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Knockdown of *DDX3Y* alleviates ovalbumin-induced allergic rhinitis in mice by regulating NF-κB pathway

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Abstract
Allergic rhinitis (AR), a type of chronic inflammatory disease that exists in the nasal mucosa, significantly impacts the quality of life. *DDX3Y* gene encodes an RNA helicase belonging to the DEAD-box protein family and is part of the DDX3 subfamily that affects the progression of multiple diseases. However, the specific role and mechanisms of *DDX3Y* in AR remain unclear. This study investigates the effects of *DDX3Y* knockdown on ovalbumin (OVA)-induced AR in mice. We found that *DDX3Y* is highly expressed in the nasal mucosa of AR mice. Knockdown of *DDX3Y* in OVA-induced AR mice significantly alleviated nasal manifestations, reduced immunoglobulin E and histamine levels, and improved nasal mucosal histopathology. Additionally, knockdown of *DDX3Y* suppressed secretion of inflammatory factor nuclear factor kappa B (NF-κB) phosphorylation, thereby mitigating local inflammatory responses. These findings suggested that targeting *DDX3Y* could offer a novel therapeutic strategy for managing AR by modulating the NF-κB pathway.

Introduction

Allergic rhinitis (AR) is a type of noninfectious chronic inflammatory disease of the nasal mucosa, primarily mediated by immunoglobulin E following allergen exposure in atopic individuals.[1,2] AR is featured by recurrent symptoms such as nasal itching, sneezing, and nasal congestion. Epidemiological data indicate that AR affects approximately 40% of the global population, with a notable increase of 20–40% in prevalence observed in children in recent years.[3] The rising incidence of AR significantly impacts quality of life, highlighting the urgency for improved management strategies.[4,5] AR is a prototypical T helper 2 (Th2)

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cell-driven immune disorder where inflammation plays a vital role throughout the disease course, making it a primary target for therapeutic intervention.[6] Inhibiting the excessive activation of local inflammatory responses in the nasal mucosa is an ideal strategy for both prevention and treatment of AR.[7] It is required to further uncover its mechanism and identify new targets.

DDX3Y gene encodes an RNA helicase belonging to the DEAD-box protein family and is part of the DDX3 (or Ded1p) subfamily, located on sex chromosomes because of autosomal translocation.[8] A high expression of *DDX3Y* is observed in patients with chronic obstructive pulmonary disease (COPD), and its expression is upregulated in human bronchial epithelial (HBE) cells injured by cigarette smoke extracts (CSE).[9,10] Targeting *DDX3Y* can modulate the toll-like receptor 4–nuclear factor kappa B (TLR4/NF-κB) pathway to alleviate CSE-induced cellular damage.[9] Despite these findings, the specific role and mechanism of *DDX3Y* in AR remains unclear.

Interestingly, a previous study indicated that microRNA-497 could serve as an inflammatory suppressor by targeting *DDX3Y* and modulating NF-κB pathway in cigarette smoke extract-stimulated human bronchial epithelial cells, suggesting a correlation between *DDX3Y* and NF-κB pathway.[10] The NF-κB family comprises proteins such as p50, p52, p65, etc. These factors form homodimers and heterodimers, which bind to various target genes associated with immune and inflammatory responses.[11] In their inactive state, NF-κB dimers are bound to IkappaB kinase (IκB) proteins to inhibit their activity.[11] Upon activation, the NF-κB/IκB complex undergoes degradation, leading to the phosphorylation of NF-κB, which then drives the expression of pro-inflammatory genes.[11] The NF-κB pathway is implicated in AR, with studies demonstrating that downregulating NF-κB phosphorylation can mitigate nasal inflammation induced by ovalbumin (OVA) in AR models.[12]

We analyzed the GSE46171 expression profile, and found significantly higher *DDX3Y* expression in nasal mucosal tissues of AR patients, compared to normal tissues, suggesting a potential role for *DDX3Y* in AR pathogenesis.[9] This study aimed to elucidate the effects of *DDX3Y* knockdown on OVA-induced AR in mice and its regulation of NF-κB pathway. We hypothesized that knocking down *DDX3Y* would alleviate AR symptoms, thereby reducing nasal inflammation and lessening clinical manifestations of AR.

