexamethasone treatment (Figure 4(A)). MUC5AC is the main mucin secreted by airway surface epithelium, and its expression level represents the degree of mucus secretion, which plays an important role in asthma. Immunohistochemical results indicated that the expression of MUC5AC was

significantly up-regulated in the lung tissue of OVA induced allergic, asthmatic mice compared to the CON group. With treatment of MglG, the expression of MUC5AC was significantly repressed in MglG and DXM groups ($p < 0.01$, Figure 4(B,D)).

MglG reduced pro-inflammatory cytokines expression in serum of asthma mice

ELISA was performed to determine the level of important inflammatory factors, TNF- α and IL-6. Results indicated that OVA sensitization and challenge induced an obvious increase TNF- α and IL-6 levels in the serum of mice from MDL group compared to CON group ($p < 0.05$ or $p < 0.01$, Figure 5(A,B)). Also, MglG treatment could significantly suppress the

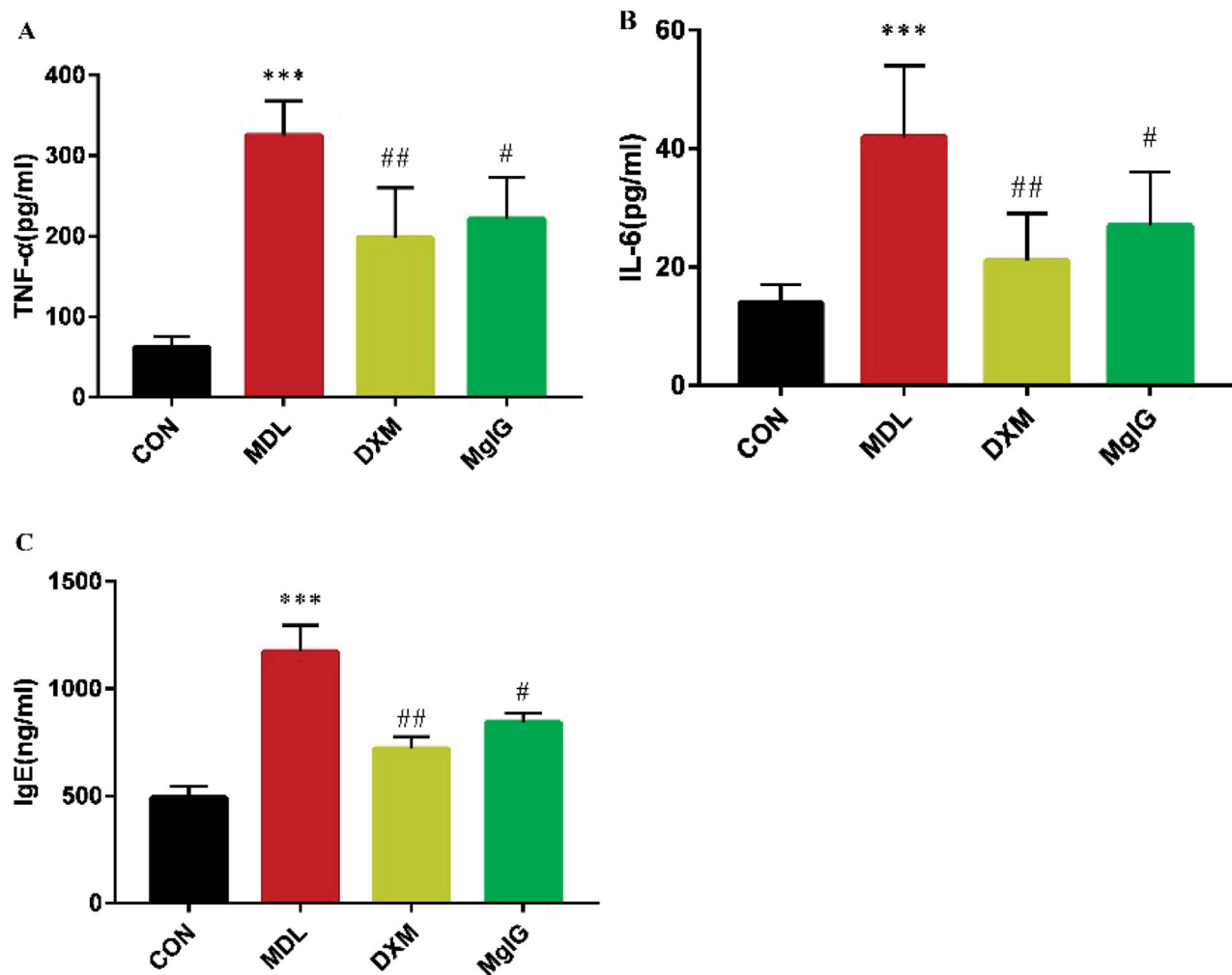


Figure 5. Serum TNF- α , IL-6, and IgE levels in control and OVA-sensitized and challenged mice with or without MglG or dexamethasone treatment. Mice were sacrificed and the serum was collected for ELISA detection. The levels of TNF- α (A), IL-6 (B), and IgE (C) were shown as above. All data were presented as means $\pm$ SD ($n = 10$ per group). Statistical significance of differences were determined by one-way ANOVA. *** $p < 0.001$ compared to CON group. ### $p < 0.001$, ## $p < 0.01$ and # $p < 0.05$ compared to MDL group.

expression of TNF- α and IL-6 as dexamethasone treatment ($p < 0.05$ or $p < 0.01$, Figure 5(A,B)).

