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ORIGINAL RESEARCH

IL-17A as a Key Mediator of Pulmonary-Intestinal Immune Interactions in a Mouse Model of Asthma and Colitis

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Background: The immunological interaction between the lung and gut remains underexplored, particularly in the context of coexisting mucosal inflammation. While IL-17A has been implicated in both asthma and colitis independently, its role in coordinating systemic immune responses across tissue compartments is not well defined.

Methods: In this study, we developed a combined house dust mite-induced asthma model and dextran sulfate sodium-induced colitis model to investigate the role of IL-17A in driving inflammation in both the lungs and the intestines.

Results: Our findings demonstrate that IL-17A neutralization markedly reduced airway and intestinal inflammation, attenuated mucus hypersecretion, downregulated pro-inflammatory cytokine expression, and alleviated colitis severity. Histopathological analysis revealed decreased infiltration of immune cells, including eosinophils, lymphocytes, and macrophages, in both the lungs and colonic tissues following IL-17A blockade. Additionally, we observed a reduction in mucus production, particularly in the airways, highlighting IL-17A's direct role in mucin regulation. Transcriptomic analysis confirmed that IL-17A blockade downregulated several immune-related pathways in colon tissues, further supporting its central role in mediating multi-organ inflammation.

Conclusion: These findings indicate that IL-17A represents a systemic immunomodulator, which orchestrates compartmentalized immune responses along the lung-gut axis. The observed tissue-specific redistribution of IL-17A and the therapeutic benefit of its neutralization suggest that IL-17A may serve as a clinically actionable target in patients with overlapping asthma and colitis. The study also shows that IL-17A plays a reciprocal role in influencing immune responses in both lung and gut.

Keywords: IL-17A, asthma, colitis, lung-gut axis, inflammation

Introduction

The lung-gut axis represents a bidirectional communication network between the intestine and the lung that shapes immune responses and disease progression in both systems.[1] This axis involves interactions between the microbiota, immune cells, and epithelial barriers in both organs, with dysregulation of these processes potentially contributing to the pathogenesis of various inflammatory diseases.[1,2] Much of the current research has focused on how disturbances in the gut can exacerbate or even initiate respiratory diseases.[3] Hence, it is now well established that microbial metabolites such as short-chain fatty acids can

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influence lung immunity, promoting either protective or harmful outcomes.[4,5] However, there remains a critical gap in understanding how chronic respiratory inflammation affects gut health. This lung-to-gut direction of the lung-gut axis is insufficiently investigated, despite growing evidence that respiratory conditions like asthma may directly contribute to intestinal inflammation and gastrointestinal diseases such as colitis.[6–9]

Asthma, a chronic inflammatory disease of the airways, is characterized by airway hyperresponsiveness, mucus hypersecretion, and persistent inflammation driven by immune cells such as type 2 immune cells and Th17 lymphocytes.[10] These cells and their cytokines are critical in sustaining airway inflammation and remodeling.[11] Although the lungs are the primary site of inflammation in asthma, the systemic nature of the immune response suggests that the effects of the disease may extend beyond the lungs. Current research has identified several immune-mediated pathological links between asthmatic lung and other diseased organs as these illnesses have a common immunological base.[12–19] A number of studies indicates that asthma-associated cytokines, including IL-17A and IL-18, may also play a pivotal role in promoting intestinal inflammation, thus linking respiratory diseases to gut diseases.[20,21] Indeed, a recent study has identified a causal relationship between asthma and an increased risk of ulcerative colitis (UC), with IL-17A potentially acting as a key mediator in this process.[21]

UC, a chronic inflammatory disease of the colon, is characterized by continuous inflammation beginning in the rectum and extending proximally without skip lesions.[22] Symptoms include bloody diarrhea, rectal bleeding, and an increased risk of colorectal cancer, and the disease typically follows a relapsing-remitting course.[22] Like asthma, UC involves immune dysregulation, with elevated levels of proinflammatory cytokines contributing to its pathogenesis.[23] Therefore, the presence of these cytokines in both asthma and UC suggests a shared inflammatory pathway that could explain the co-occurrence of these conditions. The lung-to-gut axis, while less studied than the gut-to-lung pathway, offers important insights into how chronic lung inflammation might influence gut health, particularly through cytokine-driven inflammation.

The bidirectional nature of the lung-gut axis is exemplified in diseases such as chronic obstructive pulmonary disease (COPD), where intestinal dysbiosis is both a cause and a consequence of lung inflammation.[24,25] COPD patients frequently exhibit gut dysbiosis, which has been linked to exacerbations of respiratory symptoms and an increased risk of gastrointestinal diseases.[25] Similarly, asthma patients may be predisposed to developing colitis and other gastrointestinal disorders through cytokine-mediated inflammation and alterations in the microbiota.[26–28] Therefore, understanding this relationship between the lungs and the gut is critical to developing a more holistic approach to managing patients with co-occurring diseases.

Despite these findings, current research on those proinflammatory factors has predominantly focused on their role in either respiratory or gastrointestinal inflammation, leaving an unmet need to explore how they drive inflammation when these diseases co-occur. Patients suffering from both asthma and colitis may require unique therapeutic approaches that address the shared inflammatory pathways affecting both the lungs and the intestines. To address this gap, the present study introduces a combined mouse model that replicates both house dust mite (HDM)-induced asthma and dextran sulfate sodium (DSS)-induced colitis. This model allows for the investigation of how pulmonary lesion affects colonic inflammation, providing a unique framework for studying the interaction between these two systems. By coupling this model with transcriptomic analysis, we comprehensively investigated the shared immune mechanisms driving inflammation in these diseases. Our results highlight IL-17A as a central mediator of inflammation in both the lungs and the colon, offering new perspectives on therapeutic interventions that could significantly improve patient outcomes by targeting systemic inflammation across both organ systems.

Materials and Methods

Mouse Model of HDM Induced Asthma

Six to eight weeks old Balb/C mice wild type (WT) were obtained from the Experimental Animal Centre of Zhengzhou University. The animals were housed under a 12-hour light/dark cycle in a temperature- and humidity- controlled environment with free access to food and water. The publicly available data used in this study and all animal experiments were approved by the Ethics Committee of Zhengzhou University (ZZU-LAC20230915[11]). All procedures involving animals conducted in accordance with The Guide for the Care and Use of Laboratory Animals (NRC, 8th edition). Mice

were randomly assigned to two groups (n = 5 per group). The HDM group underwent intratracheal (i.t) sensitization with 50 μg of house dust mite (HDM; XPB91D3A25, GREER, USA) in 50 μL phosphate-buffered saline (PBS), administered on three consecutive days (days 1–3), followed by airway challenge with 5 μg HDM in 50 μL PBS on days 14–17 under isoflurane anesthesia, as previously described.[29] The PBS group received an equivalent volume of PBS following the identical administration schedule and anesthetic protocol.

Asthmatic Model Combined with DSS-Induced Colitis

Mice were randomly allocated into four groups (n = 5 per group): 1. PBS+DSS group received intranasal PBS daily followed by 2% dextran sulfate sodium (DSS; Cat# 160110, MP Biomedicals, USA) in drinking water for 7 consecutive days to induce colitis.[30] 2. HDM+DSS group underwent intranasal HDM sensitization as described above, immediately followed by 2% DSS administration for 7 days. 3. HDM+Vehicle group received HDM sensitization followed by normal drinking water. 4. PBS+Vehicle group received intranasal PBS and normal water.

For IL-17A blockade experiments, mice were divided into three additional groups (n = 4 per group): 1. HDM+DSS +α-IL-17A group received intraperitoneal injections of 100 μg/mouse of neutralizing anti-IL-17A monoclonal antibody (Clone TC11-18H10.1, BioLegend, USA) on days 2 and 5 after DSS initiation. 2. HDM+DSS+Isotype group received equivalent doses of IgG1 isotype control antibody (Clone MOPC-21, BioXCell, USA) on the same schedule. 3. PBS +Vehicle group (for antibody comparison) received intranasal PBS, normal drinking water, and concurrent IgG1 isotype antibody injections.

Bronchoalveolar Lavage Fluid (BALF) and Peripheral Blood

BALF was obtained by two washes of the right lung lobes using 1mL sterile HBSS. Following this, the BALF was centrifuged to separate the cellular infiltrates, and the supernatant was stored at −80°C for subsequent cytokine analysis. Red blood cells were eliminated using a hypotonic lysis buffer, as previously described.[31] BALF samples were centrifuged using a Cytospin™ system (Thermo Fisher Scientific) at 350 rpm for 5 minutes to concentrate cellular components onto glass slides. Cytospin preparations were sequentially stained with May-Grünwald solution (G3100; Solarbio, China) followed by Giemsa stain (G1015; Solarbio, China). Differential cell counts were performed via light microscopy at 1000× magnification (BX51, Olympus) and were based on established morphological criteria: neutrophils were identified by segmented nuclei and pale cytoplasm; eosinophils by bilobed nuclei and abundant eosinophilic granules; lymphocytes by their high nuclear-to-cytoplasmic ratio; and macrophages by their foamy cytoplasm and eccentrically positioned nuclei.

