

ORIGINAL ARTICLE

Indole-3-Propanoic Acid Alleviates Pulmonary Inflammation in a Mouse Model of Bronchial Asthma by Regulating PD-1/PD-L1

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ABSTRACT

Background: Bronchial asthma is a prevalent chronic inflammatory disorder of the airways, with children representing a particularly vulnerable population. Early intervention is critical for the management of pediatric asthma. The pathogenesis of asthma is primarily characterized by a Th2-immune response that drives excessive secretion of inflammatory cytokines, leading to allergic airway inflammation. Emerging evidence indicates that gut microbiota-derived metabolites modulate immune cells and influence asthma development and progression. Among these metabolites, indole derivatives with immunomodulatory properties have attracted increasing interest; however, the role of specific indole compounds in asthma remains poorly defined. This study aimed to investigate the effect of indole-3-propionic acid (IPA), a key microbiota-derived indole metabolite, on allergic airway inflammation in a juvenile murine model of asthma, and to elucidate the underlying immunological mechanisms, with a focus on regulatory T cells (Tregs) and the Programmed cell death protein 1 (PD-1)/Programmed cell death ligand 1 (PD-L1) pathway.

Methods: An asthma model was established in young mice via sensitization and challenge with ovalbumin (OVA). We evaluated the impact of IPA on pulmonary inflammation, airway hyperresponsiveness, inflammatory cell infiltration, cytokine profiles, and OVA-specific immunoglobulins. In addition, we analyzed Treg populations and the expression of PD-1 and PD-L1 in lung tissues.

Results: Our results demonstrated that OVA-induced asthmatic mice exhibited significantly enhanced airway reactivity and pronounced inflammatory cell infiltration in lung histology. Bronchoalveolar lavage fluid (BALF) analysis revealed elevated total leukocyte counts, predominantly eosinophils and neutrophils. Levels of Th2 cytokines (IL-4, IL-5, and IL-13) were markedly increased in BALF, while concentrations of the anti-inflammatory cytokine IL-10 were decreased. Serum levels of OVA-specific IgE and IgG1 were elevated, further confirming a Th2-skipped immune response. Furthermore, a significant reduction in Treg frequency was observed in the lung tissues of asthmatic mice, accompanied by upregulation of PD-1 and PD-L1. Treatment with IPA effectively mitigated airway inflammation and reversed these immunological alterations by restoring Treg levels and modulating PD-1/PD-L1 expression.

Conclusions: In conclusion, our findings indicate that IPA alleviates allergic airway inflammation in asthmatic juvenile mice by promoting Treg recruitment and function, potentially through the PD-1/PD-L1 axis. This study highlights the therapeutic potential of targeting microbial metabolite-mediated immunoregulation and provides new insights into early prevention and treatment strategies for asthma.

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INTRODUCTION

Bronchial asthma is a prevalent chronic respiratory disorder characterized by airway hyperresponsiveness, variable airflow obstruction, and persistent airway inflammation. The global incidence of childhood asthma has been rising steadily, posing a significant burden on pediatric health and development [1,2]. The pathogenesis of asthma is multifactorial, involving genetic predisposition, environmental exposures, and dysregulated immune responses. In particular, aberrant activation of the adaptive immune system - especially a Th2-skewed response - plays a central role in driving allergic airway inflammation [3].

Immune checkpoint molecules, such as programmed cell death protein 1 (PD-1) and its ligand PD-L1, are critical regulators of immune homeostasis. By modulating T-cell activation and tolerance, the PD-1/PD-L1 axis helps prevent excessive inflammation and autoimmunity. Dysregulation of this pathway has been implicated in the pathogenesis of several immune-mediated diseases, including bronchial asthma [4-6]. Despite advances in asthma management, a substantial number of patients remain poorly controlled due to the complexity and heterogeneity of the disease mechanisms. Thus, identifying novel therapeutic targets is urgently needed. Accumulating evidence from epidemiological and experimental studies underscores the importance of the gut-lung axis in asthma development. The gut microbiota and its metabolites are known to influence pulmonary immunity through systemic immunomodulatory effects. For instance, specific microbial metabolites can either promote or suppress airway inflammation [7,8]. Indole-3-propionic acid (IPA), a tryptophan-derived metabolite produced by gut commensal bacteria, has recently gained attention for its anti-inflammatory and barrier-strengthening properties. It has been shown to reduce intestinal permeability and mitigate inflammatory injury in various models [9]. However, the role of IPA in asthma, particularly its impact on pulmonary immune regulation, remains largely unexplored.