Materials and Methods

Animals and treatment

A total of 30 C57BL/6 mice, aged 6–8 weeks and weighing 18–20 g, were purchased from Beijing Vital River Co. Ltd. (Beijing, China) for this study. The gender distribution was balanced, with an equal number of male and female mice to avoid gender bias in results. All experimental procedures were approved by the Laboratory Animal Ethics Committee of Nanjing Medical University (Approval No. IACUC-20240126036).

OVA-induced AR model

In order to establish an AR model, mice were sensitized with injections of 100-μL saline containing 50 μg of ovalbumin (OVA; A5503; Sigma-Aldrich, St. Louis, MO, USA) on days 0, 7, and 14. From days 21–28, the mice were challenged intranasally with 20-μL saline containing 400-μg OVA daily.

AAV-shRNA treatment

Recombinant adeno-associated viruses (AAV) encoding short hairpin RNA (shRNA) targeting *DDX3Y* (AAV-sh-*DDX3Y*) and a negative control shRNA (AAV-sh-NC) were constructed by Heyuan Biology Co. Ltd. (Shanghai, China). Mice were intranasally administered with 10^{11} viral particles of AAV-sh-*DDX3Y* or AAV-sh-NC in 20-μL phosphate-buffered saline solution (PBS). The efficiency of the construct was confirmed through immunoblot assays, which demonstrated significantly reduced DDX3Y protein levels in the nasal tissues of mice treated with AAV-sh-*DDX3Y*, compared to control and AAV-sh-NC groups.

Immunoblot assays

Proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membranes (IPVH00010; Millipore, Billerica, MA, USA). Membranes were blocked with 5% non-fat milk and incubated overnight with primary antibodies against *DDX3Y* (1:1000; ab70531; Abcam, Cambridge, UK), p65 protein (1:1000; ab8242; Abcam), phosphorylated (p)-p65 (1:1000; ab3033; Abcam), IκBα protein (1:1000; ab9242; Abcam), and p-IκBα (1:1000; ab2859; Abcam) at 4°C. After washing, membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies (1:5000; ab7074; Abcam) and detected using an electrochemiluminescence (ECL) detection kit (32106; Thermo, MA, USA).

Histopathological analysis

Nasal tissues were fixed in 4% paraformaldehyde (PFA), embedded in paraffin, and cut into 5-μm thickness sections. Sections were stained with hematoxylin and eosin (H&E; C0105; Beyotime Biotechnology, Beijing, China) and examined under a light microscope (Olympus, Tokyo, Japan).

Behavioral assessment of nasal symptoms

The frequency of nasal rubbing and sneezing was monitored. Mice were observed for 20 min, and the number of nasal rubs and sneezes was recorded.

Enzyme-Linked Immunosorbent Serological Assay (ELISA)

Serum levels of OVA-specific immunoglobulin E (IgE), interleukin (IL)-4, IL-5, IL-13, and IL-6 were measured by using ELISA kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

Statistical analysis

Data were presented as mean ± SD. Statistical analyses were performed by using GraphPad 8. Differences were determined by one-way ANOVA, followed by Tukey's *post hoc* test. $P < 0.05$ was considered statistically significant.

Results

DDX3Y *significantly upregulated in nasal mucosal tissues of AR mice*

In order to explore the role of *DDX3Y* in AR progression, we first analyzed its levels. The analysis of the GSE46171 chip data revealed that *DDX3Y* expression levels were significantly higher in the nasal mucosal tissues of AR mice, compared to healthy subjects ($P < 0.0001$; Figure 1). This indicated that *DDX3Y* was potentially involved in the pathogenesis of AR.