Peripheral blood was collected from the mice via the tail vein for immune cell analysis.[32] Mice were briefly restrained, and the tail was cleaned with 70% ethanol. A small incision was made at the tip of the tail with a sterile scalpel. A small volume of the collected blood was smeared onto glass slides using a standard wedge technique. The blood smears were air-dried and subsequently fixed in methanol and stained with May-Grunwald-Giemsa solution. The percentage of immune cell subsets, including lymphocytes, monocytes, and granulocytes, was calculated from the total number of cells counted.

Disease Activity Index (DAI)

Mice were monitored daily for clinical signs of colitis. DAI was evaluated by summing the scores of three parameters: body weight loss, stool consistency, and rectal bleeding. Body weight was recorded daily using a precision balance, and the percentage of weight loss was calculated relative to the baseline (Day 0): 0 =no weight loss, 1 = 1–5%, 2 = 5–10%, 3 = 10–15% and 4 = more than 15% weight loss, as described previously.[33] Stool consistency was evaluated daily using freshly collected fecal samples, categorized by a validated 4-tier scoring system: 0 = normal, well-formed cylindrical pellets with intact morphology; 1 = soft, formed stool with maintained shape and reduced surface tension; 2 = pasty, shapeless stool adhering to collection surfaces; 3 = liquid stool with complete structural loss, indicative of diarrhea. Visual inspection was combined with the Fecal Occult Blood Qualitative Test Kit (TC0511, Leagene, China). Scoring was based on both macroscopic bleeding and reagent-based chromogenic reaction: 0 = no visible blood; no detectable color change within 2 minutes; 1 = visible bleeding with delayed pale green to green transition; 2 = blood streaks visible;

pale green color on reagent contact, evolving into bluish-brown; 3 = ≥50% of stool surface visibly blood-coated; immediate bluish-brown color upon reagent application. DAI was then calculated by averaging the scores from these parameters.

IL-17A Elisa

To measure IL-17A levels, mice were sacrificed, and serum was collected as described previously.[34] Serum IL-17A levels were quantified using the Mouse IL-17A ELISA Kit (EK217; MultiScience; China) according to the manufacturer's instructions.

Pathological and Inflammatory Scoring

Mice were euthanized 24 hours after the final HDM intranasal challenge. Left lower lung lobes and distal colon segments (1 cm from anal verge) were harvested, fixed in 4% neutral-buffered formalin, paraffin-embedded, and sectioned at 3 μm thickness. Sections were stained with hematoxylin and eosin (H&E). For each animal, three non-overlapping fields (200× magnification) were selected per section, and scoring was conducted in a blinded manner by two independent pathologists. Final histopathological scores were calculated as the average of both readers' evaluations, as described previously.[35]

Pulmonary inflammation was quantified using a composite histological scoring system comprising three subscores: (1) Airway inflammation (0–4) based on peribronchial cellular infiltration: 0 = none; 1 = sparse infiltration near occasional airways; 2 = dense infiltration near occasional airways; 3 = moderate infiltration around most airways; 4 = dense infiltration surrounding the majority of airways. (2) Vascular inflammation (0–4) graded identically for perivascular infiltration. (3) Parenchymal inflammation (0–5) determined by the percentage of inflamed lung area: 0 = <1%; 1 = 1–9%; 2 = 10–29%; 3 = 30–49%; 4 = 50–69%; and 5 = >70%. The total inflammation score (maximum 13 points) was calculated as the sum of the three component scores.

PAS score was assessed by calculating the ratio of PAS-positive cells to total airway epithelial cells in bronchial sections. The scoring criteria were: 0 = <5%; 1 = 5–25%; 2 = 25–50%; 3 = 50–75%; and 4 = >75%.

Colonic pathology was assessed using a dual-component scoring system. Epithelial alterations were graded as: 0 = normal; 1 = goblet cell loss; 2 = extensive goblet cell loss; 3 = crypt loss; 4 = extensive crypt loss. Inflammatory infiltration scoring followed: 0 = none; 1 = infiltration around crypts; 2 = infiltration into muscularis mucosa; 3 = diffuse muscularis mucosa infiltration with mucosal thickening; 4 = Submucosal infiltration. Total colonic pathology score equals epithelial alteration score + inflammatory infiltration score.[33]

Quantitative Real-Time PCR

Total RNA from lung and colon tissues was isolated using the Trizol method, as described previously.[36] One microgram of RNA was reverse transcribed into cDNA using the First-Strand cDNA Synthesis Kit. Primer sequences for IL-17A, TNF-α, IL-5, IL-13, IFN-γ, and GAPDH are listed in Supplement Table 1. Quantitative real-time PCR was conducted on the QuantStudio™ 6 Flex PCR system with SYBR® Green as the fluorescent dye for detection. Quantitative real-time PCR was performed in triplicate for each biological replicate. Expression levels were calculated using the ΔΔCt method, and data were presented as the mean of technical replicates for each individual mouse. Gene expression levels were normalized to GAPDH as the internal control.

Bioinformatic Analysis

RNA-sequencing data from asthma (GSE43696 and GSE63142) and ulcerative colitis (GSE16879, GSE38713, and GSE92415) patients were downloaded from Gene Expression Omnibus (GEO). RNA sequencing was performed on the airway and colon tissues of mice from the PBS+Vehicle, HDM+Vehicle, PBS+DSS, and HDM+DSS groups by PANOMIX Biomedical Tech Co., LTD (Suzhou, China). Additionally, we conducted RNA sequencing on the colon tissues of mice from the HDM+DSS+Isotype and HDM+DSS+αIL-17A groups. Differential gene expression analyses were performed using the DESeq package in R, as described previously.[35] Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, and Gene Set Enrichment Analysis (GSEA) were performed utilizing the ClusterProfiler package in R.[37]

Statistical Analysis

Data analysis was conducted using SPSS 20.0 software. Parametric data were analyzed using an unpaired Student's *t*-test for comparisons between two groups or two-way analysis of variance (ANOVA) with Tukey's post hoc test for multiple groups. Statistical significance was set at $p < 0.05$, and data are presented as mean ± SEM.

Results

HDM Exposure Promotes Pulmonary Inflammation and Colonic Changes

To investigate how HDM affect intestinal changes, we employed our well-established mouse model of HDM-induced asthma (Supplement Figure 1A).[38] WT mice were i.t. sensitized and challenged with HDM as described in the Methods, to minimize the direct impact on intestinal system. This model effectively induces asthma-like inflammation in the airways. Analysis of inflammatory cellular profile in BALF revealed a substantial increase in inflammatory cell infiltration in HDM-treated mice compared to PBS-treated mice. The levels of eosinophils, lymphocytes, macrophages, and neutrophils were significantly elevated in HDM-treated mice (Supplement Figure 1B). Assessment of eosinophil levels in lung sections by histology further revealed similar findings. HDM-treated mice displayed extensive peribronchial and perivascular infiltration of inflammatory cells, as well as increased mucus production (Supplement Figure 1C). The histopathological scores and periodic acid-Schiff (PAS) scores were both significantly higher in HDM-treated mice compared to PBS controls (Supplement Figure 1D and E).

Next, we quantified the levels of key pro-inflammatory cytokines in the lungs by quantitative PCR. Significant upregulation of IL-17A, TNF-α, IL-5, and IL-13 mRNA levels was observed in lung tissues from HDM-treated mice compared to PBS-treated mice (Supplement Figure 1F). Interestingly, IFN-γ expression did not show a significant increase, suggesting a predominantly Th2/Th17-driven response. Differential analysis of immune cells in peripheral blood demonstrated that HDM treatment induced a significant increase in the eosinophil percentage (Supplement Figure 1G).

In addition to respiratory inflammation, HDM-treated mice displayed notable changes in the architecture of the colon. Histological analysis of colonic sections stained with H&E revealed increased intercrypt distance and thickening of both the mucosal and muscular layers in HDM-treated mice, compared to PBS controls (Supplement Figure 1H). Quantitative measurements showed significant increases in intercrypt distance, mucosal thickness, and muscular thickness (Supplement Figure 1I–K), suggesting that HDM-induced systemic inflammation extends to the gut, potentially contributing to colonic remodeling. These results collectively demonstrate that HDM exposure not only induces airway inflammation and mucus production but also promotes structural changes in the colon, indicating a possible lung-to-gut inflammatory axis in this model.