Immunomodulatory strategies represent a promising frontier in asthma therapeutics. Targeting T-cell function and their interactions with antigen-presenting cells offers a viable approach for restoring immune balance. The PD-1/PD-L1 pathway, widely studied in cancer and autoimmunity, serves as a key mechanism for restraining T-cell activity and maintaining peripheral tolerance [10,11]. Given the anti-inflammatory potential of IPA and the central role of PD-1/PD-L1 in asthma pathogenesis, we hypothesize that IPA may alleviate allergic airway inflammation via modulation of this pathway.

In this study, we aim to investigate the therapeutic potential of IPA in a murine model of ovalbumin (OVA)-induced asthma, with a specific focus on its influence on the PD-1/PD-L1 signaling axis. We will assess the effects of IPA on airway inflammation, inflammatory cell infiltration, Th2 cytokine production, and OVA-specific immunoglobulin levels. Furthermore, we will

examine how IPA regulates Treg populations and the expression of PD-1 and PD-L1 in lung tissues. By integrating immunological and histopathological analyses, this study seeks to provide a comprehensive understanding of how a gut microbiota-derived metabolite may ameliorate asthma through immune checkpoint regulation. Our findings may offer new insights into microbiome-based interventions and pave the way for novel asthma therapeutics.

METHODS AND MATERIALS

Reagents

Chicken ovalbumin (OVA) was obtained from Sigma-Aldrich, USA. Enzyme-linked immunosorbent assay (ELISA) kits for interleukin-4 (IL-4), IL-5, and IL-13 were purchased from Wuhan Huamei Biotechnology Co., Ltd., China. Fluorescently labeled antibodies including anti-CD4-FITC, anti-CD25-PC5, and anti-CD8-FITC were sourced from Proteintech Group, Inc. Horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG, as well as anti-PD-1 and anti-PD-L1 antibodies, were acquired from Abcam plc. Acetylcholine, BCA protein assay kit, western blot chromogenic reagent, and protein molecular weight markers were supplied by Beyotime Biotechnology.

Animal modeling

Female BALB/c young mice (3 - 4 weeks old) were acclimatized for 3 days under specific pathogen-free (SPF) conditions and then randomly assigned into four groups (n = 10 per group) using a simple randomization procedure: normal control, asthma model, high-dose IPA (50 mg/kg), and low-dose IPA (25 mg/kg) groups. The OVA-induced asthma model was established as previously described with minor modifications. The procedure consisted of a sensitization phase (days 0, 7, and 14) via intraperitoneal injection of 0.2 mL sensitization solution containing 10% OOVA adsorbed in aluminum hydroxide adjuvant, whereas control mice received 0.2 mL sterile saline. From days 19 to 26, sensitized mice underwent daily airway challenge with 3% OVA aerosol for 30 minutes in a sealed chamber. Control mice were exposed to saline aerosol. Behavioral signs of asthma (e.g., dyspnea, wheezing, scratching, reduced activity) were monitored to confirm model success. IPA or vehicle was administered daily by oral gavage from day 0 to 26. After the final challenge, blood, bronchoalveolar lavage fluid (BALF), and lung tissues were collected for analysis.

Airway responsiveness measurement

Airway resistance was assessed using a non-invasive lung function system (Buxco, USA) 24 hour after the last challenge. Mice were placed in whole-body plethysmography chambers, and baseline specific airway resistance (sRaw) was recorded after aerosolized saline exposure. Subsequently, mice were challenged with in-

creasing concentrations of methacholine (Mch; 0 - 80 mg/mL) via nebulization. sRaw was recorded after each Mch dose and normalized to baseline values.

Histopathological analysis

Lung tissues were fixed in 4% paraformaldehyde, embedded in paraffin, and sectioned at 4 μ m. After deparaffinization and rehydration, sections were stained with hematoxylin and eosin (H&E) according to standard protocols. Images were captured under a light microscope (Leica DM1000, Germany) at 400 x magnification. Six randomly selected fields per sample were evaluated for inflammatory cell infiltration and structural changes.

ELISA of cytokine levels

Levels of IL-4, IL-5, and IL-13 in lung homogenates and BALF were quantified using commercial ELISA kits according to the manufacturer's instructions. Absorbance was measured at 450 nm using a microplate reader (BioTek, USA). Cytokine concentrations were determined from standard curves.