DDX3Y *knockdown reduces nasal symptoms in OVA-induced AR mice*

The expression of *DDX3Y* was suppressed by the infection of AAV-sh-DDX3Y. Immunoblot assays confirmed effective knockdown of *DDX3Y* in the nasal tissues of mice treated with AAV-sh-DDX3Y, compared to both control and AAV-sh-NC groups ($P < 0.0001$ and $P = 0.0059$; Figure 2A). The frequency of nasal rubbing ($P < 0.0001$; Figure 2B) and sneezing ($P < 0.0001$; Figure 2C) per 20 min was significantly reduced, and serum OVA-IgE levels were notably lower in the AAV-sh-DDX3Y-treated group, compared to the AAV-sh-NC group ($P < 0.0001$; Figure 2D). These results implied that *DDX3Y* knockdown alleviated nasal symptoms and reduced allergic inflammation in AR mice.

DDX3Y *knockdown mitigates histopathological changes in nasal mucosa of AR mice*

Histopathological examination of nasal mucosal tissues showed that *DDX3Y* knockdown in OVA-induced AR mice led to a marked reduction in inflammatory cell infiltration and tissue damage (Figure 3). The AR + AAV-sh-DDX3Y group exhibited significantly less inflammation and improved tissue morphology, compared to the OVA and OVA + AAV-NC groups (Figure 3), indicating that *DDX3Y* knockdown mitigated histopathological changes associated with AR.

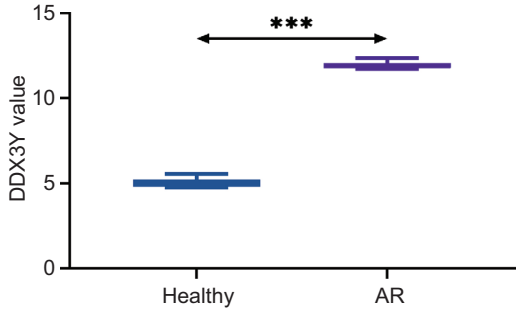

Figure 1 DDX3Y expression in nasal mucosal tissues of AR patients and control subjects. GSE46171 chip showed the value of DDX3Y in nasal mucosal tissues from AR patients and control subjects. Data are presented as mean ± SD values.

DDX3Y *knockdown suppresses inflammatory cytokine production in AR mice*

Inflammatory response in OVA-induced AR mice was assessed by measuring serum levels of IL-4, IL-5, IL-13, and IL-6 by using ELISA. ELISA indicated the increased levels of these factors in the mice of OVA group ($P < 0.0001$; Figure 4). Knockdown of *DDX3Y* significantly reduced the levels of these cytokines in the OVA + AAV-sh-DDX3Y group, compared to the OVA + AAV-sh-NC group ($P < 0.0001$ for IL-4, IL-5, IL-13, and $P = 0.0006$ for IL-6; Figure 4), suggesting that *DDX3Y* knockdown suppressed the production of inflammatory cytokines and had a critical role in modulating inflammatory response in AR.

DDX3Y *knockdown inhibits NF-κB pathway activation in AR mice*

In order to elucidate mechanism behind the anti-inflammatory effects of *DDX3Y* knockdown, the NF-κB pathway activation was examined by analyzing the expression as well as phosphorylation levels of p65 and IκBα. Immunoblot analysis showed that the phosphorylation of p65 (p-p65) and IκBα (p-IκBα) was significantly reduced in the nasal mucosal tissues of the OVA + AAV-sh-DDX3Y group ($P < 0.0001$; Figure 5). Further, expression of IκBα was increased in the IκBα group ($P < 0.0001$; Figure 5). Densitometric analysis of IκBα expression and p-p65/p65 and p-IκBα/IκBα ratio confirmed these findings ($P < 0.0001$; Figure 5), indicating that *DDX3Y* knockdown inhibited the NF-κB pathway. These results suggested that the effects of *DDX3Y* knockdown were mediated through the inhibition of the NF-κB pathway.

