Immunological Mechanisms Underlying Allergic Asthma Exacerbations Induced by Rhinovirus, Respiratory Syncytial Virus, and Influenza Virus

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Abstract: Allergic asthma is a chronic airway inflammatory disease driven by allergen sensitization and atopic predisposition. Respiratory allergens may interact with viruses that infect epithelial cells of the respiratory tract, thereby aggravating allergic asthma. Rhinovirus (RV), Respiratory Syncytial Virus (RSV), and Influenza virus (IAV) are among the predominant respiratory viruses affecting both children and adults. The immunological pathways of allergic asthma and viral respiratory infections intersect through the innate immune system, which subsequently activates the adaptive T helper-2 (Th2) and T helper-1 (Th1) responses, respectively. In individuals with asthma, interferon (IFN) production is reduced, resulting in insufficient antiviral defensive. Similar to allergen exposure, viral infection triggers the release of alarmin cytokines by airway epithelial cells, the recruitment of neutrophils and eosinophils, and the induction of a Th2 immune response, leading to eosinophilia, excessive mucus secretion, airway hyperresponsiveness, and structural remodelling. The combined of allergic inflammation and viral infection underlies the occurrence of asthma exacerbations.

1. INTRODUCTION

Asthma constitutes a persistent inflammatory disorder of the lower respiratory tract and continues to rank among the most pressing public health challenges globally. The disease manifests through heightened bronchial reactivity in response to diverse exogenous and endogenous stimuli, precipitating recurring clinical episodes characterized by wheezing, dyspnea, and cough, all of which correlate with airflow limitation that responds favorably to treatment. Globally, asthma remains a major public health concern, affecting more than 300 million people with a steadily increasing prevalence (Mikhail and Grayson, 2019; Wu et al., 2025).

Asthma exacerbations in asthma control, commonly described as asthma attacks or flare-ups, involve a rapid worsening of respiratory symptoms alongside measurable decline in pulmonary function. According to the Global Initiative for Asthma (GINA), such episodes are defined by the necessity for therapeutic adjustment and frequently signal suboptimal long-term disease management. These acute events contribute disproportionately to hospitalizations, urgent care consultations, and broader healthcare resource consumption at an international scale (Bakakos et al., 2023; Du and Yang, 2025).

Respiratory viral infections have been identified as the major triggers of asthma exacerbations, contributing to approximately 60–80% of cases in both adults and children. Among these, human RV is most commonly implicated, especially in school-aged children, while RSV is more prevalent in infants and young children (Kelly and Busse, 2008; Hayashi et al., 2022; Nakagome and Nagata, 2022; Du and Yang, 2025). Other viral agents, including IAV virus, has also been associated with asthma exacerbation, with infection rates of 20–25% among adults reported during influenza seasons (Mikhail and Grayson, 2019; Xiong *et al.*, 2023).

Elucidating the immunological mechanisms underlying allergic asthma exacerbations induced by respiratory virus could present valuable opportunities for advancing disease management strategies. Currently, pharmacological interventions for virus-induced asthma exacerbations show limited efficacy, underscoring the requirement for alternative therapeutic approaches aimed at modulating viral pathogenesis (Jackson and Johnston, 2010). The component involved in the immunological mechanisms may serve as potential targets for developing immunotherapy strategies to effectively manage this disease.

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2. ALLERGIC ASTHMA

Asthma is a chronic respiratory disease characterized by reversible expiratory airflow obstruction, persistent airway inflammation, and increased airway hyperresponsiveness (AHR), which collectively contribute to clinical manifestations such as wheezing, dyspnea, chest tightness, and coughing (Nguyen et al., 2025). The epithelial lining of the airway assumes a dual function in asthma pathobiology, serving both as a structural defensive barrier and as a cellular source of inflammatory mediators. Airway remodeling, involving cell turnover, smooth muscle hypertrophy, and fibrosis, leads to hyperplasia and impaired respiration (Hayashi et al., 2022).