Combined Effects of HDM and DSS on Pulmonary Inflammation

To investigate whether HDM-induced pulmonary inflammation exacerbates colonic pathology, we challenged HDM-treated animals with DSS following the final i.t. instillation of HDM. Histopathological analysis and mucus examination of lung tissues revealed significantly increased mucus production in the HDM+DSS group compared to the PBS+Vehicle and PBS+DSS groups. However, these levels were notably lower than those observed in the HDM+Vehicle group (Figure 1A–C). Both HDM+DSS and HDM+Vehicle treatments significantly increased the infiltration of eosinophils, lymphocytes, macrophages, and neutrophils in the BALF compared to PBS+DSS and PBS+Vehicle groups, and the HDM+DSS group exhibited a significant reduction in lymphocytes, macrophages, and neutrophils compared to the HDM+Vehicle group, suggesting a potential attenuation of airway inflammation when both agents were administered (Figure 1D). In contrast, no synergistic effects were observed on immune cell populations in peripheral blood (Figure 1E). Quantitative PCR analysis of lung tissues showed significantly elevated expression of pro-inflammatory cytokines, including IL-17A, TNF-α, IL-13, and IFN-γ, in both the HDM+Vehicle and HDM+DSS groups as compared to their PBS+Vehicle and PBS+DSS counterparts (Figure 1F). Interestingly, only IL-17A expression was significantly lower in the HDM+DSS group compared to the HDM+Vehicle group (Figure 1F). ELISA analysis showed elevated IL-17A levels in the lungs of both HDM+Vehicle and HDM+DSS groups compared to PBS controls, indicating that HDM induces pulmonary IL-17A expression. However, IL-17A levels were lower in the HDM+DSS group than in the HDM+Vehicle group, suggesting that co-existing colitis may suppress IL-17A

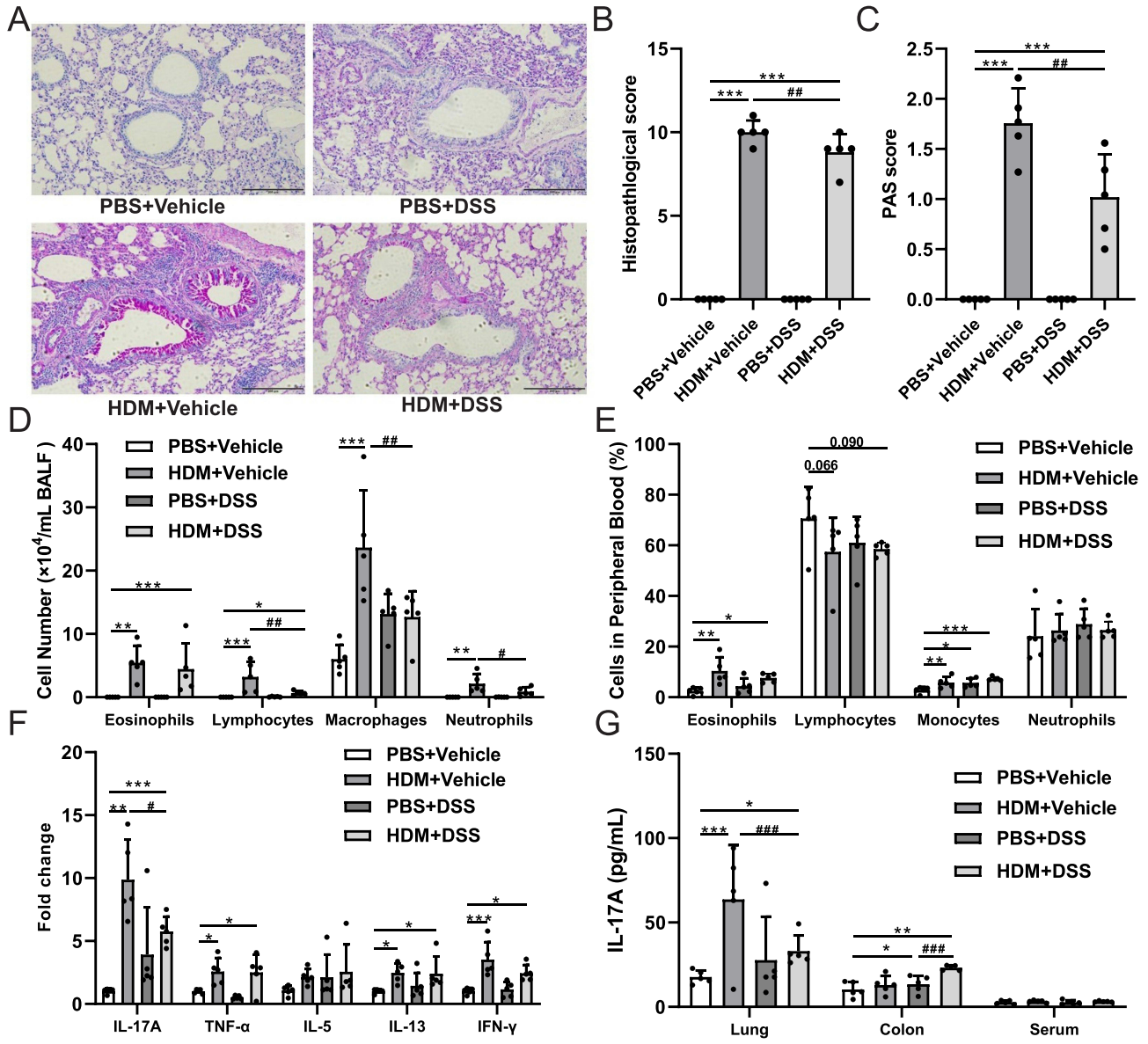

Figure 1 Co-administration of HDM and DSS attenuates HDM-induced airway inflammation. (**A**) Representative H&E and PAS-stained lung sections (scale bars = 200 μm). (**B** and **C**) Quantitative scoring of histopathology and mucus production. (**D**) BALF differential inflammatory cell counts by cytospin. (**E**) Analysis of peripheral leukocyte populations. (**F**) Lung cytokine mRNA expression (IL-17A, TNF-α, IL-5, IL-13, IFN-γ) by RT-qPCR. (**G**) IL-17A protein concentrations in lung, colon, and serum measured by ELISA. Data are shown as mean ± SEM (n = 5 per group). Statistical analysis performed using two-way ANOVA. *p < 0.05, **p < 0.01, ***p < 0.001 vs PBS+Vehicle group; #p < 0.05, ##p < 0.01, ####p < 0.001 vs HDM+DSS group.

production in the lung (Figure 1G). These findings suggest that HDM and DSS co-treatment not only attenuates airway inflammation and mucus secretion but also induces a tissue-specific shift in IL-17A expression, with reduced levels in the lung and elevated levels in the colon, reflecting a coordinated redistribution of immune activity.

Synergistic Effects of HDM and DSS on Colonic Inflammation

Interestingly, co-exposure to HDM and DSS led to pronounced weight loss, an increase in disease activity and exacerbation of colonic inflammation, and colon shortening. Body weight and DAI were monitored daily for 7 days following DSS administration. Although the HDM+DSS group experienced more pronounced weight loss compared to other groups, the differences were not statistically significant over time (Figure 2A). DAI scores, which assess colitis severity, were significantly higher in the HDM+DSS group compared with PBS+Vehicle and HDM+Vehicle