Discussion

Allergic rhinitis significantly impacts the quality of life and presents a considerable economic burden, affecting approximately 40% of the global population.[1,13] Understanding the complex pathophysiology of AR, which involves various immune and inflammatory pathways, is essential for developing new therapeutic strategies.[14-16] Our study provided compelling evidence that *DDX3Y* had a crucial role in the pathogenesis of allergic rhinitis (AR) by regulating NF-κB pathway. The main findings of our research are summarized as follows: We found that *DDX3Y* was significantly upregulated in the nasal mucosa of AR mice, suggesting its potential involvement in the disease process. Knocking down of *DDX3Y* in an OVA-induced AR mouse model significantly alleviated nasal symptoms, such as nasal rubbing and sneezing, which are common indicators of AR. *DDX3Y* knockdown resulted in a notable reduction in serum IgE and histamine levels, which are key mediators of allergic reactions. Additionally, there was a significant decrease in

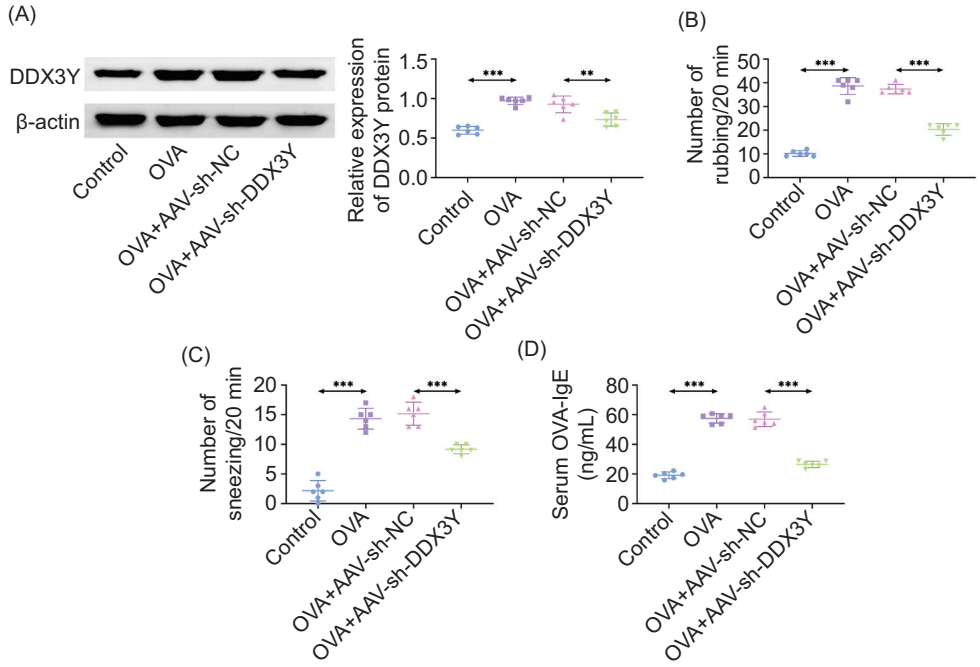

Figure 2 Effects of DDX3Y knockdown on nasal symptoms in OVA-induced AR mice. (A) Immunoblot assays showed DDX3Y expression in OVA-induced AR mice treated with AAV-sh-DDX3Y, compared to control and AAV-sh-NC groups. (B) Frequency of nasal rubbing per 20 min in OVA-induced AR mice treated with AAV-sh-DDX3Y, compared to control and AAV-sh-NC groups. (C) Frequency of sneezing per 20 min in OVA-induced AR mice treated with AAV-sh-DDX3Y, compared to control and AAV-sh-NC groups. (D) ELISA showed the levels of serum OVA-IgE in OVA-induced AR mice treated with AAV-sh-DDX3Y, compared to control and AAV-sh-NC groups. Data are presented as mean ± SD values.