Flow cytometric analysis of Tregs

Single-cell suspensions from lung tissues were prepared by mechanical dissociation. Cells (100 μ L) were incubated with anti-CD4-FITC and anti-CD25-PC5 antibodies for 20 minutes at room temperature in the dark. Erythrocytes were lysed, and cells were washed and fixed in 1% paraformaldehyde. Data were acquired on a flow cytometer (BD Accuri C6, USA) and analyzed using FlowJo software (v10.0). CD4⁺CD25⁺ cells were defined as Tregs.

Immunohistochemistry (IHC) for PD-1 and PD-L1

Paraffin-embedded lung sections underwent antigen retrieval in citrate buffer (pH 6.0) and blocking with 5% BSA. Sections were incubated overnight at 4°C with rabbit anti-PD-1 or anti-PD-L1 antibodies (1:100), followed by HRP-conjugated secondary antibody (1:500) for 30 minutes at room temperature. Diaminobenzidine (DAB) was used as the chromogen, and hematoxylin was applied for counterstaining. Staining intensity and area were quantified blindly using ImageJ software (v1.53) in three fields per sample.

Quantitative real-time PCR (qRT-PCR)

Total RNA was extracted from lung tissues using TRIzol reagent. Reverse transcription was performed using a PrimeScript RT kit (Takara, Japan). qPCR was conducted with SYBR Green Master Mix on a QuantStudio 5 system (Applied Biosystems, USA). The $2^{-\Delta\Delta C_t}$ method was used to calculate relative mRNA expression of PD-1 and PD-L1, with β -actin as the endogenous control. Primer sequences are listed in Table 1.

Statistical analysis

All data are expressed as mean $\pm$ standard deviation (SD). Differences among multiple groups were analyzed

by one-way ANOVA followed by Student-Newman-Keuls post-hoc test using SPSS 19.0. A p-value < 0.05 was considered statistically significant.

RESULTS

IPA attenuates airway hyperresponsiveness in a juvenile mouse model of asthma

Airway responsiveness was assessed by measuring lung resistance in response to increasing concentrations of methacholine (Mch). In the asthma model group, airway resistance rose progressively with Mch challenge (20, 40, and 80 mg/mL), indicating significant airway hyperresponsiveness compared to the normal control group ($p < 0.05$). By contrast, IPA treatment markedly attenuated this response, with statistically significant reductions in airway resistance at Mch concentrations of 40 and 80 mg/mL ($p < 0.05$) (Figure 1).

IPA ameliorates lung inflammation and pathological injury in asthmatic mice

Histopathological evaluation of lung tissues via H&E staining revealed normal bronchial structure, intact alveolar septa, and minimal inflammatory cell infiltration in the control group (Figure 2A). In contrast, the asthma model group exhibited marked pathological alterations, including bronchial wall thickening, luminal narrowing, epithelial disorganization, peribronchial inflammatory cell infiltration, mucus hypersecretion, and alveolar septal rupture (Figure 2B). Treatment with IPA significantly alleviated these changes, as evidenced by reduced bronchoconstriction, diminished inflammatory cell infiltration, absence of luminal secretions, relatively well-organized bronchial epithelium, and preserved alveolar architecture (Figure 2C, D).

IPA modulates cytokine and immunoglobulin levels in BALF and serum

Levels of Th2-associated cytokines (IL-4, IL-5, and IL-13) in bronchoalveolar lavage fluid (BALF) were significantly elevated in the asthma model group relative to controls ($p < 0.05$). IPA treatment significantly suppressed these cytokines ($p < 0.05$) (Figure 3A - C). Similarly, serum levels of OVA-specific IgE and IgG1 were markedly increased in asthmatic mice, whereas the anti-inflammatory cytokine IL-10 was significantly decreased ($p < 0.05$). IPA intervention reversed these changes, reducing OVA-IgE and OVA-IgG1 and elevating IL-10 levels ($p < 0.05$) (Figure 3D - F).