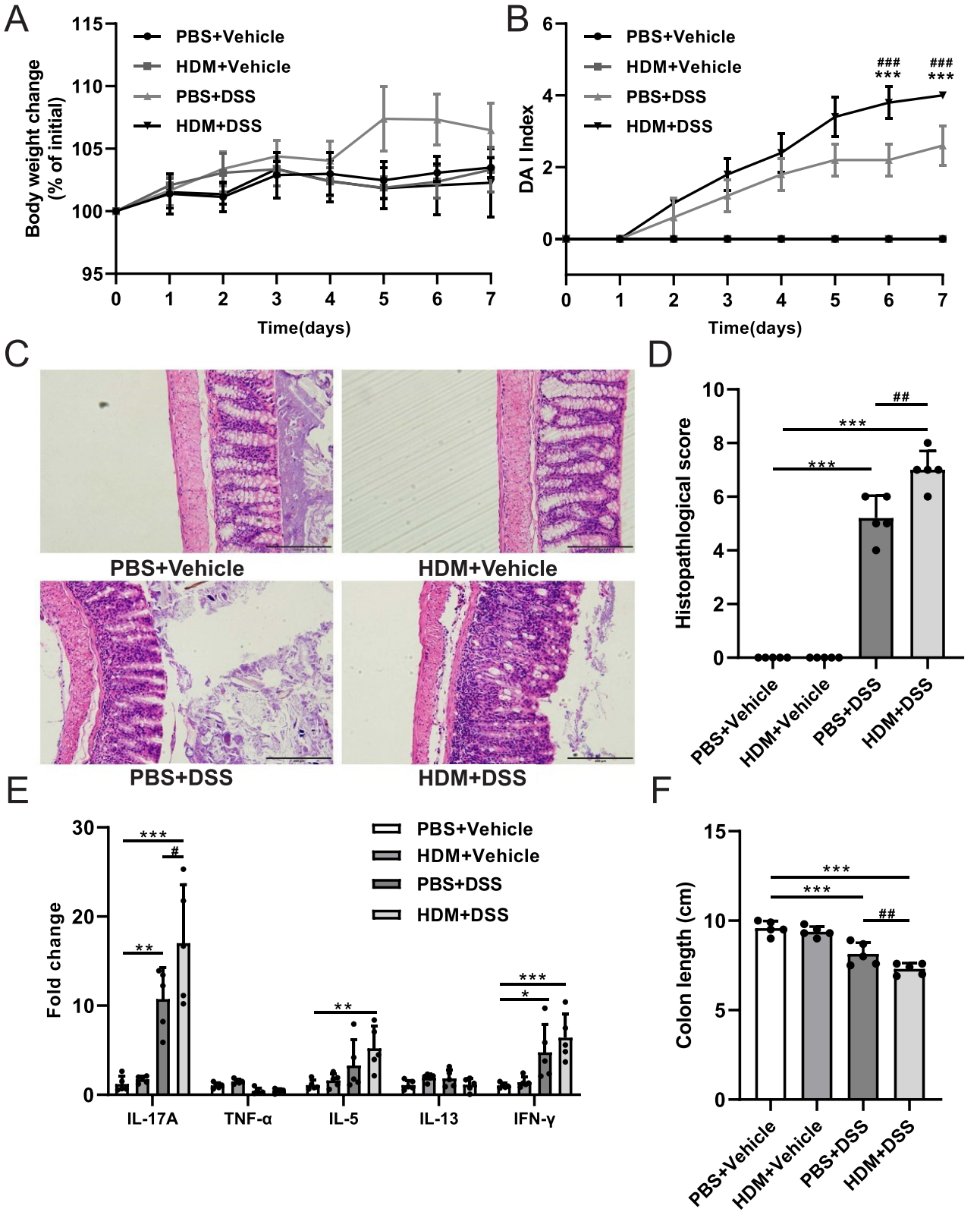

Figure 2 HDM pre-sensitization exacerbates DSS-induced colonic inflammation. (**A**) Percentage of body weight change over time. (**B**) Disease Activity Index (DAI) scores during DSS exposure. (**C**) Representative H&E-stained sections of distal colon from each treatment group, illustrating differences in crypt structure, epithelial integrity, and inflammatory infiltration. (Scale bars = 200 μm). (**D**) Histopathological scoring of colonic inflammation. (**E**) RT-qPCR quantification of colonic cytokine expression (IL-17A, TNF-α, IL-5, IL-13, IFN-γ). (**F**) Colon length measurements at endpoint. Data are presented as mean ± SEM (n = 5 per group). Statistical analysis conducted using two-way ANOVA. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs PBS+Vehicle; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ vs HDM+DSS group.

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groups from day 3 onward (Figure 2B). By day 7, DAI scores in the HDM+DSS group were significantly elevated compared to all other groups, indicating a worsening of colitis. Histopathological analysis of colonic tissues demonstrated exacerbated inflammation in the HDM+DSS group, with extensive infiltration of inflammatory cells and destruction of colonic architecture, comparable to the PBS+DSS group (Figure 2C and D). Colonic inflammation scores were significantly higher in the HDM+DSS group compared to all other groups, including the PBS+DSS group. Quantitative PCR analysis revealed significantly increased expression of IL-17A and IFN-γ in the colonic tissues of both PBS+DSS and HDM+DSS groups, with IL-17A levels being notably higher in the HDM+DSS group compared to the PBS+DSS group (Figure 2E). Colonic IL-17A was elevated in both PBS+DSS and HDM+DSS groups relative to controls. The HDM+DSS group displayed a further increase, indicating that prior airway inflammation enhances IL-17A expression in the colon during DSS-induced injury. In contrast, serum IL-17A levels remained stable across all groups, suggesting that cytokine modulation occurs primarily at the tissue level (Figure 1G). Additionally, colon length was markedly shorter in the HDM+DSS group compared to all other groups (Figure 2F). Collectively, these findings indicate that the co-administration of HDM and DSS synergistically exacerbates colonic inflammation, resulting in more severe epithelial damage, crypt distortion, and inflammatory infiltration compared to DSS alone.

IL-17 Pathway Enrichment in Both Asthma and Colitis Models

Next, we profiled the whole lung and colon tissues transcriptome in HDM+Vehicle vs HDM+DSS and PBS+DSS vs HDM+DSS to investigate the mechanisms of synergistical action of HDM and DSS treatments. KEGG pathway enrichment analysis of differentially expressed genes (DEGs) in endobronchial brushing samples from GSE43696 and GSE63142, two public datasets of severe asthma, revealed significant enrichment of the IL-17 signaling pathway, as well as pathways involved in salivary secretion, TNF signaling, and immune response to infection (Figure 3A). IL-17 signaling pathway was the most prominently enriched pathway in asthma. The heatmap of DEGs in lung tissues showed distinct expression patterns between HDM+Vehicle and HDM+DSS groups, highlighting differences in inflammatory responses (Figure 3B). KEGG pathway enrichment of those DEGs of the HDM+DSS group in lung tissues demonstrated significant activation of immune and inflammatory pathways, with IL-17 and TNF signaling pathways prominently enriched (Figure 3C).

Similarly, KEGG pathway enrichment analysis of DEGs in colonic tissues from GSE16879, GSE38713, and GSE92415, three datasets of patients with UC, showed significant enrichment of the IL-17 signaling pathway, alongside cytokine-cytokine receptor interactions and chemokine signaling (Figure 3D). Heatmap of colonic DEGs reveals differential expression between HDM+Vehicle and HDM+DSS groups (Figure 3E). KEGG pathway enrichment those DEGs of the HDM+DSS group in colon tissues indicated enrichment of pathways related to immune response, among which IL-17 signaling pathway was also significantly enriched (Figure 3F). To further clarify the contribution of HDM exposure to colonic immune remodeling, we conducted KEGG enrichment analysis of differentially expressed genes between the HDM + DSS and PBS + DSS groups. This comparison revealed enrichment in pathways such as neuroactive ligand–receptor interaction, suggesting a transcriptional reprogramming effect driven by prior pulmonary inflammation (Supplement Figure 2A and B). This translation strictly adheres to the original content, maintains scientific terminology, and avoids any interpretative additions.

These results demonstrate that the IL-17 signaling pathway is a critical mediator in the inflammatory cross-talk between the lungs and the colon in the HDM and DSS co-administration model.

IL-17A Neutralization Attenuates Airway Inflammation in HDM+DSS Treated Mice

To determine the central role of IL-17A in airway inflammation and mucus production, we neutralized IL-17A by monoclonal antibody against this cytokine in HDM+DSS treated animal. We focused on IL-17A as this cytokine, unlike others, was uniquely decreased in lungs and increased in colon of HDM-DSS-treated mice. IL-17A neutralization significantly decreased the number of eosinophils, lymphocytes and macrophages in BALF in HDM+DSS-treated mice as compared to those mice receiving an isotype control (Figure 4A). Neutrophil numbers also showed a downward trend, though this did not reach statistical significance. Although monocyte and neutrophil levels were