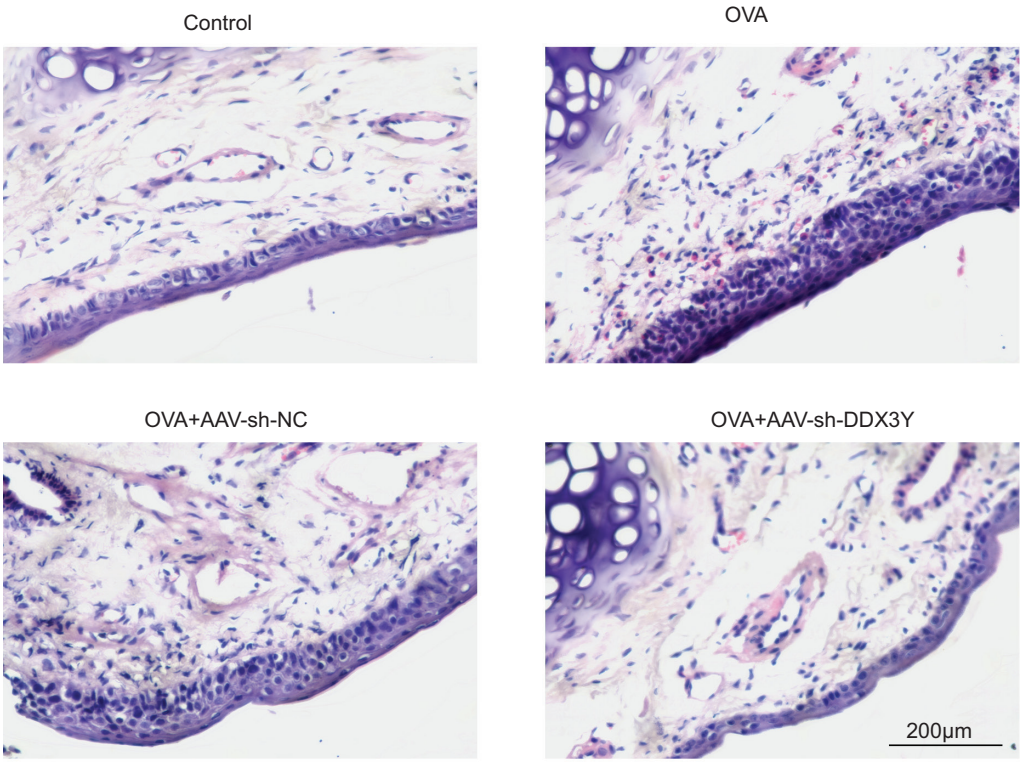

Figure 3 Histopathological analysis of nasal mucosa in OVA-induced AR mice with DDX3Y knockdown. Hematoxylin and eosin (H&E) staining of nasal mucosal tissues of mice in control, AR, AR+AAV, and AR+AAV-sh-DDX3Y groups. Images show the extent of inflammatory cell infiltration and tissue damage.