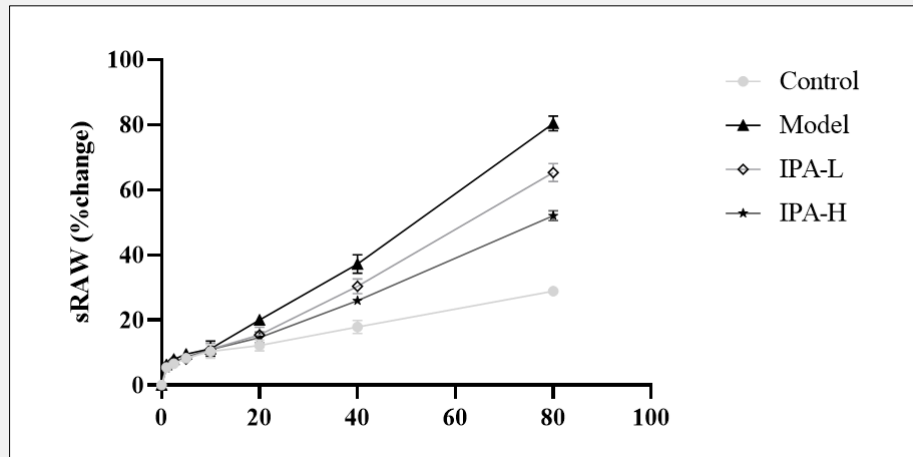
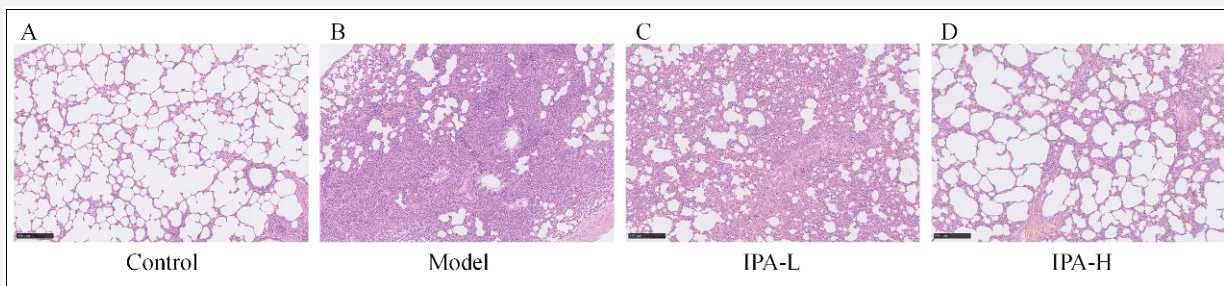
IPA downregulates PD-1 and PD-L1 expression in lung tissues

Immunohistochemical analysis revealed enhanced expression of PD-1 and PD-L1 in lung sections from the asthma model group, with stronger staining intensity compared to controls ($p < 0.05$). IPA treatment significantly reduced the protein expression of both immune checkpoint molecules ($p < 0.05$) (Figure 4).

Table 1. Primer sequences for qRT-PCR.

Gene	Forward primers	Reverse primers
PD-1	CTTCGTCGCAGCTCTTACAC	GCCTTGCTTGGATCAGCAG
PD-L1	GCTCCAAAGGACTTGTACGTG	CTGCTTGTCCAGATGACTTCGG
β -actin	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT

Sequences: 5' to 3'.

**Figure 1. The effect of IPA on airway reactivity in young mice (n = 10).**IPA-L: indole-3-propionic acid low dose (5 mg/kg), IPA-H: indole-3-propionic acid high dose (20 mg/kg) vs. model group, * $p < 0.05$.**Figure 2. HE staining results of lung tissue in young mice (x 400; n = 6).**

IPA-L: indole-3-propionic acid low dose (5 mg/kg), IPA-H: indole-3-propionic acid high dose (20 mg/kg).

Consistently, RT-PCR results showed that PD-1 and PD-L1 mRNA levels were significantly upregulated in

asthmatic mice and were effectively suppressed by IPA administration ($p < 0.05$) (Figure 5A, B).

