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IFN-γ cocultured mesenchymal stem cells promote substantial immunomodulatory effects in mice models of allergic asthma

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Abstract
Asthma is a debilitating lung disease characterized by airway inflammation and airflow obstruction. Immune cells, particularly T helper 2 (Th2) lymphocytes, are central players in the pathogenesis of asthma and mesenchymal stem cells (MSCs) have shown the capability of softening pathological inflammatory responses in asthma. Hence, we researched the immunopathologic effects MSCs cocultured with interferon (IFN)-γ, the main Th1 cytokine, in asthmatic mice. After isolation, MSCs were cocultured with IFN-γ and administered to asthmatic mice. Subsequent analyses included enumeration of broncho-alveolar lavage (BAL) fluid's inflammatory cells, determination of the levels of immunoglobulin E (IgE), leukotrienes (LTs), cytokines, chemokines, and histopathology assessment. The administration of IFN-γ-cocultured MSCs reduced the percentage of eosinophils in the BAL fluid and levels of IgE, LTs, cytokines, and chemokines. Also, there was a decrease in the eosinophilic infiltration of perivascular areas and periairways. IFN-γ cocultured MSCs could modulate immune responses and harness pathological events in allergic asthma.

Introduction

Asthma is a noncommunicable lung disease characterized by airway inflammation and airflow obstruction. More than 350 million people across the world suffer from asthma, imposing a high economic burden not only on families but also on the health systems.[1-4] Pathological events in asthma are the outcomes of intricate interactions between several types of immune cells within the asthmatic niche, predominantly T helper 2 (Th2) and eosinophils. From a mechanistic

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standpoint, asthma is categorized into the allergic and non-allergic forms. Allergic asthma is quite often triggered from the overproduction of immunoglobulin E (IgE), leading to the active recruitment of Th2 cells into bronchioles via releasing different types of cytokines such as interleukin (IL)-4, IL-5, and IL-13, and also their upper hand cytokines IL-25 and IL-33.[5-9]

Stem cells possess a great variety of characteristics or qualities, including plasticity and the ability to translocate to inflamed tissues, where they promote their regulatory effects on immune cells. Adult bone marrow (BM) stem cells encompass different lineages such as mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and endothelial progenitor cells (EPCs). The transplantation of MSCs has shown impressive results for tissue repair and healing by modulating inflammatory reactions, promoting collagen deposition in the lung parenchyma, recruiting immune cells, rebalancing the Th1/Th2 ratio, and changing the dynamics of pro- and anti-inflammatory cytokines.[10,11] MSCs can easily migrate toward inflammatory sites in response to the gradients of cytokines' concentrations, which are capable of suppressing pathological tissue remodeling and inflammatory responses in asthma. It seems that the therapeutic effects of MSCs are mainly promoted for their potential in releasing an array of mediators acting in a paracrine manner to modify cell-based and humoral immune responses.[10,12,13]

The aim of this study was to investigate the potential therapeutic role of MSCs pretreated with interferon (IFN)-γ in suppressing pathophysiological events in mice models of allergic asthma and the applicability of manipulated stem cells as an antiasthma therapy.

Materials and Methods

MSCs isolation, culturing, and priming

BM-derived MSCs (BM-MSCs) were isolated and cultured, as described previously. Briefly, tibia and fibula of mice were cut and after flashing, MSCs were extracted by seeding in specific culture media. During incubation, the medium was changed every 3 days. The characterization and differentiation of MSCs were performed using specific markers. Finally, MSCs were cocultured with IFN-γ at concentrations of 50 ng/mL and 100 ng/mL for 24 hours. Next, the cells were collected for transplantation.[14-18]

Mouse asthma model

Allergic asthma Bagg Albino (BALB/c) mouse model was created by administering ovalbumin (OVA) with alum adjuvant via the intraperitoneal (IP) route; also, OVA solution was delivered to the lungs via a nebulizer for sensitization and the challenge test, according to previous studies.[2,5,8,9] Mice were kept in standard housing conditions (temperature 20–24¤C, humidity 50–60%, 12 hours dark/light cycle, free access to food and water) and allocated to four groups: allergic asthma (group A), healthy control (group B, receiving Phosphate buffered saline [PBS]), and two experimental groups in which mice with allergic asthma were treated with MSCs cocultured with either 50 ng/mL (group M50) or 100 ng/mL (group M100) IFN-γ on day 25. On day 31, all mice were euthanized for obtaining samples.