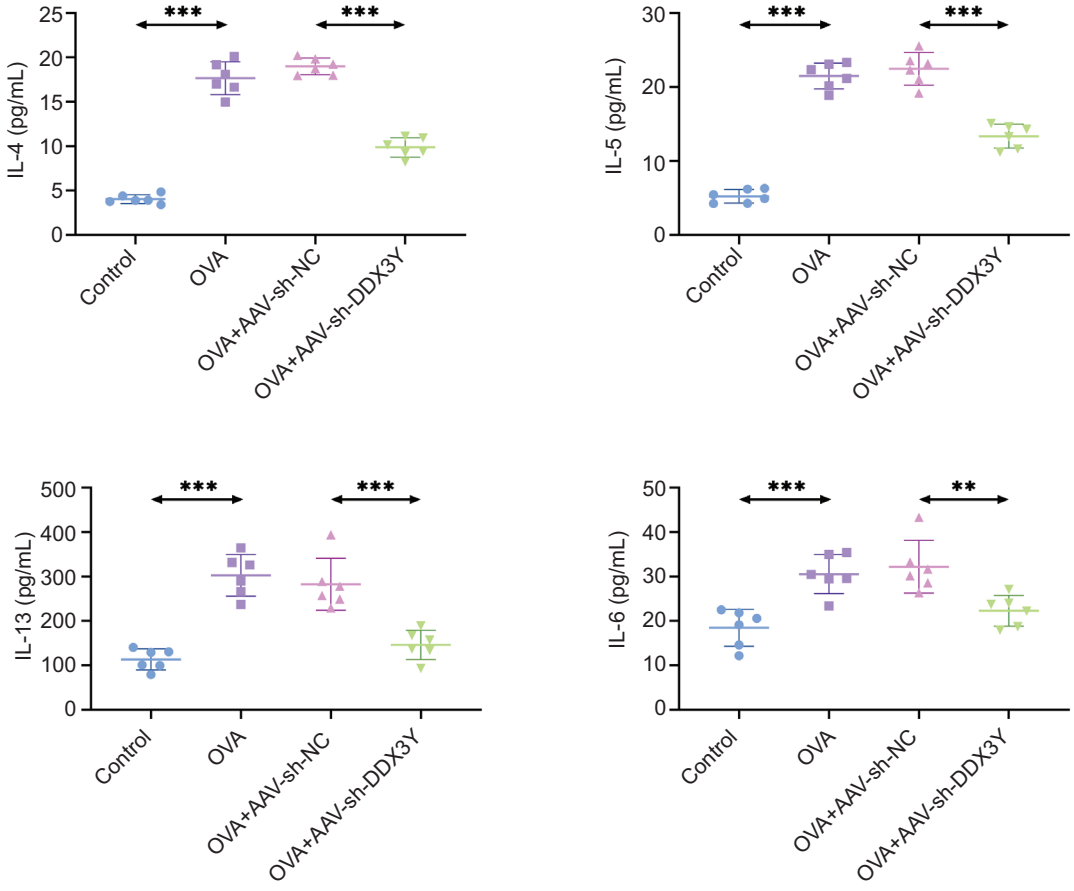

Figure 4 Effects of DDX3Y knockdown on the inflammatory response in OVA-induced AR mice. ELISA assays showed the levels of IL-4, IL-5, IL-13, and IL-6 in the serum of mice in control, AR, AR+AAV, and AR+AAV-sh-DDX3Y groups. Data are presented as mean ± SD values.

the levels of inflammatory cytokines (IL-4, IL-5, IL-13, and IL-6). Histopathological analysis revealed that *DDX3Y* knockdown mitigated inflammatory cell infiltration and tissue damage in the nasal mucosa, indicating an overall improvement in tissue morphology. Mechanistically, *DDX3Y* knockdown suppressed the phosphorylation of NF-κB pathway components, specifically p65 and IκBα, thereby reducing local inflammatory response. These findings underscored the therapeutic potential of targeting *DDX3Y* in managing AR. By inhibiting the NF-κB pathway, *DDX3Y* knockdown effectively reduced inflammation and lessened clinical manifestations. This study not only identified *DDX3Y* as a novel therapeutic target but also provided a foundation for further research into its mechanisms and potential applications in human AR patients.

Inflammation is a central feature of AR, driven primarily by a Th2-skewed immune response that leads to the release of cytokines and other mediators.[17] These inflammatory processes are responsible for the clinical manifestations of AR.[18] Our study focused on *DDX3Y*, a protein whose role in AR was not elucidated in the past. We found that *DDX3Y* was highly expressed in the nasal mucosa of AR mice. Knocking down *DDX3Y* in an OVA-induced AR mice model significantly alleviated nasal manifestations, reduced IgE and histamine levels, and improved nasal mucosal histopathology. These results suggested that *DDX3Y* had a crucial role in the inflammatory response associated with AR, and targeting this protein could be a promising therapeutic approach.