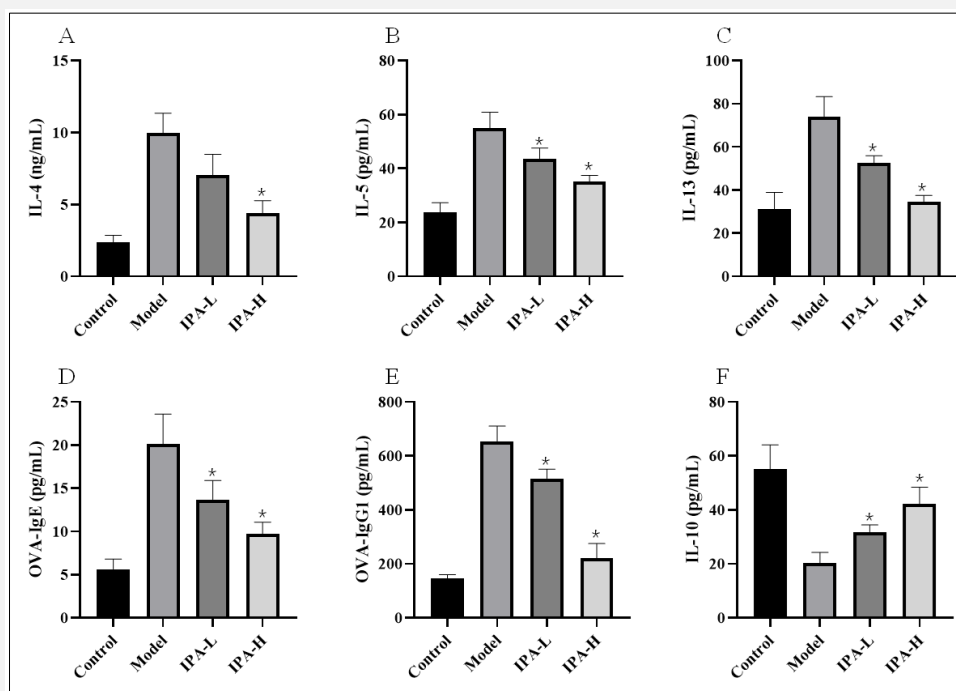


Figure 3. Cytokine levels in BALF and serum of young mice.

A: level of IL-4, B: level of IL-5, C: level of IL-13, D: level of OVA-IgE, E: level of OVA-IgG1, F: level of IL-10. IPA-L: indole-3-propionic acid low dose (5 mg/kg), IPA-H: indole-3-propionic acid high dose (20 mg/kg) vs. model group, * $p < 0.05$.

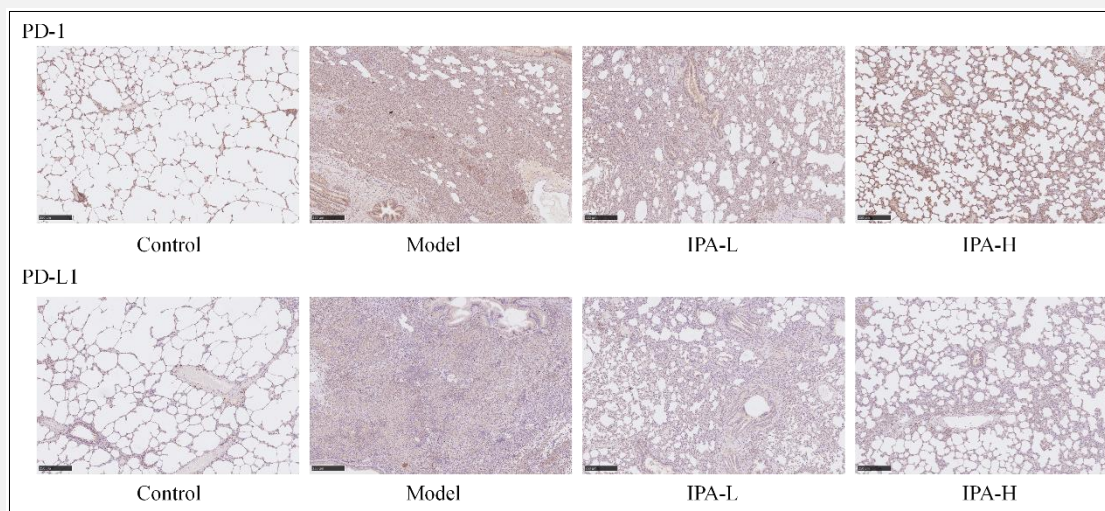


Figure 4. Immunohistochemical staining results of PD-1 and PD-L1 in lung tissue of young mice (x 400; n = 6).

IPA-L: indole-3-propionic acid low dose (5 mg/kg), IPA-H: indole-3-propionic acid high dose (20 mg/kg).