MglG treatment reduced the serum IgE level in asthmatic mice

The serum IgE level was further detected, and results showed that OVA sensitization and challenge also induced an evident increase in IgE serum level of mice from the MDL group. Although MglG and dexamethasone treatment could significantly suppress IgE serum level, it was higher compared to CON group ($p < 0.05$ or $p < 0.01$, Figure 5(C)).

MglG inhibits the expression of NLRP3 inflammasome in OVA sensitized mice

Western blotting analysis was performed to examine the expression level of NLRP3 and cleaved caspase-1 in lung tissue. Results revealed that the high expression of NLRP3 and cleaved caspase-1 induced by OVA sensitization and

challenge was dramatically suppressed with treatment of MglG and dexamethasone ($p < 0.05$ or $p < 0.01$, Figure 6(A–C)).

Discussion

Allergic asthma is characterized by allergen-induced airway bronchoconstriction, eosinophil inflammation, and mucus hypersecretion and airway remodeling [28]. MglG is clinically used as a hepatocyte protective agent, which has the effects of anti-inflammatory, protecting hepatocyte membrane, and improving liver function, specifically in hepatitis [29]. However, the effects of MglG on airway inflammation and remodeling remain ambiguous. Recently, it has been reported that MglG has certain therapeutic effects on respiratory diseases due to its strong anti-inflammatory and antioxidant effects [23]. Previously, a study confirmed that MglG could reduce lung injury and pulmonary fibrosis induced by paraquat poisoning in rats [22]. This study showed that mice exposed to OVA for 4 weeks, induced infiltration of white blood cells into their lungs and more infiltration of