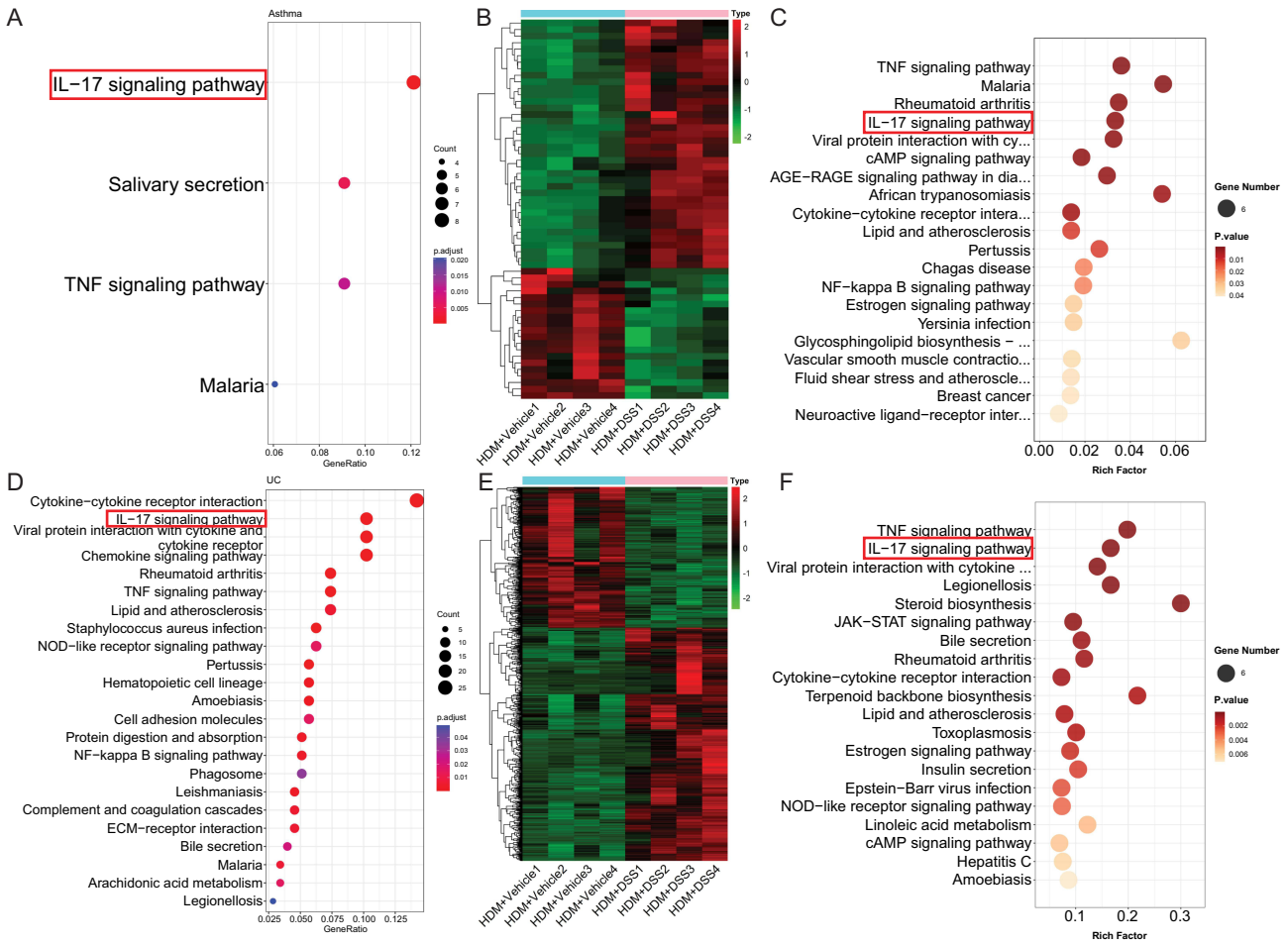

Figure 3 IL-17 signaling pathway is enriched in both asthma and colitis transcriptomes. (**A**) KEGG pathway enrichment analysis of lung differentially expressed genes (DEGs), with dot size indicating gene count and color scale indicating significance. (**B**) Heatmap of lung DEGs comparing HDM+DSS vs HDM+Vehicle groups. (**C**) Top enriched KEGG pathways from lung tissue, based on differentially expressed genes comparing HDM + DSS to HDM + Vehicle. Dot size reflects gene ratio, and color denotes adjusted p-value significance. (**D**) KEGG pathway enrichment analysis of colonic DEGs. (**E**) Heatmap of colonic DEGs comparing HDM+DSS vs HDM+Vehicle groups. (**F**) Top enriched KEGG pathways from colonic tissue, comparing HDM + DSS to HDM + Vehicle. Enrichment scores reflect significance and gene contribution within each pathway. The red boxes highlight the IL-17 signaling pathway.

also significantly increased, a significant decrease in eosinophils and neutrophils was observed in the blood of mice treated with anti-IL-17A compared to the isotype control (Figure 4B).

Histopathological analysis of lung tissues demonstrated reduced infiltration of inflammatory cells and levels of mucus-producing cells in HDM+DSS mice treated with anti-IL-17A, compared to those receiving the isotype control (Figure 4C). This was quantitatively confirmed by the histopathological score and PAS score (Figure 4D and E). Additionally, IL-17A neutralization significantly reduced the mRNA expression levels of key pro-inflammatory cytokines, including IL-17A, TNF-α, IL-5, IL-13, and IFN-γ (Figure 4F). What's more, IL-17A neutralization significantly decreased the IL-17A concentrations in lung compared to the isotype control (Figure 4G). These data indicate that blocking IL-17A downregulates the expression of cytokines involved in both Th2 and Th17 immune responses, thereby alleviating airway inflammation and reducing mucus secretion.

IL-17A Neutralization Reduces Colonic Inflammation and Severity of Colitis in HDM+DSS-Treated Mice

To determine if IL-17A blockade affects the development of colitis, colonic inflammation of severity of the disease were examined. Body weight was monitored over 7 days following DSS administration. Although the differences were not statistically significant across the groups, IL-17A neutralization appeared to prevent further weight loss compared to

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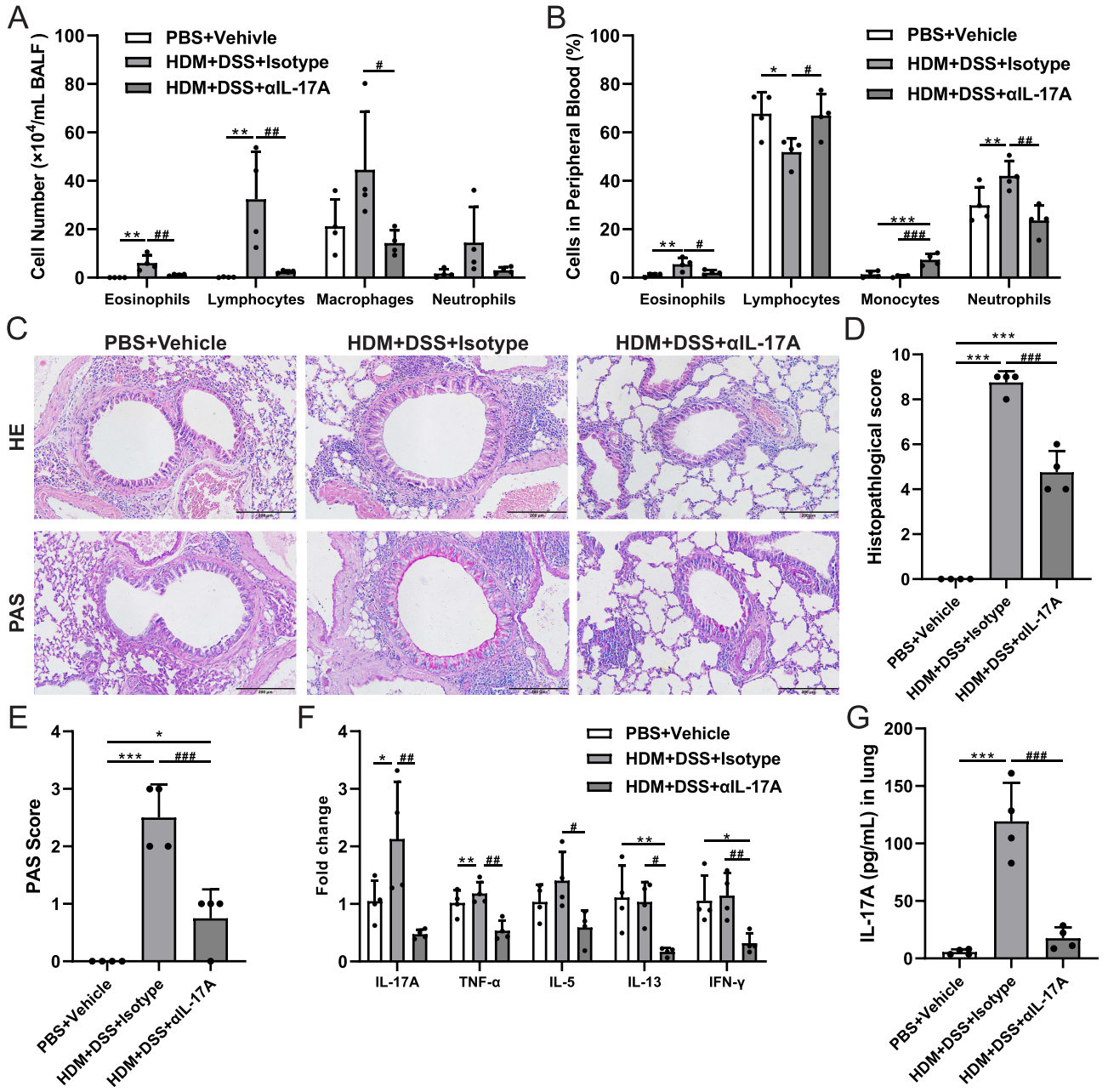

Figure 4 IL-17A neutralization alleviates airway inflammation and mucus hypersecretion in HDM+DSS-treated mice. (**A**) BALF inflammatory cell counts determined by cytospin analysis. (**B**) Peripheral leukocyte profiling by flow cytometry. (**C**) Representative lung sections stained with H&E and PAS (scale bars = 200 μm). (**D** and **E**) Quantification of lung histopathology and mucus production scores. (**F**) Lung cytokine mRNA expression levels (IL-17A, TNF-α, IL-5, IL-13, IFN-γ) measured by RT-qPCR. (**G**) Lung IL-17A protein levels quantified by ELISA. Data represent mean ± SEM (n = 4 per group). Two-way ANOVA was used for statistical comparison. *p < 0.05, **p < 0.01, ***p < 0.001 vs PBS+Vehicle; #p < 0.05, ##p < 0.01, ####p < 0.001 vs HDM+DSS+Isotype.

isotype control group (Figure 5A). The protective effect of neutralization IL-17A was demonstrated by significantly improved DAI in the HDM+DSS+αIL-17A group compared to those receiving the isotype control starting from day 3 onward (Figure 5B).