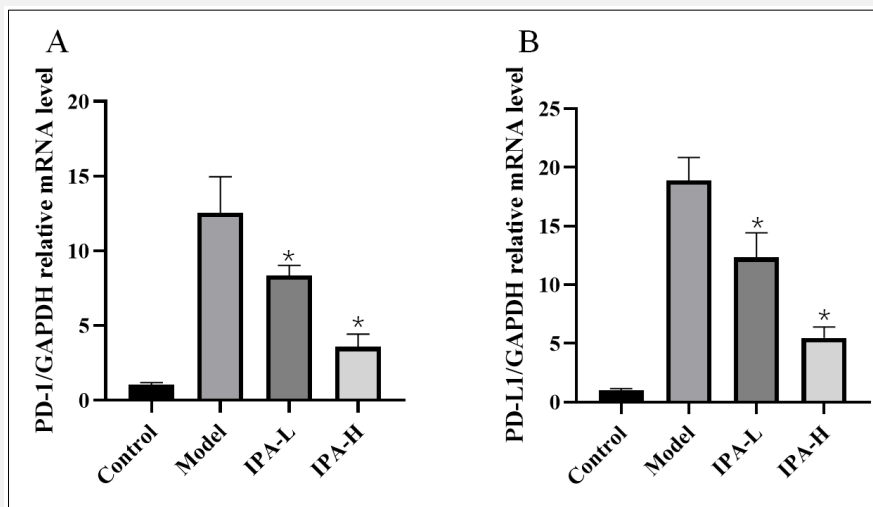


Figure 5. mRNA results of PD-1 and PD-L1 in lung tissue of young mice.

A: Relative mRNA level of PD-1, B: Relative mRNA level of PD-L1. IPA-L: indole-3-propionic acid low dose (5 mg/kg), IPA-H: indole-3-propionic acid high dose (20 mg/kg) vs. model group, * $p < 0.05$.

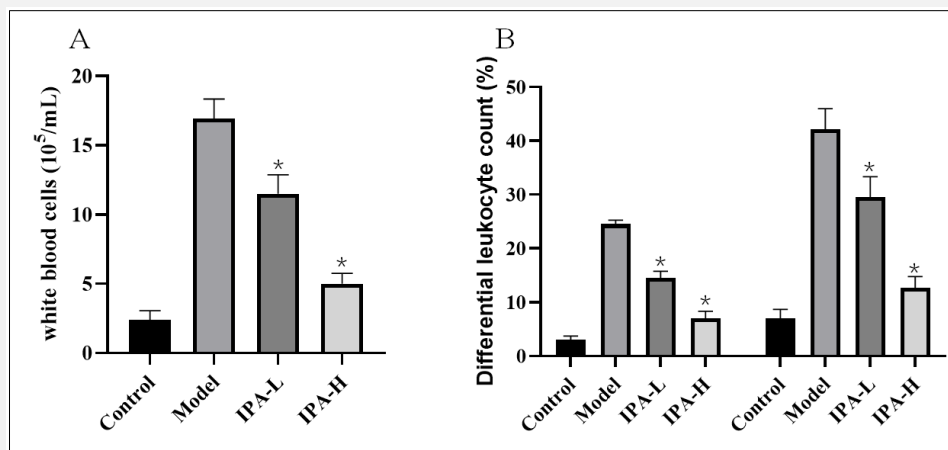


Figure 6. Total number and classification count of white blood cells in BALF of young mice.

A: Total number of white blood cells, B: classification count of white blood cells. IPA-L: indole-3-propionic acid low dose (5 mg/kg), IPA-H: indole-3-propionic acid high dose (20 mg/kg) vs. model group, * $p < 0.05$.

IPA reduces inflammatory cell counts in BALF

Total leukocyte numbers in BALF were significantly higher in the asthma model group than in controls ($p < 0.05$). IPA treatment substantially reduced total cell

counts ($p < 0.05$) (Figure 6A).

Differential counting further indicated pronounced elevations in eosinophils and neutrophils in asthmatic mice ($p < 0.05$), both of which were significantly lowered by