DDX3Y, an RNA helicase of the DEAD-box protein family, is involved in various processes, such as RNA splicing, transportation, and translation.[19] It regulates the TLR4/NF-κB pathway to mitigate cellular damage induced by cigarette smoke extract, suggesting its effects on cell inflammation.[19] Extending these findings, our study demonstrated that *DDX3Y* knockdown in AR mice suppressed NF-κB phosphorylation, which was crucial for reducing local inflammatory responses. This indicated that *DDX3Y* is a significant regulator of inflammation in AR, contributing to the disease's pathogenesis and progression. By modulating the NF-κB pathway, *DDX3Y* knockdown effectively mitigated inflammation and lessened manifestations in AR.

The NF-κB pathway is a key regulator of immune and inflammatory responses, involving transcription factors, such as p50 and p52. These factors control the expression of genes involved in inflammation, immunity, and survival.[20,21] In AR, the NF-κB pathway is activated, leading to the transcription of pro-inflammatory genes and exacerbation of symptoms.[21] Our study showed the upregulation of *DDX3Y* on this pathway, thereby inhibiting its activity

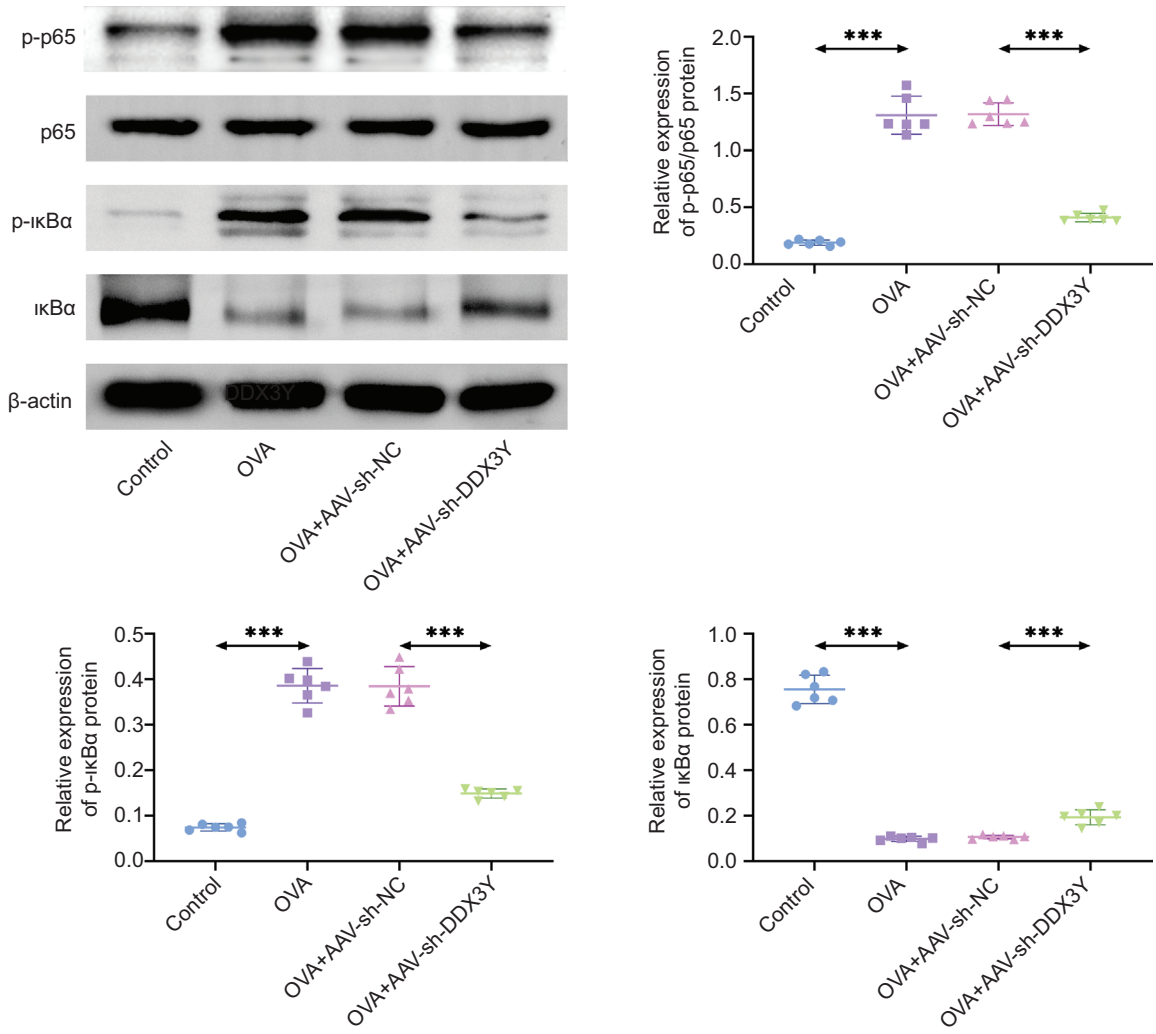

Figure 5 Effects of DDX3Y knockdown on NF-κB pathway activation in OVA-induced AR mice. Immunoblot analysis of p-p65 and p65, and p-IκBα and IκBα levels of nasal mucosal tissues in control, AR, AR+AAV, and AR+AAV-sh-DDX3Y groups. Densitometric analysis of p-p65/p65 and p-IκBα/IκBα ratios, and expression of IκBα. Data are presented as mean ± SD values.

and reducing inflammation. This finding underscored the potential of targeting NF-κB pathway as a therapeutic strategy for AR and highlighted the role of *DDX3Y* in this regulatory mechanism.

While our study provided significant insights into the role of *DDX3Y* in AR through the upregulation of the NF-κB pathway, there were several limitations to consider. First, our findings were based on a mouse model, which, although valuable, could not fully replicate the complexity of human AR. Therefore, the results need to