Histopathological analysis of colonic tissues confirmed reduced inflammation following IL-17A neutralization (Figure 5C). The HDM+DSS+Isotype group exhibited extensive inflammatory cell infiltration, loss of crypt architecture, and epithelial damage. By contrast, the HDM+DSS+αIL-17A group displayed marked improvement in histological features, with less infiltration and more preserved epithelial structures. Quantitative scoring confirmed these observations, with significantly lower inflammation scores in the anti-IL-17A group compared to the isotype control (Figure 5D). Furthermore, HDM+DSS

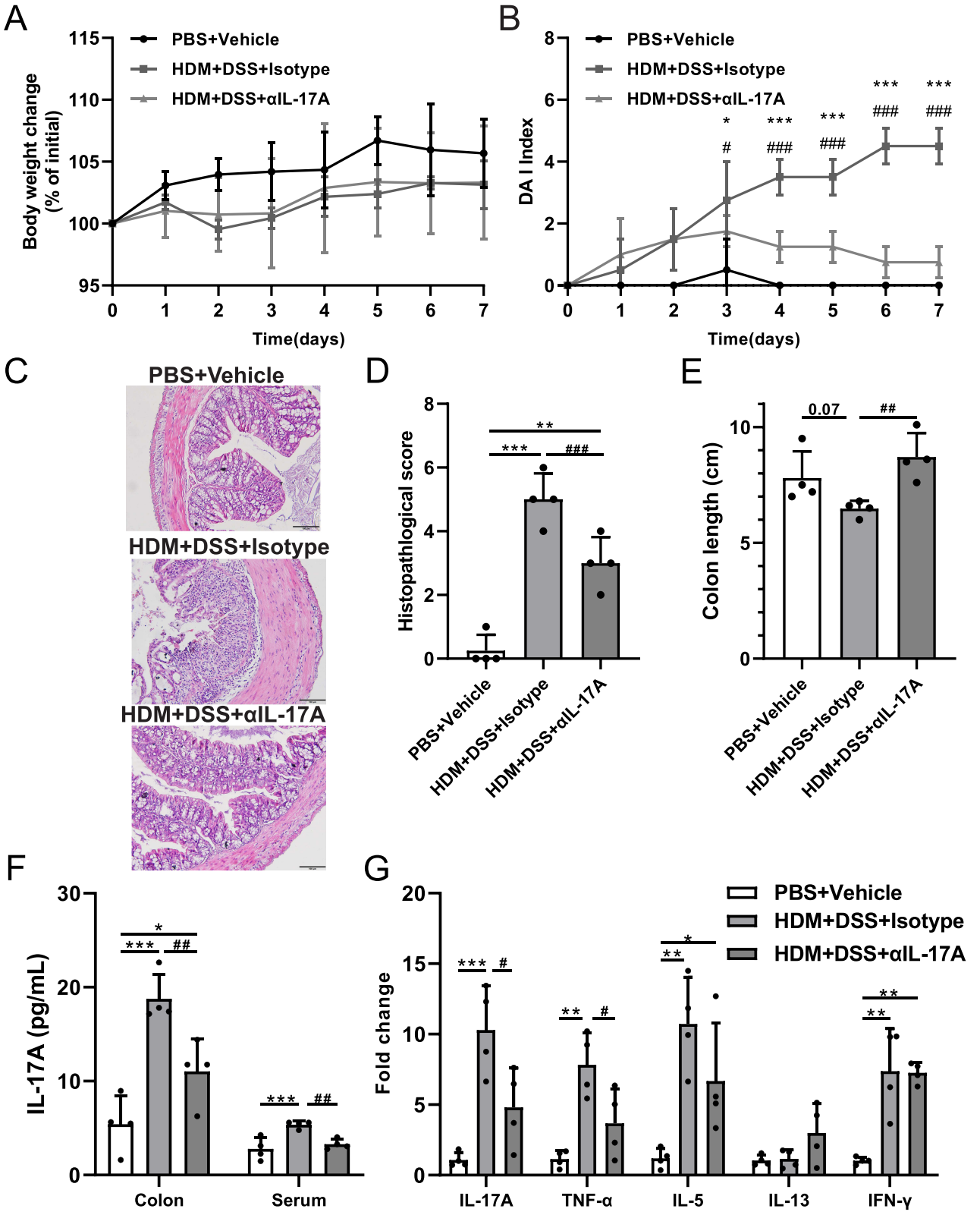

Figure 5 IL-17A blockade reduces colonic inflammation and disease severity in HDM+DSS-treated mice. (**A**) Body weight trajectories during DSS exposure. (**B**) DAI score progression over time. (**C**) H&E-stained colon sections showing mucosal injury and inflammatory cell infiltration (scale bars = 200 μm). (**D**) Histopathological scoring of colitis severity. (**E**) Colon length measurements at study endpoint. (**F**) IL-17A protein levels in colon and serum by ELISA. (**G**) RT-qPCR analysis of colonic cytokines (IL-17A, TNF-α, IL-5, IL-13, IFN-γ). Data shown as mean ± SEM (n = 4 per group). Statistical significance assessed via two-way ANOVA. *p < 0.05, **p < 0.01, ***p < 0.001 vs PBS +Vehicle; $^{\#}$p < 0.05, $^{\#\#}$p < 0.01, $^{\#\#\#}$p < 0.001 vs HDM+DSS+Isotype.

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treatment led to substantial colon shortening, while IL-17A neutralization partially restored colon length, with the HDM+DSS +αIL-17A group showing significantly longer colons compared to the HDM+DSS+Isotype group (Figure 5E). Blocking IL-17A significantly downregulated the concentrations of IL-17A in colon and serum (Figure 5F). Quantitative PCR analysis revealed that IL-17A neutralization significantly reduced the expression of key pro-inflammatory cytokines, including IL-17A, TNF-α, IL-5, IL-13, and IFN-γ in colonic tissues compared to the HDM+DSS+Isotype group (Figure 5G). These results indicate that blocking IL-17A not only reduces immune cell infiltration and tissue damage in the colon but also mitigates the expression of inflammatory mediators driving the colitis response.

Differential Gene Expression Analysis Reveals Significant Transcriptional Changes After IL-17A Neutralization

To determine the downstream effect of IL-17A on colonic inflammation, we performed the transcriptional analysis of diseased colon tissues. The comparison between the HDM+DSS+αIL-17A and HDM+DSS+Isotype groups showed 272 increased DEGs and 454 decreased DEGs (Figure 6A). A large number of genes related to immune response pathways were downregulated upon IL-17A neutralization, suggesting that IL-17A plays a pivotal and profound role in regulating immune-related gene expression in this model. Heatmap analysis of the DEGs (Figure 6B) showed clear clustering between the HDM+DSS+αIL-17A and HDM+DSS+Isotype groups. The heatmap revealed that multiple immune-related genes, such as Tao2 and Bcl2a2, were significantly downregulated after IL-17A neutralization. These data indicate that IL-17A neutralization dramatically alters the gene expression profile of key immune regulators involved in the inflammatory response.