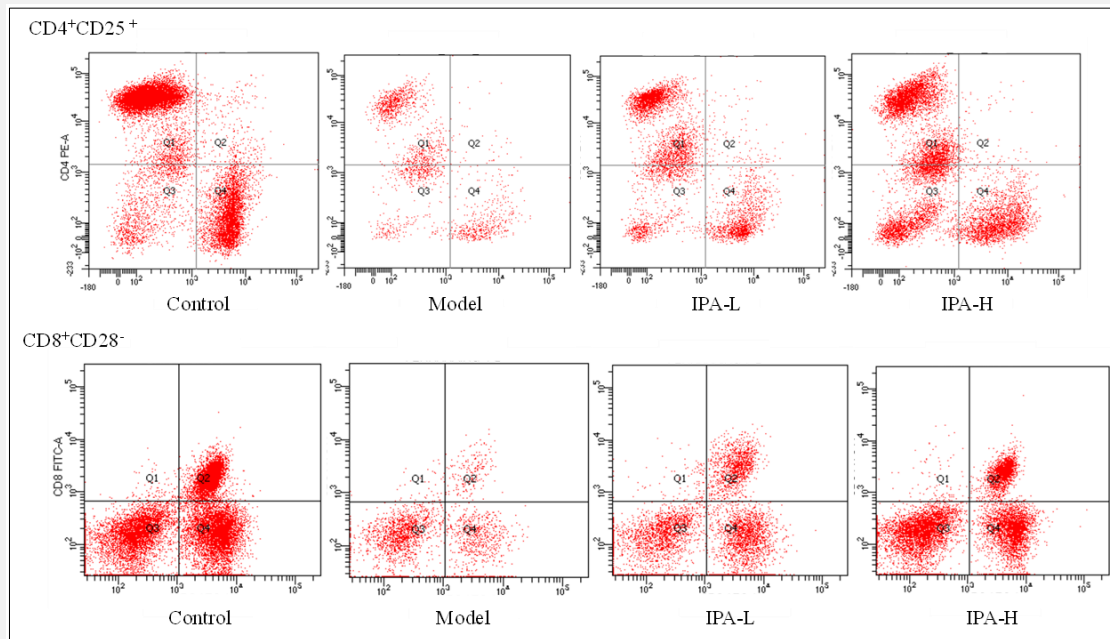


Figure 7. Flow cytometry of CD4+CD25+ and CD8+CD28- in lung tissue of young mice.

IPA-L: indole-3-propionic acid low dose (5 mg/kg), IPA-H: indole-3-propionic acid high dose (20 mg/kg).

IPA ($p < 0.05$) (Figure 6B). Given the prominence of eosinophilic and neutrophilic inflammation in asthma pathogenesis, lymphocytes and macrophages were not analyzed in this comparison.

IPA enhances regulatory T cell populations in lung tissue

Flow cytometric analysis demonstrated a significant decrease in the proportion of CD4+CD25+ T cells - a population enriched for regulatory T cells (Tregs) - in the lungs of asthmatic mice compared to the control group ($p < 0.05$). A reduction in CD8+CD28- T cells, which may also exhibit immunoregulatory properties, was also observed. These findings reflect impaired immunoregulatory capacity in the asthma model.

Following IPA treatment, the frequencies of CD4+CD25+ and CD8+CD28- T cells were significantly restored ($p < 0.05$) (Figure 7), indicating that IPA enhances immunomodulatory cell populations in the asthmatic lung.

DISCUSSION

Bronchial asthma is a chronic inflammatory airway disorder characterized by acute symptomatic episodes, airway hyperresponsiveness (AHR), eosinophil and neu-

trophil infiltration in the lungs, and elevated levels of type 2 inflammatory cytokines [12]. These pathological processes are driven by inflammatory mediator release, immune cell activation, and airway smooth muscle contraction, collectively leading to airflow limitation and worsened asthma exacerbations. The rising global incidence of childhood asthma highlights an urgent need for improved preventive and therapeutic strategies [13]. In this study, we utilized ovalbumin (OVA) to induce asthma in juvenile mice - a model that recapitulates key clinical features of the human disease [14]. Although modeling pediatric asthma in young animals remains technically challenging, our OVA-sensitized mice exhibited typical asthma phenotypes, including tachypnea, facial itching, elevated AHR, marked inflammatory infiltration in lung tissues, increased total leukocyte and eosinophil counts in bronchoalveolar lavage fluid (BALF), and elevated levels of Th2 cytokines and OVA-specific immunoglobulins. These findings collectively confirm the successful establishment of an experimental asthma model in juvenile mice.

Indole-3-propionic acid (IPA), a gut microbiota-derived metabolite of tryptophan, exhibits multiple biological activities and plays important roles in various physiological and pathological processes [15]. Accumulating evidence suggests that IPA modulates immune function and attenuates inflammatory responses across multiple

organ systems. It influences host immunity both directly and through modulation of gut microbial composition. Notably, IPA has been shown to regulate T-cell differentiation and function, particularly the balance between T helper (Th) cell subsets. Contrary to promoting Th1-to-Th2 shift, current evidence indicates that IPA helps restore immune homeostasis in Th1/Th2 imbalance-related disorders, thereby ameliorating autoimmune and allergic conditions [16-18]. Additionally, IPA modulates inflammatory cascades by regulating cytokine and chemokine expression. Previous studies report that IPA reduces pro-inflammatory mediators such as TNF- α , IL-6, and IL-1 β , while enhancing anti-inflammatory cytokines including IL-10, thereby mitigating Th2-driven inflammatory responses and disease severity [19,20].