BAL fluid cells

The broncho-alveolar lavage (BAL) fluid was collected from the lung and used to prepare tissue smears after cell separation, and then stained to determine the percentage of eosinophils. The supernatant (liquid portion) was used for other experiments or measurements beyond the initial separation.

IgE level

The level of total serum IgE was measured in serum by an enzyme-linked immunosorbent assay (ELISA) kit using samples collected on day 31.

Luminex assay

A multiplex kit was used to measure cytokines, chemokines, growth factors, IL-4, IL-5, and IL-13, and eotaxin in BAL fluid, according to the manufacturer's instructions.

Leukotrienes' levels

After centrifugation for cell separation, the supernatant of the BAL fluid was used to measure leukotriene (LT) C4 and LTB4 levels using specific ELISA kits.

Histopathology

To prepare the histopathology sections, the lungs of the mice were isolated and then fixed, which were subsequently stained with hematoxylin and eosin (H&E), Alcian blue (AB), Periodic Acid Schiff (PAS), H&E-Trichrome, H&E-PAS, and AB-PAS. The tissues were evaluated under light microscopy to survey mucus production in airways, goblet cell metaplasia, and perivascular and periairway eosinophilic inflammation.[2,5,8,9]

Statistical analysis

All results were expressed as means ± SD (standard deviation). Differences between experimental groups were analyzed by the independent student t-test and a P-value of 0.05 or lower was considered statistically significant. GraphPad Prism 6 software was used to analyze and present the data.

Results

BAL fluid cells

The percentage of eosinophils was elevated in the BAL fluid samples of asthmatic mice (67%) compared to the control

group (4%). The administering of MSCs cocultured with IFN-γ (50 ng/mL or 100 ng/mL) could significantly decrease ($p < 0.05$) the eosinophil percentage in the BAL fluid (M50: 40% and M100: 39%).

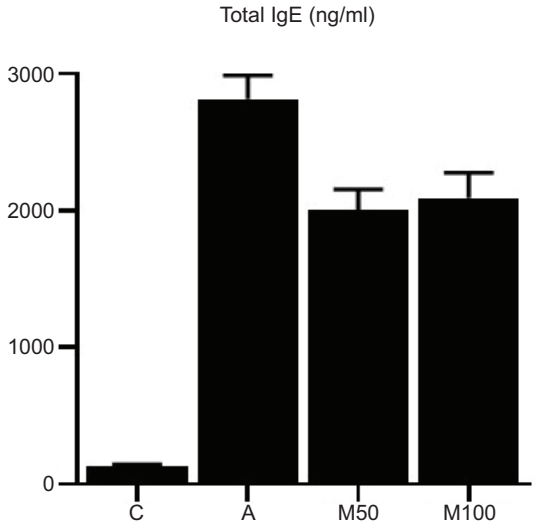

Figure 1 IgE serum level. The total IgE level was measured in sera of mice.

IgE level

The level of IgE was increased in mice with allergic asthma (2816 ng/mL) compared to healthy control animals (127 ng/mL) (Figure 1) as well as asthmatic mice treated with MSCs cocultured with either 50 ng/mL or 100 ng/mL IFN-γ (M50 = 2005 ng/mL and M100 = 2093 ng/mL).

Cytokine levels

The levels of main Th2 cytokines (IL-4, IL-5, and IL-13) related to allergic asthma pathophysiology and eotaxin were significantly higher in asthmatic mice (101 pg/mL, 111 pg/mL, 182 pg/mL, and 64 pg/mL, respectively) compared to control animals (38 pg/mL, 43 pg/mL, 69 pg/mL, and 19 pg/mL, respectively) (Figure 2). The administering of MSCs cocultured with IFN-γ could significantly reduce the levels of these cytokines and the chemokine ($p < 0.05$) except for IL-13, whose decline was not statistically significant ($p > 0.05$).