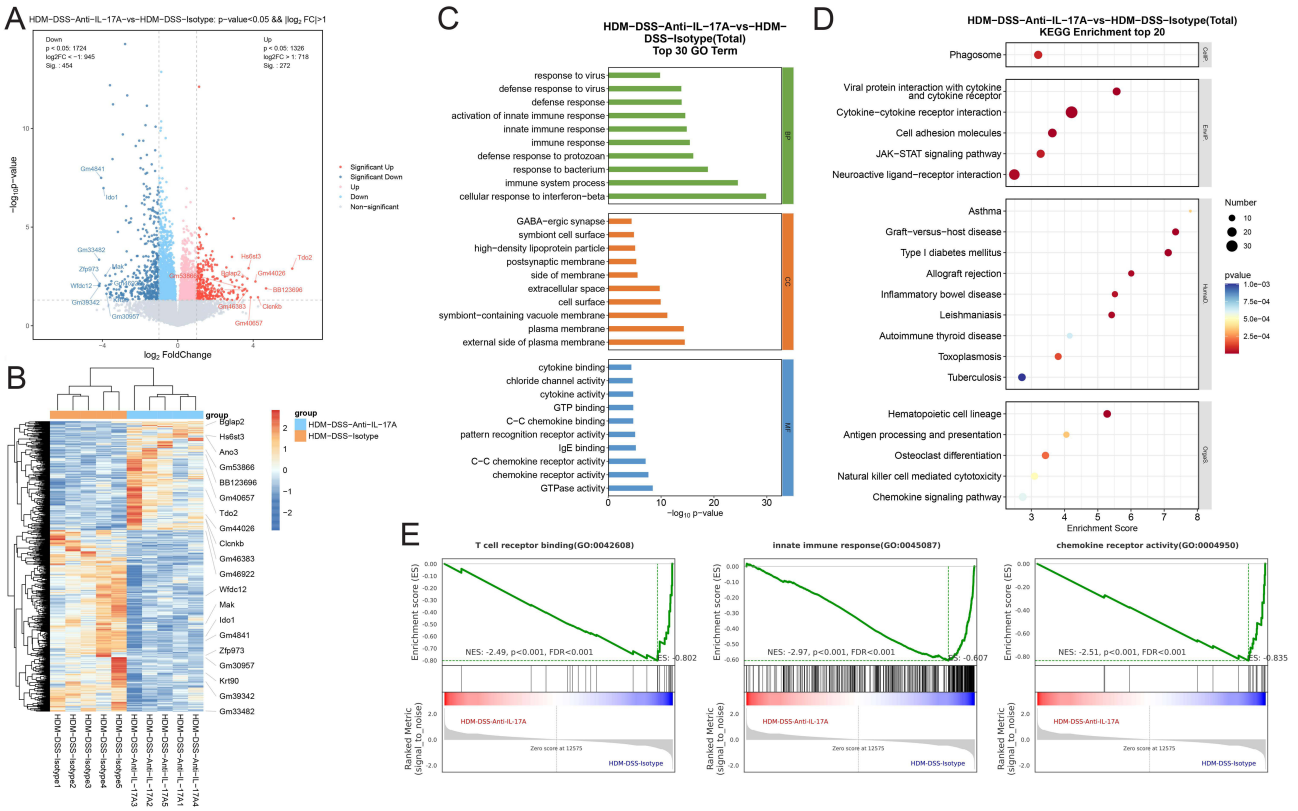

Figure 6 IL-17A neutralization drives significant transcriptomic remodeling and immune pathway suppression in colonic tissue. (**A**) Volcano plot of DEGs between HDM +DSS+αIL-17A and HDM+DSS+Isotype groups; red indicates upregulated, blue downregulated genes. (**B**) Heatmap visualization of colonic DEGs across treatment groups. (**C**) Gene Ontology (GO) enrichment analysis showing top 30 downregulated terms across biological processes (green), cellular components (Orange), and molecular functions (blue). (**D**) KEGG pathway enrichment of top 20 downregulated pathways in the αIL-17A treatment group. (**E**) GSEA enrichment plots for representative gene sets: "T cell receptor binding", "innate immune response", and "chemokine receptor activity".

Furthermore, GO enrichment analysis (Figure 6C) identified several biological processes and molecular functions enriched with those down-regulated DEGs in the HDM+DSS+αIL-17A group. Notably, pathways involved in immune responses, such as "defense response to virus", "activation of innate immune response", and "cellular response to interferon-beta", were significantly affected. Additionally, membrane and receptor activities, including "C-C chemokine receptor activity" and "pattern recognition receptor activity", were down-regulated, suggesting that IL-17A modulates key aspects of immune receptor function and signaling in the context of HDM- and DSS-induced inflammation.

KEGG pathway enrichment analysis (Figure 6D) with those down-regulated DEGs in the HDM+DSS+αIL-17A group showed that pathways involved in "cytokine-cytokine receptor interaction", "JAK-STAT signaling", and "cell adhesion molecules" were negatively impacted following IL-17A neutralization. Notably, IL-17A blockade also affects "chemokine signaling pathway" and "antigen processing and presentation" pathways, which play critical roles in immune activation and pathogen defense.

Gene Set Enrichment Analysis (Figure 6E) also highlights the significant suppression of immune-related gene sets in the HDM+DSS+αIL-17A group. Specifically, pathways such as "T cell receptor binding" (NES = −2.49, FDR < 0.001), "innate immune response" (NES = −2.97, FDR < 0.001), and "chemokine receptor activity" (NES = −2.51, FDR < 0.001) were significantly downregulated upon IL-17A neutralization. These findings underscore the pivotal role of IL-17A in regulating immune responses.

Discussion

To investigate how chronic airway disorders influence intestinal pathophysiological changes, we developed a complex animal model incorporating an existing HDM-induced asthma model followed by a DSS-induced colitis model. We identified that IL-17A plays a crucial role in mediating inflammatory responses in both airway and colonic tissues. Notably, neutralization of IL-17A significantly attenuated airway and intestinal inflammation, reduced mucus hypersecretion, downregulated pro-inflammatory cytokine expression, and alleviated colitis severity. These findings provide novel insights into the shared immune mechanisms driving inflammation in both the airway and colon and highlight IL-17A as a promising therapeutic target for managing co-occurring inflammatory diseases, such as asthma and UC.

IL-17A is a cytokine produced predominantly by Th17 cells and has been implicated in the pathogenesis of several chronic inflammatory diseases, including asthma and inflammatory bowel disease (IBD).[39] In asthma, IL-17A promotes the recruitment of neutrophils to the airways, exacerbates inflammation, and contributes to airway remodeling and mucus hypersecretion.[40] Similarly, in IBD, IL-17A drives mucosal inflammation by recruiting immune cells, disrupting the epithelial barrier, and promoting the release of pro-inflammatory cytokines and chemokines.[41] Our findings confirm that IL-17A is a central mediator of inflammation in both the lungs and the colon in the HDM+DSS model, as IL-17A neutralization significantly reduced the infiltration of eosinophils, lymphocytes, and macrophages in both tissues. This suggests that IL-17A is involved in both the initiation and perpetuation of inflammation in these organs, and tissue-specific IL-17A levels reflect dynamic immune adaptation (Figure 7).

Interestingly, while IL-17A has been traditionally associated with neutrophilic inflammation,[42,43] our study demonstrates that IL-17A neutralization also reduced eosinophil infiltration in both the lungs and blood. This finding suggests that IL-17A may have broader effects on immune cell recruitment than previously understood. It is possible that IL-17A interacts with other cytokine pathways, such as IL-5 and IL-13, which are known to regulate eosinophil recruitment and activation. Indeed, several lines of evidence indicate that IL-17A can indirectly promote Th2- and/or ILC2-mediated immune responses through its interaction with other cytokines. For example, IL-17A positively regulates the conversion of T cells into a Th2 subtype in mouse models of dermatitis.[44] Notably, deficiency or blockade of IL-17 impairs type 2 immunity, as demonstrated in several animal models of allergic inflammation.[45,46] Further evidence suggests that IL-17A suppresses Th1 response by inhibiting IFN-γ, thereby creating an environment conducive to Th2- and/or ILC2-driven inflammation.[47,48] Although we did not observe a decrease in IFN-γ, our findings support this notion, as the reduction in eosinophil numbers following IL-17A neutralization highlights the cytokine's potential role in modulating not only Th17 but also type 2 immune responses, particularly in diseases such as asthma, where both pathways are activated.

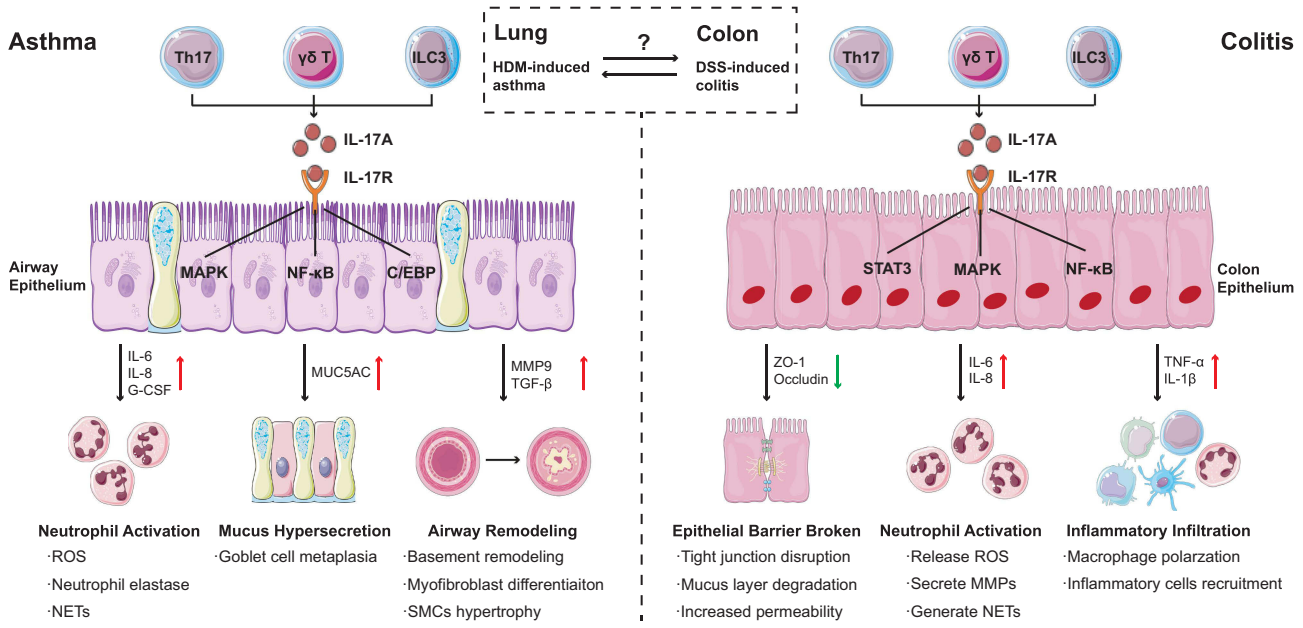

Figure 7 The role of IL-17A in asthma and colitis. This schematic illustrates the distinct and overlapping mechanisms mediated by IL-17A in asthma (left panel) and colitis (right panel). In asthma, IL-17A binding to IL-17R on airway epithelium triggers MAPK, NF-κB, and C/EBP signaling, driving neutrophil activation, mucus hypersecretion (via MUC5AC), and airway remodeling (via MMP9 and TGF-β). In colitis, IL-17A/IL-17R interaction on colonic epithelium activates STAT3, MAPK, and NF-κB pathways, leading to epithelial barrier disruption (reduced occludin), neutrophil activation (IL-8, G-CSF), and inflammatory infiltration (IL-6, TNF-α, IL-1β).
Abbreviations: ILC3, group 3 innate lymphoid cells; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B Cells; MMP9, matrix metalloproteinase 9; TGF-β, transforming growth factor β; ROS, reactive oxygen species; NETs, neutrophil extracellular traps; SMCs, smooth muscle cells; STAT3, signal transducer and activator of transcription 3; TNF-α, tumor necrosis factor α.

