

Asthma



The Interplay Between Viral Infections and Allergic Diseases

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KEYWORDS

• Asthma • Viral infection • Rhinovirus • Atopy • Allergy • Immunoglobulin E
• Type I interferon • Dendritic cells

KEY POINTS

- Respiratory viruses, especially rhinoviruses, are associated with both the development and exacerbation of asthma.
- Allergic sensitization increases the risk of virus-induced asthma exacerbation.
- Immunoglobulin E-mediated pathways block critical type I interferon responses after viral infection, representing one mechanism whereby viruses and allergens cooperatively induce asthmatic disease.
- Cytokine and chemokine responses between the epithelium, innate immune cells, and adaptive immune responses are regulated by both allergens and virus infection, and contribute to the synergistic effects of these factors on asthma pathogenesis.
- Therapeutic strategies targeting both viral and allergic inflammation may provide clinical benefit in asthma.

INTRODUCTION

The interaction between viral respiratory infections and allergic diseases, especially asthma, has long been appreciated. Much has been learned through both clinical and basic science studies on the synergy between these pathologic processes. This review discusses the clinical and molecular findings relevant to this intersection of viral

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and allergic diseases. The article focuses on recent studies investigating how these 2 disparate disease processes cooperatively affect asthma pathogenesis.

VIRAL INFECTIONS AND ASTHMA: CLINICAL ASSOCIATIONS

Viruses, Genetics, and Asthma Development

Multiple studies demonstrate strong correlations between early viral respiratory illness in childhood and the development of asthma.^{1–3} Results of prospective birth cohort studies^{4–7} have established correlations between the age at initial wheezing onset, severity of respiratory viral infection, and persistence of wheezing episodes with an increased risk of asthma at school age. Genetic predisposition (ie, family history of atopic disease) and concurrent atopy represented additional critical contributors to asthma pathogenesis,^{4,8,9} suggesting a synergistic relationship between viral infections and allergic diseases.

The Childhood Origins of ASThma study (COAST) specifically targeted a high-risk cohort of children based on a parental history of atopy.⁵ Whereas early respiratory syncytial virus (RSV) infection increased asthma risk at age 6 years by 3-fold, early-life human rhinovirus (RV) infection increased the risk by almost 10-fold in COAST participants,¹⁰ suggesting a stronger link between early rhinovirus infection and asthma development in children genetically at risk.

Details regarding such genetic factors are beginning to emerge. Recent genomic analyses targeted the 17q21 chromosomal locus. A meta-analysis from 2 cohorts, the COAST and Copenhagen Studies on Asthma in Childhood (COPSAC), indicated a link between certain 17q21 genotypes and RV-related wheezing and asthma development.¹¹ Two genetic loci in this region, the *ORMDL3* and *GSDMB* genes, were significantly upregulated in peripheral blood mononuclear cells (PBMCs) after in vitro RV exposure. Furthermore, COAST cohort participants homozygous for a specific single-nucleotide polymorphism (SNP) in the *GSDMB* gene had a 26-fold increased risk of developing asthma when combined with a history of prior rhinovirus infection. More studies are needed to define the exact functions of these genes and the specific host-virus interactions relevant to individuals with asthma.

Similarly, a second study linked SNPs in innate immunity genes to the development of asthma and atopy. Specifically, SNPs in the interleukin (IL)-1 receptor 2 and toll-like receptor (TLR)-1 genes linked picornavirus and RSV infections with airway hyperreactivity.¹² Although others have reported SNP associations with asthma and atopy,^{13–15} these studies connect specific genotypes to asthma and virus-induced wheezing episodes, suggesting genetic interactions between viruses and atopy. However, not every child with risk factors develops asthma. Instead, a complex interplay of multiple risk factors, including genetic phenotypes prone to allergen sensitization, respiratory virus susceptibility, and atopic disease, all intersect, increasing an individual's risk for asthma development.

As described by the “2-hit hypothesis” of asthma development, genetic predisposition to atopy (the first hit) combined with a second environmental insult, specifically early respiratory viral infection (the second hit), may lead to asthma.¹⁶ This hypothesis highlights the collaborative roles of genetics, viruses, and allergens in promoting asthma.

Viruses: Role in Asthma Exacerbations

In addition to their role in asthma development, respiratory viruses also contribute to ongoing disease as major causes of asthma exacerbations. The seasonality of RV-associated asthma exacerbations has been well described,¹⁷ and multiple studies have shown a close temporal relationship between respiratory viral infection and

disease exacerbation.^{18–21} Rhinoviruses are most commonly isolated during asthma exacerbations, but other viruses, including human metapneumovirus²² and influenza,^{18,21} represent important contributors. During the 2009 influenza pandemic, an increase in disease severity and exacerbations was noted in pediatric asthmatic patients, with a disproportionate number requiring intensive care.²³

Many studies point to diminished antiviral responses (**Box 1**) as one potential mechanism underlying viral-induced asthma exacerbations. For example, interferon (IFN)- γ production by viral or mitogen-stimulated cord blood monocytes inversely correlated with the number of wheezing episodes and respiratory viral infections during infancy.^{24,25} Thus, one proposed mechanism of viral-induced wheezing and asthma development is increased susceptibility to respiratory viral infections secondary to diminished antiviral response. In addition, airway epithelial cells and immune cells recovered from asthmatic patients had diminished type I, II, and III IFN responses after rhinovirus exposure,^{26–28} resulting in decreased release of IFN-dependent cytokines such as IL-15.²⁹ Deficient IFN- α secretion on in vitro exposure to viruses including influenza and RV has also been demonstrated in PBMCs and purified plasmacytoid dendritic cells (pDCs).^{30,31} Furthermore, in vivo experimental RV inoculation of volunteers revealed more severe symptoms in asthmatics than in controls.³² However, the inefficient innate immune response does not result in enhanced viral replication,³³ suggesting that a combination of factors including concomitant allergen exposure contributes to worsened viral disease. The remainder of this review focuses on clinical associations and potential mechanisms involved in the interplay between allergens and viral infection in asthma.