Levels of LTs

The levels of LTB4 and LTC4 were significantly elevated in asthmatic animals (342 ng/mL and 167 ng/mL, respectively)

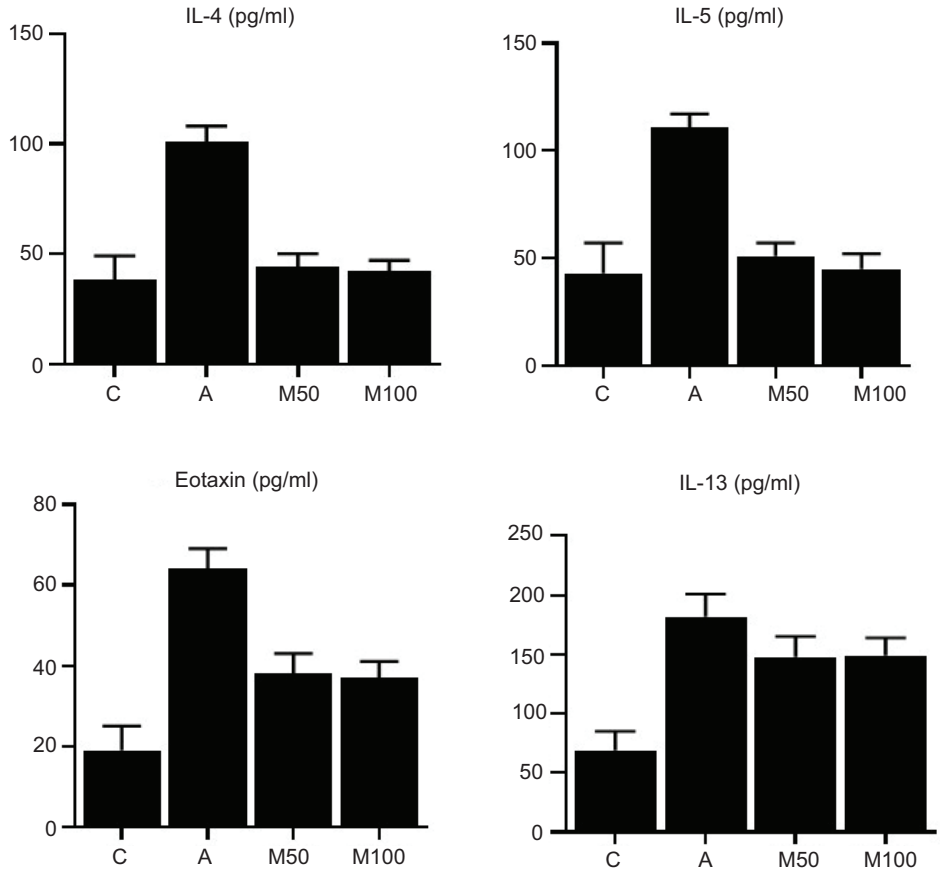

Figure 2 Levels of inflammatory mediators. The levels of the main allergy-associated cytokines, IL-4, IL-5, and IL-13 as well as eotaxin as the main allergy-related chemokine were measured in BAL fluid samples.

compared to controls (168 ng/mL and 73 ng/mL, respectively, $p < 0.05$) (Figure 3). In asthmatic mice treated with MSCs cocultured with IFN-γ, the levels of these LTs were significantly reduced ($p < 0.05$).

Histopathology

In asthmatic mice, mucus production in airways, goblet cell metaplasia, and perivascular and periairway eosinophilic infiltration were remarkable in comparison to control animals ($p < 0.05$) (Figures 4 and 5). The treatment with MSCs cocultured with IFN-γ could significantly decrease perivascular and periairway eosinophilic inflammation ($p < 0.05$) but not mucus production in airways or goblet cell metaplasia ($p > 0.05$) compared to the control.