Allergic asthma is one of the main manifestations of atopy, a hereditary disease associated with Immunoglobulin E (IgE) sensitization to environmental allergens. Clinical outcome of atopy presents with food allergies, allergic rhinitis, and allergic asthma (Soleha and Iswanti, 2021).

3. RESPIRATORY VIRUS INDUCED ASTHMA EXACERBATIONS

Individuals diagnosed with asthma are particularly susceptible to experiencing recurrent and intensified respiratory episodes following viral infection of the respiratory tract. Viruses including RV, RSV, and IAV collectively account for asthma exacerbations in approximately 80% of affected children and 50% of adults. Dysregulated antiviral response mediated by type I and type III interferon (IFN-I/III), along with excessive Th2 immune response, have been implicated as key factor contributing to asthma exacerbation (Papadopoulos *et al*., 2011).

Several distinct yet interrelated viral mechanisms contribute to the precipitation of asthma exacerbations. These encompass elevated circulating IgE levels, structural and functional disruption of the airway epithelium, attenuation of antiviral immunity through reduced IFN output, perturbation of systemic immune regulation, promotion of localized respiratory inflammation, and direct viral invasion of the lower airways. Epithelial disruption following viral infection facilitates the liberation of danger-signaling molecules known as alarmins, which orient the immune response toward a type 2–biased phenotype by activating T helper-2 (Th2) lymphocytes and group 2 innate lymphoid cells (ILC2). These effector populations elaborate IL-4, IL-5, and IL-13, cytokines that collectively drive eosinophilic airway inflammation, goblet cell metaplasia, and bronchial hyperresponsiveness. Moreover, type 2–dominated inflammation further suppresses antiviral signaling pathways, creating a feedback loop wherein inflammation and viral persistence mutually reinforce each other, ultimately culminating in asthma exacerbation (Kim, 2022; Wu et al., 2025).

Eosinophils, neutrophils, ILC2, Th2, and Th17 cells, contribute to epithelial chemokines production in virus-induced asthma exacerbation (Fukuda *et al.*, 2020).

3.1. RHINOVIRUS (RV)

Rhinovirus (RV), which is categorized into three genomic species (RV-A, RV-B, and RV-C), constitutes a primary etiological agent of bronchiolitis in infancy and plays a well-documented role in asthma disease progression. Early-life RV infections can induce a Th2-skewed immune response, adversely affecting lung maturation and predisposing individuals to chronic respiratory diseases. Moreover, the interaction between RV and environmental allergens enhances the release of IL-33 and other proinflammatory cytokines, promoting airway inflammation, remodeling, and the subsequent exacerbation of asthma symptoms during childhood (Kierbiedź-Guzik and Sozańska, 2025).

Airway remodeling is a complex pathological process involving structural and functional alteration in airway cells, followed by extracellular matrix (ECM) composition changes. Airway remodeling is linked to worse clinical outcomes in individuals with asthma, while therapeutic interventions specifically target its symptoms (Spector *et al.*, 2023).

Human RV primarily infects airway epithelial cells through intercellular adhesion molecule-1 (ICAM-1) or cadherin-related family member 3 (CDHR3) receptors, resulting in epithelial injury and subsequent activation of innate immune responses. In asthmatic airways, defective IFN-I/III production and impaired natural killer (NK) cell activation contribute to viral persistence and enhanced airway inflammation. The virus additionally subverts host antiviral mechanisms by deploying viral proteases 2A and 3C to degrade critical signaling proteins — including Toll-like receptor 3 (TLR3), melanoma differentiation-associated protein 5 (MDA5), TRIF, and mitochondrial antiviral signaling protein (MAVS). The consequent liberation of epithelial-derived alarmins activates ILC2s and Th2 lymphocytes, stimulating the elaboration of type 2 cytokines encompassing IL-4, IL-5, and IL-13. These mediators orchestrate eosinophil tissue recruitment, IgE isotype switching, excessive mucus production, and progressive airway remodeling. Eosinophilic infiltration compounds the degree of tissue injury through the secretion of cytotoxic granular proteins — notably eosinophil-derived neurotoxin (EDN) and eosinophil cationic protein (ECP) — which exert both

antiviral and pro-inflammatory effects. The resulting cascade contributes to airway hyperresponsiveness, chronic remodeling, and the development of asthma exacerbations (Price and Kennedy, 2022).