Asthma pathogenesis involves not only clinical symptoms and AHR but also profound alterations at tissue, cellular, and molecular levels. Histopathologically, asthma is associated with inflammatory cell infiltration, goblet cell hyperplasia, and collagen deposition in the airways, ultimately impairing pulmonary function. At the immune level, asthma is defined by a Th2-skewed cytokine profile. IL-5 promotes eosinophil proliferation and activation, whereas IL-4 and IL-13 stimulate B cells to produce IgE, further polarizing immunity toward a Th2 phenotype [21-23]. In our model, IPA treatment significantly alleviated acute asthma symptoms, reduced AHR, attenuated inflammatory cell infiltration in lung tissues, and decreased total leukocyte, eosinophil, and neutrophil counts in BALF. Given the central role of IL-4, IL-5, and IL-13 in asthma pathogenesis [24], the observed suppression of these cytokines, along with reduced OVA-specific antibodies and elevated IL-10 levels following IPA intervention, strongly indicates that IPA ameliorates allergic airway inflammation via inhibition of Th2 immunity.

Recurrent asthma exacerbations are closely linked to dysregulated immune responses. Antigen-induced T cell activation represents a pivotal step in asthma pathogenesis. CD4⁺CD25⁺ and CD8⁺CD28⁻ T cells constitute critical regulatory T cell (Treg) populations essential for maintaining self-tolerance and immune homeostasis [25]. CD4⁺CD25⁺ Tregs exert immunosuppressive functions primarily through direct cell contact-dependent inhibition of effector T cell activation and proliferation [26]. Alterations in CD4⁺CD25⁺ Treg frequency or function can predispose individuals to hypersensitivity reactions and autoimmune disorders, including asthma. More recently, CD8⁺CD28⁻ T cells have been identified as another important regulatory subset capable of suppressing immune responses via upregulation of inhibitory receptors on antigen-presenting cells [28]. Our flow cytometry data revealed a significant reduction in both CD4⁺CD25⁺ and CD8⁺CD28⁻ T cell populations in the lungs of asthmatic mice, which was reversed by IPA treatment. These results suggest that IPA enhances immunoregulatory capacity in asthmatic airways by restoring Treg numbers.

The PD-1/PD-L1 pathway serves as a critical immune

checkpoint involved in the regulation of immune tolerance and inflammation across various diseases, including asthma [5,6]. Its role in allergic inflammation, however, appears context-dependent. While some studies suggest that PD-1/PD-L1 signaling activates iNKT cells and enhances Th2 responses - potentially contributing to AHR - others indicate that PD-L1 can inhibit allergic airway inflammation [28,29]. Clinical observations also reveal an inverse correlation between serum PD-L1 levels and symptom severity in allergic rhinitis patients [30]. In our study, IPA treatment significantly downregulated both PD-1 and PD-L1 expression in lung tissues at the protein and transcript levels, suggesting that modulation of this pathway may represent one mechanism through which IPA exerts its anti-inflammatory effects. We propose that IPA may promote Treg expansion and function, at least in part, through the PD-1/PD-L1 axis, thereby restraining excessive Th2 inflammation in asthma.

CONCLUSION

This study demonstrates that IPA alleviates allergic airway inflammation in a juvenile murine asthma model by modulating immune responses through multiple mechanisms. We provide evidence that IPA reduces Th2 cytokine production, restores regulatory T cell populations, and downregulates the PD-1/PD-L1 signaling axis. These findings support the potential of IPA as a novel microbiota-derived immunomodulator and highlight the PD-1/PD-L1 pathway as a promising target for future asthma therapeutics. This work lays a foundation for further investigation into gut microbiota-host immune interactions in pediatric asthma and offers new insights for developing targeted diagnostic and treatment strategies.

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Declaration of Generative AI in Scientific Writing:

During the preparation of this manuscript, the authors used Chat GPT solely for the purpose of improving grammar, spelling, and sentence clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the intellectual content of the publication.

Declaration of Interest:

The authors declare that they have no conflict of interest.

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