Discussion

MSCs isolated from different tissue sources show excellent restorative capacity, with BM being the primary source for MSC isolation.[19,20] It has been elucidated that MSCs isolated from the placenta and adipose tissues elicit robust immunomodulatory effects in experimental allergic asthma models compared to MSCs isolated from the BM.[21,22] Recent research evaluating the antiasthmatic properties of placental MSCs within the pulmonary niche showed that these cells could mitigate eosinophil infiltration into the BAL fluid, reduce IgE and IL-4 production, interrupt lymphocyte polarization toward Th2, and restore mucus generation and goblet cell proliferation to near-normal levels.[10,23] In another study, the administration of placental-derived MSCs upregulated IL-10, reduced IL-17, and blunted the Th17/Treg ratio in asthma models.[24] The intratracheal administration of MSCs from three different tissues (BM, adipose tissue, and lungs) modulated structural remodeling and inflammatory responses in allergic asthma animal models possibly via favoring distinct secretome profiles, leading to distinct outcomes.[25] In our study, the level of eotaxin and the percentage of eosinophils in the BAL fluid were reduced in asthmatic mice administered with MSCs (pretreated with IFN-γ).

Furthermore, MSCs well known for their immunomodulatory capacity without causing adverse immunogenic responses. Even in the presence of type 1 cytokines such as IFN-γ, MSCs acquire immunosuppression phenotype and preserve their immunomodulatory properties by producing prostaglandin E2 and indoleamine 2,3-dioxygenase.[26] MSCs seem to promote their immunomodulatory effects in asthma by harnessing immune responses at the site of inflammation.[27-30] These cells have the ability to balance the Th2/Th1 ratio, the synthesis of interleukins (such as IL-13, IL-5, and IL-4), and IgE as well as mucus production after residing in the asthmatic niche. Additionally, in the presence of IFN-γ, MSCs could abort untamed allergic responses.[30-32] In this study, MSCs cocultured with IFN-γ reduced total IgE level in the sera of asthmatic mice as well as the levels of the main Th2 cytokines (IL-4, IL-5, and IL-13), indicating a shift from Th2 to Th1 immune responses. Moreover, MSCs exposed to IFN-γ could control mucus production in airways, but this was not statistically significant.

The control of the Th2 immune response can be an efficient strategy to control allergic reactions in asthma.[29-32] It has been reported that BM-MSCs administered by the IP route can easily migrate to the pulmonary niche and modulate allergic asthma reactions via exerting immunomodulatory effects shortly after treatment.[33,34] In addition to immunomodulatory properties, other mechanisms have been suggested to explain the antiasthmatic effects of MSCs, such as mitochondria transference, cell fusion, transdifferentiation, and paracrine effects mediated via microvesicles and exosomes.[35] Data have shown that MSCs promote tissue regeneration through transferring mitochondria in response to external stimuli, a process that can induce tunnel tube formation, gap junctional channels, and Rho-(guanosine triphosphate)GTPases such as Miro1 in damaged cells.[36,37] A study reported that the administration of pluripotent stem cell-derived MSCs via the intratracheal route improved mitochondrial dysfunction in epithelial cells.[38] In addition to mitochondrial transfer, MSCs can inhibit both mitochondrial and nonmitochondrial apoptosis