The rationale for focusing on IL-17A over other inflammatory mediators is supported by both our data and clinical context. Our cytokine panel captured key features of Th1, Th2, and Th17 responses, which are variably implicated in asthma and colitis. However, only IL-17A exhibited a compartment-specific and bidirectional shift. This reciprocal modulation, absent in TNF-α, IL-5, IL-13, and IFN-γ, highlighted IL-17A as a candidate immunological bridge between inflamed mucosal sites. Functionally, IL-17A neutralization alone was sufficient to attenuate inflammation, improve histopathology, and suppress pro-inflammatory transcriptional programs in both lung and colon. These findings underscore its role as a downstream effector of mucosal injury, with therapeutic relevance extending beyond individual compartments.

While upstream Th17 regulators such as IL-6 and IL-23 are biologically significant, their blockade has produced inconsistent clinical outcomes in asthma and ulcerative colitis, particularly among non-Type 2 or neutrophilic subtypes.[49–51] In contrast, IL-17A-targeting therapies have demonstrated consistent efficacy in mucosal diseases such as psoriasis and ankylosing spondylitis.[52,53] Our data suggest that IL-17A may similarly represent a rational therapeutic target in coexisting pulmonary and intestinal inflammatory disease, particularly in patients with neutrophilic or steroid-refractory phenotypes.

Mucus hypersecretion is a hallmark of asthma and contributes to airway obstruction and impaired lung function.[54] Our study shows that IL-17A neutralization significantly reduced mucus production in the airways of HDM+DSS-treated mice, as evidenced by lower PAS scores. This finding aligns with previous research showing that IL-17A can upregulate mucin expression in the airways. Specifically, IL-17A directly induces mucin production, particularly MUC5AC and MUC5B, by activating key signaling pathways such as NF-κB and ERK1/2 in airway epithelial cells.[55] This leads to goblet cell hyperplasia and increased mucus secretion, particularly in conditions such as asthma and chronic rhinosinusitis.[56] Indirectly, IL-17A also influences mucin production by modulating the immune environment, promoting the release of pro-inflammatory cytokines such as IL-1β, IL-13, and IL-22, which further stimulate mucin synthesis.[57] By blocking IL-17A, we were able to reduce both inflammation and mucus hypersecretion, suggesting that IL-17A plays a critical role in driving mucin production in the pathogenesis of asthma.

Elevated levels of IL-17A have been observed in the intestinal tissues of IBD patients, where it promotes the release of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α, contributing to the pathogenesis of intestinal diseases.[58] Experimental

colitis models have shown that blocking IL-17A reduces inflammation and tissue damage, suggesting its role in promoting intestinal inflammation.[33] However, IL-17A also plays a protective role in certain conditions by supporting mucosal integrity and homeostasis, making its role in gut diseases complex. In the combined HDM- and DSS- treatment model, we showed that IL-17A neutralization significantly attenuated colonic inflammation and reduced the severity of DSS-induced colitis. Histopathological analysis of colonic tissues revealed that IL-17A blockade reduced inflammatory cell infiltration, preserved crypt architecture, and partially restored colon length, which is typically shortened in severe colitis. These findings are consistent with previous studies demonstrating the pro-inflammatory role of IL-17A in IBD, where it drives mucosal inflammation by promoting the recruitment of neutrophils and the release of pro-inflammatory cytokines, such as TNF-α and IL-6.[59,60] These findings support that the interaction in this model is directional and mediated by immune signaling, not merely the coexistence of pathology in two organs, and immune activation in airway mucosal site directly alters responses in the mucosal site of colon. The enhanced colonic response likely reflects not only additive tissue injury, but also immunological reprogramming initiated in the lung and propagated along the mucosal axis.

It appears that IL-17A regulates cellular and molecular changes in a reciprocal manner between the lungs and intestines. In the lungs, IL-17A drives inflammation and fibrosis by inducing the production of cytokines such as IL-1β and TNF-α, while also promoting the expression of intracellular adhesion molecules that facilitate immune cell infiltration.[57] This pro-inflammatory environment in the lungs is mirrored in the intestines, where IL-17A activates similar pathways, particularly the ERK and PI3K signaling cascades, which are crucial for epithelial barrier integrity.[61] However, dysregulation of IL-17A can disrupt epithelial homeostasis in both organs, exacerbating inflammation and tissue damage. Conversely, during intestinal disorders, IL-17A also influences lung pathology. As inflammation in the intestines intensifies, IL-17A exacerbates pulmonary inflammation and immune cell recruitment, creating a feedback loop where gut inflammation reciprocally worsens lung inflammation. The divergence in inflammation severity across tissues reflects a shift in immune system priorities, likely orchestrated by IL-17A.

The shared immune mechanisms driving inflammation in both the lungs and the colon suggest the complexity of a lung-gut axis, where inflammation in one organ system potentially influences the other via a variety of cellular and molecular pathways. Our study provides further evidence of this axis, showing that allergic airway inflammation induced by HDM can exacerbate colitis, and that neutralization of IL-17A can attenuate inflammation in both organs. The transcriptomic analysis of anti-IL-17A treatment demonstrates that IL-17A neutralization leads to significant downregulation of immune-related pathways in both lung and colonic tissues. Pathways involved in cytokine-cytokine receptor interaction, chemokine signaling, and JAK-STAT signaling were significantly enriched in the HDM+DSS+Isotype group, but these pathways were suppressed following IL-17A neutralization. This suggests that IL-17A acts as a central mediator of immune signaling in both the lungs and the gut and that the consistent therapeutic response underscores IL-17A's role as a functional driver, regardless of local abundance.

While this study provides compelling evidence of IL-17A's role in both pulmonary and intestinal inflammation, several limitations should be acknowledged. First, the study utilized a murine model that may not fully recapitulate the complexity of human asthma and intestinal disease. Second, IL-17A plays a dual role in inflammatory processes, and its blockade may have variable effects depending on the disease context. For example, while IL-17A blockade showed therapeutic promise in UC, clinical trials in Crohn's disease yielded mixed results,[62] underscoring the complexity of targeting this cytokine in different patient populations. Additionally, our study focused primarily on the acute effects of IL-17A neutralization, and the long-term consequences of sustained IL-17A blockade remain unclear. Future studies should investigate the chronic effects of IL-17A inhibition and explore potential compensatory mechanisms that may arise with prolonged treatment. Finally, the heterogeneity of human inflammatory diseases suggests that not all patients may benefit from IL-17A-targeted therapies, and further research is needed to identify biomarkers that can predict therapeutic responses.

The compartmental regulation of IL-17A in our HDM+DSS model parallels clinical findings related to TSLP-targeted therapies. Agents such as tezepelumab, which inhibit TSLP and downstream activation of Th2/Th17 pathways, have demonstrated efficacy in lowering IL-17A levels in the airways of patients with severe asthma.[63] However, preclinical studies indicate that TSLP inhibition may inadvertently disrupt gut immune homeostasis, potentially amplifying IL-17A–driven colitis via compensatory responses.[64,65] This duality aligns with our findings, wherein IL-17A blockade alleviated pulmonary inflammation but prompts consideration of its tissue-specific effects in the gut.

In summary, our study highlights the pivotal role of IL-17A in mediating inflammation in both the lungs and intestines, particularly in the context of co-occurring respiratory and gastrointestinal diseases such as asthma and colitis. Neutralizing IL-17A significantly reduced inflammation, mucus hypersecretion, and tissue damage in both organ systems, suggesting that IL-17A-targeted therapies could provide dual benefits for patients with overlapping inflammatory conditions. These findings underscore the potential of IL-17A as a therapeutic target, offering a promising avenue for treating multi-organ inflammation in chronic inflammatory diseases, and positioning IL-17A as a central regulator of cross-organ mucosal inflammation. Future research is essential to better understand the long-term effects and identify patients most likely to benefit from IL-17A-targeted treatments.

In conclusion, this study identifies IL-17A as a central mediator linking immune responses in the lung and gut. Through a combined HDM and DSS murine model, we demonstrate that airway inflammation sensitizes the colon to injury and that IL-17A expression shifts in a tissue-specific manner under dual-organ stress. Neutralization of IL-17A reduces immune activation and tissue pathology in both compartments, supporting its role as a regulator of mucosal inflammation. These findings underscore the therapeutic promise of IL-17A-targeted strategies for patients with overlapping respiratory and gastrointestinal disease and highlight the need to further investigate the mechanisms governing lung–gut immune coordination.

Data Sharing Statement

All data supporting the findings from this study are available from the corresponding author upon reasonable request.

Ethics Approval

All experimental procedures were approved by the Ethics Committee of Zhengzhou University (ZZU-LAC20230915 [11]).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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