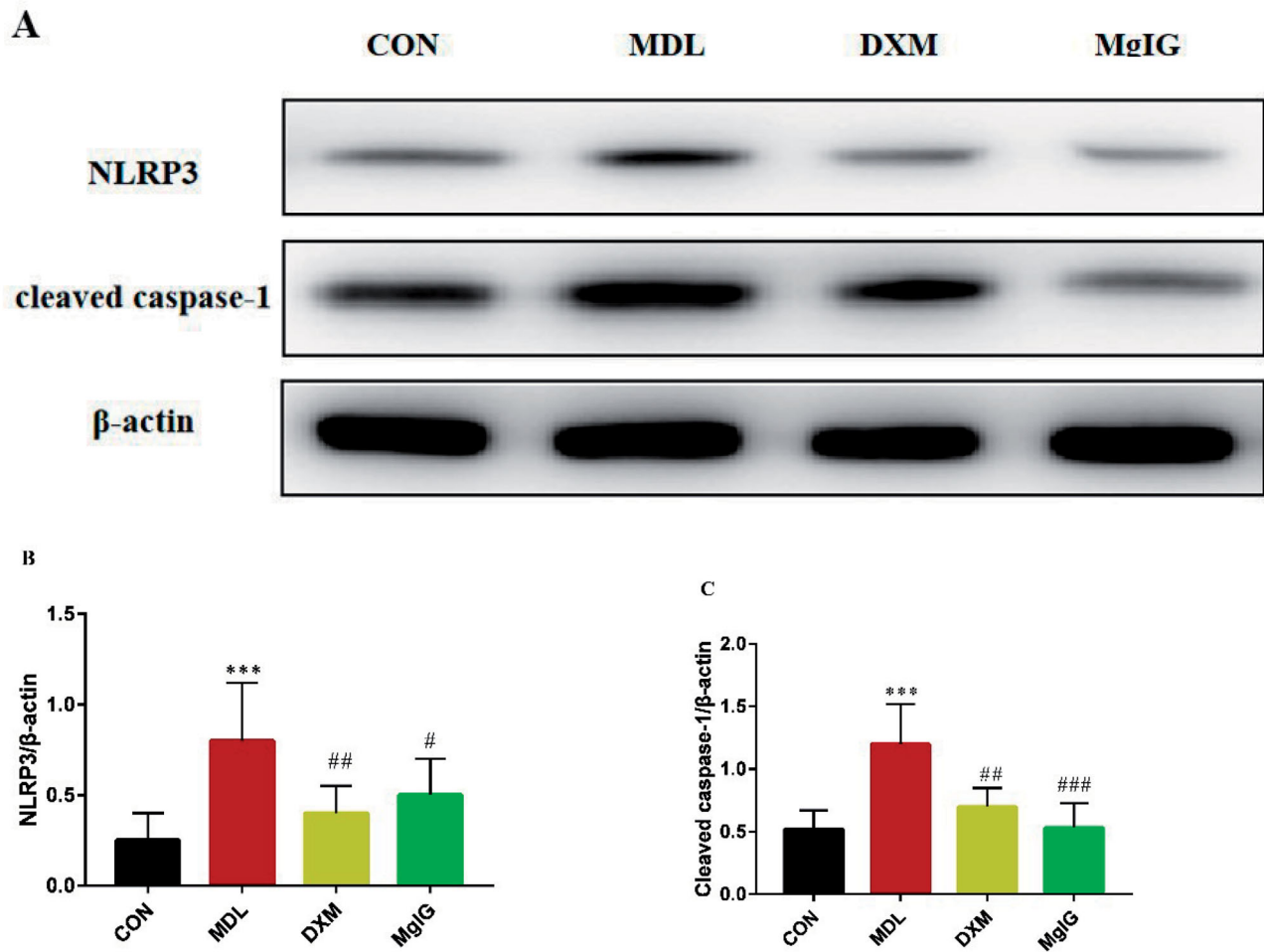


Figure 6. Expression of NLRP3 inflammasome and cleaved Caspase-1 in control and OVA-sensitized and challenged mice with or without MglG or dexamethasone treatment. After the rats were sacrificed, the upper lobe of the right lung was taken for western blotting. (A) The protein levels of NLRP3 and cleaved Caspase-1 were detected by western blotting, and the ratio of NLRP3/ β -actin (B) and cleaved Caspase-1/ β -actin (C) were shown. All data were presented as means $\pm$ SD ($n = 10$ per group). Statistical significance of differences were determined by one-way ANOVA. *** $p < 0.001$ compared to CON group. ### $p < 0.001$ and # $p < 0.05$ compared to MDL group.

eosinophils in their airways, which is a significant feature of airway inflammation in asthma. So, this suggests that the mouse asthma model was successfully established. After MglG treatment, the size and extent of leukocyte infiltration reduced significantly, and the number of eosinophils around the airway also decreased. These effects were similar to those of mice treated with dexamethasone, indicating that MglG could alleviate the allergenic asthma induced by OVA through inhibiting eosinophilic inflammation.

Asthma is usually associated with airway remodeling, the significant features of which include airway wall thickening, increased smooth muscle mass, goblet cell proliferation, and mucinous gland hypertrophy [28]. The results presented, showed that MglG treatment, similar to dexamethasone treatment, can reverse goblet cell proliferation, collagen deposition, airway smooth muscle layer thickening, and airway mucus secretion, which caused by OVA sensitization and challenge. It demonstrated that the anti-remodeling effect of MglG is also a contributor to its alleviating asthma potency.

IgE plays an important role in the inflammatory response of allergic asthma [28]. As allergens enter the body for the first time, a series of inflammatory cascade reactions are

triggered by dendritic cells. In addition, specific IgE molecules can bind to dendritic cells to enhance their antigen presentation, and enhance expression of the high-affinity IgE receptors on mast cells and basophils [30]. The present study demonstrated that similar to dexamethasone treatment, MglG treatment decreased IgE levels in serum, besides TNF- α and IL-6, which increased in mice after OVA sensitization and challenge. Consequently, MglG was able to weaken OVA-induced asthma by inhibiting IgE expression.

Although some studies have confirmed the efficacy of MglG on inflammation, mechanisms of MglG inhibiting inflammatory responses need to be fully clarified. Studies on NOD like receptor signaling pathway show that NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and caspase-1, might be a very important immune receptor responsible for self-inflammatory response [31]. When NLRP3 inflammatory bodies are over activated, it can lead to severe inflammatory states [32]. In addition, previous clinical and experimental studies have shown that the expression of NLRP3 inflammasome was up-regulated in asthmatic patients and OVA induced asthma model, suggesting that NLRP3 inflammasome plays an

important role in the pathology of asthma [33]. Our results show that the protein levels of NLRP3 and caspase-1 in the lung tissue of OVA induced asthmatic mice decreased significantly after MglG treatment, indicating that MglG could inhibit the inflammatory response in OVA induced asthma by inhibiting NLRP3 inflammatory bodies. These results indicated that the signal pathway involved in the effect of MglG on asthma, could be associated with NOD like receptors.

The present study confirmed the effect of MglG on OVA-induced allergic asthma through suppressing airway inflammation and remodeling using an established mouse asthma model, and preliminarily explored its underlying mechanism by NLRP3 signal pathway. However, data representing treatment in human patients are still limited and need to be confirmed by further clinical studies.

Conclusion

The current study indicated that MglG could alleviate airway inflammatory responses in ovalbumin-induced mouse model of allergic asthma through signaling pathway. It suggested that MglG might be an alternative drug for treating asthma.

Author contributions

YY designed the experiments, finished cells classification and inflammatory factors determination, and wrote the paper; LH finished mouse asthma model construction, immunohistochemistry, and histopathological analysis; CCT finished Western blotting; BJQ analyzed the data and revised the paper.

Disclosure statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the research funding from Jiangsu Provincial Health Commission of China [Z2019053] and Natural Science Foundation of the Jiangsu Higher Education Institutions of China [18KJB320004].

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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