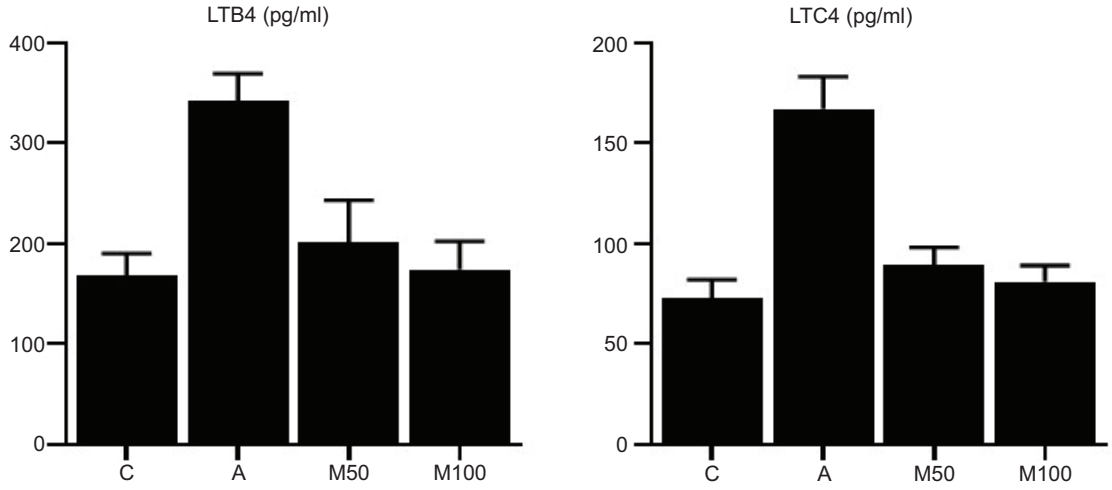

Figure 3 Leukotriene assessment. The levels of LTB4 and LTC4 were evaluated in BAL fluid of all mice.

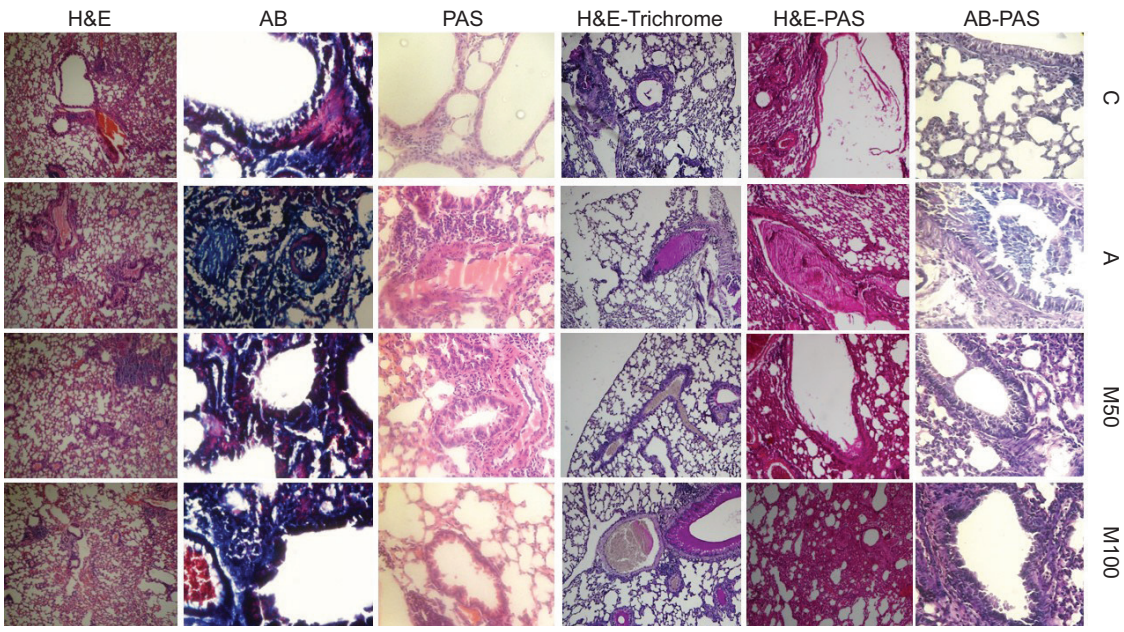

Figure 4 Histopathological staining. Lung sections of four groups of mice (C, A, M50, and M100) were prepared and stained with H&E, H&E-AB-PAS, H&E-PAS, AB-PAS, PAS, and H&E-AB (left to right, respectively).

signaling pathways.[39] Besides, MSCs administration via the intravenous route could mitigate pulmonary microvascular inflammation through engaging autophagy-related effectors and inhibiting miR-142a-5p in endothelial cells during ischemia/reperfusion in asthma animal models.[40,41] In this research, perivascular and periairway eosinophilic inflammation was significantly enhanced in asthmatic mice, which markedly subsided after the administration of MSCs cocultured with IFN-γ. It has been shown that MSCs decrease inflammatory responses in different asthma models by altering Th2-derived cytokines and other factors affecting the function of these cells.[10,42] In our study, we also noticed that goblet cell metaplasia was significantly increased in asthmatic mice and that the administration of MSCs could partly reverse these changes.