be validated in human subjects to confirm their clinical applicability. Second, we did not measure airway restriction parameters, which were crucial for understanding the full scope of respiratory changes in AR. Including such measurements in future studies would provide a more comprehensive assessment of the effects of *DDX3Y* knockdown. Third, the precise molecular mechanisms through which *DDX3Y* regulates NF-κB and other potential pathways are to be fully elucidated. Detailed mechanistic studies are necessary to identify all interaction partners and the involved downstream signaling pathways. Finally, our study did not explore the long-term effects and potential side effects of *DDX3Y* inhibition, which are important for evaluating the therapeutic potential and safety of this approach in chronic conditions such as AR.

Conclusion

Our study provided compelling evidence that DDX3Y was involved in the pathogenesis of AR by regulating the NF-κB pathway. Knockdown of *DDX3Y* in OVA-induced AR mice alleviated nasal inflammation and lessened clinical manifestations, suggesting that *DDX3Y* was a novel and promising therapeutic target for AR. These findings paved the way for future research to explore the clinical applicability of targeting *DDX3Y* and to elucidate the molecular mechanisms underlying its role in AR.

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No funding was used in this study.

Competing Interests

The authors stated that there were no conflicts of interest to disclose.

Data Availability

The authors declared that all data supporting the findings of this study were available within the paper and any raw data could be obtained from the corresponding author upon request.

Author Contributions

Wenmin Lu and Jian Wu designed and carried out the study. Ying Xu and Xiaofeng Gu supervised data collection and done data analyzation and interpretation. Ying Xu, Xiaofeng Gu, and Wenmin Lu prepared the manuscript for publication and reviewed its draft. All authors read and approved the final manuscript.

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