3.2. RESPIRATORY SYNCYTIAL VIRUS

The prospective study involving atopic asthma aged 15 to 56 years found that respiratory viruses were identified in approximately 60% of asthma exacerbation episodes accompanied by respiratory tract infection symptoms, with RSV being the predominant virus detected (Westerly and Peebles, 2010).

RSV infects airway epithelial cells, causing cellular injury and alarmin release that activate local immune responses. The virus encodes nonstructural proteins NS1 and NS2 that actively antagonize IFN-I/III production, thereby undermining antiviral host defenses and promoting viral persistence. During early developmental stages, the relative immaturity of the immune system fosters a Th2-skewed response characterized by upregulation of IL-4, IL-5, IL-13, and IL-33, which in turn activate ILC2-mediated eosinophilic inflammation, goblet cell hyperplasia, and increased airway reactivity. In allergic individuals, this Th2 dominance suppresses Th1 antiviral activity, amplifying airway inflammation and remodeling. RSV also enhances IgE production and mast cell activation, further contributing to bronchial hyperreactivity. Additionally, Th17-mediated and neutrophil-driven responses, including neutrophil extracellular trap (NET) formation, exacerbate tissue injury and obstruction. Collectively, impaired interferon signaling, Th2/Th17 polarization, and persistent inflammation establish a pro-asthmatic immune milieu that links severe RSV infection in infancy to long-term airway disease (Binns et al., 2022; Ma et al., 2025).

3.3. INFLUENZA VIRUS

Asthma exacerbations triggered by IAV arise from a complex interplay of epithelial injury, impaired antiviral immunity, and dysregulated inflammatory responses. IAV notably infects bronchial epithelial cells, disrupting epithelial tight junctions and impairing barrier integrity, which facilitates viral penetration and the upregulation of adhesion and growth factors such as ICAM-1 and insulin-like growth factor-I (IGF-I). This structural disruption triggers the release of epithelial-derived alarmin mediators — including IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) — which engage dendritic cells, ILC2s, and Th2 lymphocytes. The resulting amplification of Th2 effector cytokines — specifically IL-4, IL-5, and IL-13 — promotes eosinophilic airway inflammation, mucus overproduction, and bronchial hyperreactivity. In parallel, IAV employs its nonstructural protein NS1 to suppress type I and III interferon (IFN-α/β and IFN-λ) signaling, impairing antiviral defenses and promoting viral persistence. Eosinophils, abundant in allergic airways, act as antigen-presenting cells that enhance $CD8^+$ T cell–mediated viral clearance, but this simultaneously intensifies airway inflammation and mucus production. Moreover, transforming growth factor-β (TGF-β) released by alveolar macrophages contributes to airway remodeling and further modulates immune responses. The combined effects of epithelial barrier disruption, alarmin-driven Th2 activation, suppressed IFN signaling, and persistent granulocytic inflammation, including NET formation, culminate in structural airway remodeling, obstruction, and chronic asthma exacerbation (Veerapandian, Snyder, and Samarasinghe, 2018; Du and Yang, 2025).

4 CONCLUSIONS

Respiratory viral infections in individuals with asthma exacerbate type 2 airway inflammation and epithelial injury through impaired IFN responses and the activation of alarmin-mediated Th2 and ILC2 pathways. Among the major respiratory viruses, RV, RSV, and IAV exhibit distinct yet overlapping inflammatory profiles characterized by Th2-dominant immune activation. RV induces robust ILC2 activation, leading to pronounced type 2 cytokine release; RSV further amplifies Th2 cytokines, including IL-4, IL-5, and IL-13; while IAV elicits a mixed Th1/Th2 response, contributing to both antiviral and allergic inflammation. The predominance of type 2–driven immune responses and subsequent eosinophil recruitment culminate in mucus hypersecretion, airway remodeling, and heightened bronchial hyperreactivity; pathophysiological hallmarks of virus-induced asthma exacerbations.

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