IFN-γ priming has been shown to profoundly affect MSCs' immunomodulatory properties. It is believed that for executing their immunosuppressive function, MSCs need a "license" granted to them by IFN-γ as a key immune regulator cytokine. The survival and functional efficacy of MSCs seem to correlate with IFN-γ level.[16] The immunomodulatory effects of MSCs and their potential immunosuppressive activity toward CD4+ T lymphocytes isolated from house dust mite sensitive asthmatic patients (Der p1+) were observed to be mediated via IFN-γ.[15] In fact, IFN-γ primed MSCs to modulate T cell responses by producing anti-inflammatory mediators. Also, in allergic asthma, MSCs could deviate Th2 responses via activating T regulatory cells.[15] In this study, the increased levels of LTB4 and LTC4 in asthmatic mice subsided after the administration of MSCs and IFN-γ cocultured MSCs.

MSCs have been noted to facilitate cell proliferation and accelerate the repair of damaged tissues by secreting fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and keratinocyte growth factor (KGF). These stem cells also activate regulatory T cells, triggering the production of anti-inflammatory cytokines, which could subsequently suppress airway inflammation in asthma, suggesting that administering MSC can be a useful cell therapy approach for asthma.[43] Moreover, MSCs can suppress the proliferation of stimulated peripheral blood mononuclear cells (PBMCs), the differentiation of monocyte-derived immature dendritic cells (DCs), and overproduction of immunomodulatory cytokines. Prior treatment of MSCs with IFN-γ augmented their antiapoptotic effects on lymphocytes, promoted the generation of CD4 + CD25 + FOXP3 + Treg cells, and increased the viability of CD4 + T lymphocytes in asthma models, which was accompanied by the suppression of IL-9 (a proinflammatory cytokine) but the induction of FOXP3 (an anti-inflammatory transcription factor).[44] MSCs not only attenuated pathological remodeling in the lungs of asthmatic mice but also suppressed pulmonary inflammatory responses, evidenced by the lower eosinophilic inflammation and airway hyperresponsiveness (AHR) as well as the shifted Th1:Th2 ratio.[45] Intratracheal MSC administration was reported to modulate the activity of macrophages in the lung and ameliorate type 2 airway inflammation and AHR. In particular, MSC therapy reduced M2a and M2c macrophages and suppressed the antigen-presenting capacity of DCs. Previous studies noted that MSCs could decrease airway remodeling, goblet cell hyperplasia, and the thickness of the basement membrane/subepithelial smooth muscle layer.[46–48] Hence, MSC therapy, especially cells already exposed to IFN-γ, might be a promising strategy to control immunopathologic events in allergic asthma and mitigate nonprotective immune responses in asthmatic lungs. In this study, there were some limitations—the treatment was not studied in chronic asthma model and was not evaluated in other animal models. Several inflammatory and allergic biofactors were not evaluated.

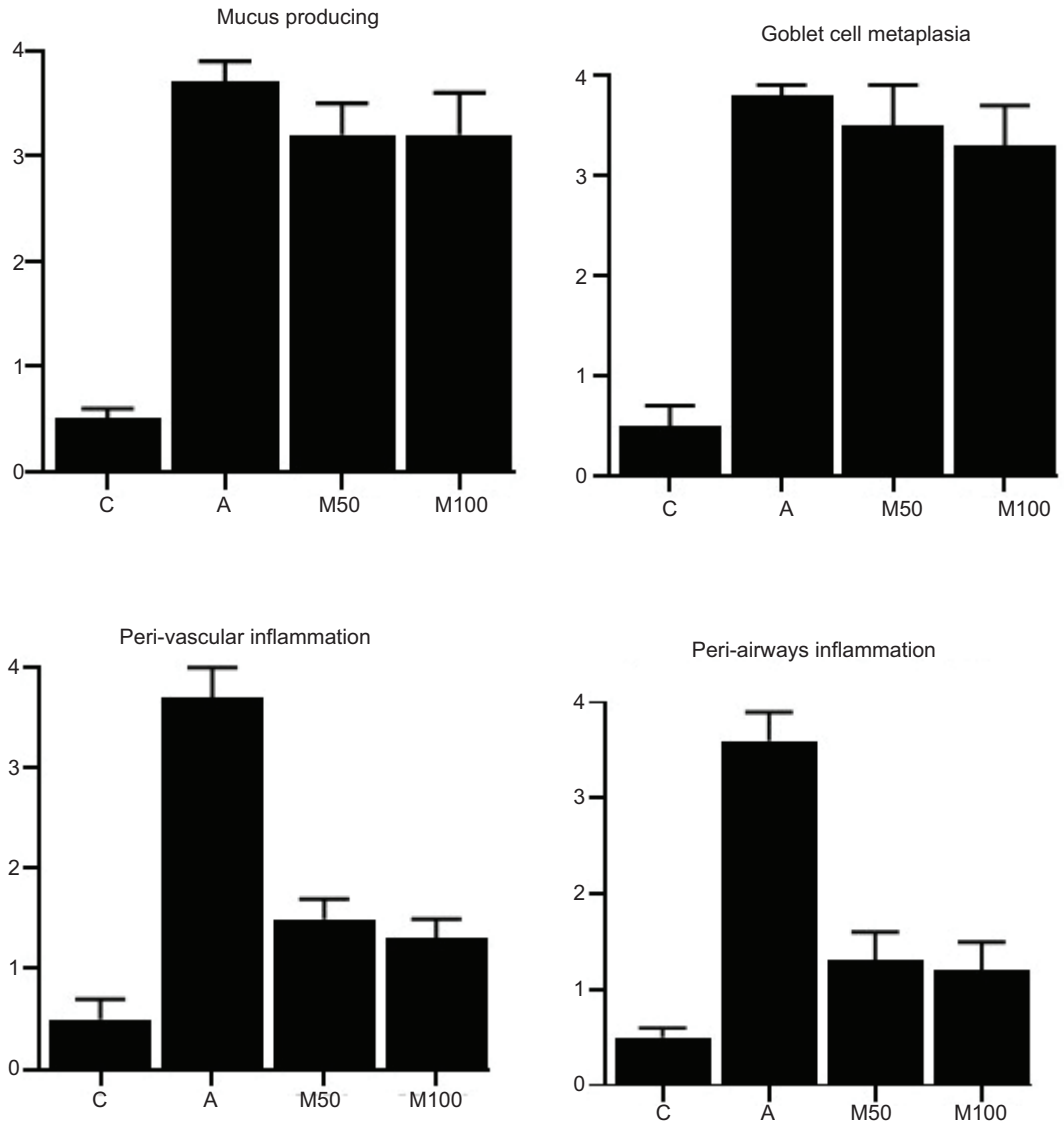

Figure 5 Histopathological findings. Eosinophilic inflammation in the perivascular and peribronchial areas, mucus production, and goblet cell metaplasia were assessed.

Ethics Approval and Consent to Participate

This study was approved by the ethic committee of animal house of ix.med.vet.dep, 2024 (No. IX.MED.VET.DEP.REC.2024.0100012.6).

Consent for Publication

Not applicable.

Availability of Data and Materials

Data are available on request from the corresponding author.

Acknowledgments

Not applicable.

Author Contributions

TC, JH, YS, XL, YW, SSA, EMN, and JG participated in the planning of project, animal study, laboratory testing, analysis of data, and writing of the manuscript.

Conflicts of Interest

There is no conflicts of interest.

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