VIRUSES AND ALLERGENS: EVIDENCE OF SYNERGISM IN ASTHMA

Viral infections and allergic sensitization/allergen exposure together have been shown to synergistically increase the risk and severity of asthma exacerbations. The

Box 1

Virus-allergen synergism: potential mechanisms in asthma

- Genetic factors
- Deficient antiviral responses
- Immunoglobulin E-mediated effects
 - Inhibition of type I interferon responses
 - Impairment of monocyte function
 - Dendritic cell–driven induction of T-helper 2 (Th2) responses
- Other dendritic cell–mediated effects
- Enhanced Th2 responses
- Respiratory epithelial damage
- Respiratory epithelial mediators
 - Thymic stromal lymphopoietin
 - Interleukin-33
 - Interleukin-25
- Altered purinergic receptor activation
- Deficient interleukin-15 responses
- Altered T-regulatory and innate lymphocyte cell responses

mechanisms underlying this interplay between virus and atopy represent an area of intense investigation. Several recently published reviews detail these associations,^{34–37} and a summary and relevant updates are discussed herein.

Clinical Associations

As previously mentioned, early-life respiratory viral infections, most notably rhinovirus and RSV, have been associated with subsequent development of allergic sensitization and asthma in children.^{1,10,38} The synergism between atopy and rhinovirus infections persists throughout childhood; exacerbation rates are increased by the presence of allergic sensitization and exposure to aeroallergens including cockroach, dust mite, and cat allergens.^{8,39,40} In a prospective study to determine relationships between rhinovirus infection and illness severity, Olenec and colleagues⁴¹ collected weekly nasal lavage samples from asthmatic children during fall and spring months that corresponded with peak rhinovirus infection rates. Although the number of viral infections was not increased in the atopic group, the allergen-sensitized group experienced a 47% increase in viral respiratory tract illness and severity, including both cold and asthma symptoms, compared with the nonsensitized group. Other studies of asthma severity also highlight this virus-atopy collaboration in disease pathogenesis. The combination of virus detection, allergic sensitization, and allergen exposure were shown to significantly increase the risk of hospitalization in studies of both children and adults with asthma exacerbations.^{42,43}

Viral-Atopy Associations in Experimental Rhinovirus Infections

Experimental rhinovirus infection directly affects components of the allergic response itself, resulting in increased histamine release and recruitment of eosinophils to the airway in adult allergic subjects,⁴⁴ suggesting that rhinovirus infection may induce an allergic state. Counter to this conclusion, however, are findings in prospective studies of children in the high-risk COAST birth cohort, which demonstrate that allergic sensitization actually precedes RV-induced wheezing.⁸ Similarly, Zambrano and colleagues⁴⁵ demonstrated that the ability of experimental RV infection to induce asthma exacerbations correlated with sensitization to relevant aeroallergens; increased serum immunoglobulin E (IgE) concentrations were also associated with reduced lung function in response to RV infection. In another study, only the asthmatic subjects displayed increased eosinophilic airway inflammation, lower respiratory symptoms, lung function impairment, and enhanced T-helper 2 (Th2) cytokine release on RV infection; healthy control subjects did not exhibit these responses.⁴⁶ These studies confirm that atopy significantly affects the immune response to rhinovirus infection in individuals with allergic asthma, and suggest that allergic sensitization and exposure contribute to increased severity of lower respiratory tract infections and asthma exacerbations associated with RV infections.

MECHANISMS UNDERLYING VIRUS-ALLERGEN SYNERGISM IN ASTHMA

Multiple potential mechanisms underlying the interplay between viral infections and allergic sensitization in asthma have been postulated (see **Box 1**), as published in recent reviews.^{34,47}

The Type I Interferon–Immunoglobulin E Axis: Evidence That Atopy Impairs Antiviral Responses

Type I IFN (IFN- α/β), a family of antiviral cytokines, is secreted in highest concentrations by pDCs, key antigen-presenting cells recruited to the airway during viral

infections.⁴⁸ IFN- α/β is especially relevant to allergic disease in its ability to negatively regulate Th2 and Th17 lymphocyte responses.^{49,50} IFN- α/β blocks Th2 effector cell secretion of IL-4, IL-5, and IL-13, and inhibits Th2 development in human CD4 T cells by suppressing GATA3, a major Th2 transcription factor.⁴⁹

Counterregulation between antiviral responses and IgE-mediated pathways in pDCs represents a newly recognized mechanism by which allergens and viruses may cooperatively promote asthma exacerbations. Serum IgE and expression of its high-affinity receptor, Fc ϵ RI α , are inversely correlated with IFN- α secretion from purified pDCs and PBMCs stimulated with viruses including influenza and rhinovirus in vitro.^{30,31} In addition, IgE cross-linking significantly impairs viral and TLR-9 agonist-induced pDC IFN- α secretion, suggesting that allergen exposure in sensitized individuals may inhibit antiviral responses via in vivo cross-linking of allergen-specific IgE.^{31,51} Exposure of pDCs from dust-mite allergic individuals to dust mite allergen (Der p 1) in vitro also significantly impaired pDC IFN- α responses to influenza.³¹ Treatment of cat-allergic subjects with omalizumab, an anti-IgE monoclonal antibody that decreases both serum IgE and Fc ϵ RI expression on innate immune cells, diminished the capacity of allergen-exposed DCs to drive Th2 inflammatory responses.⁵²

Results of the recent National Institutes of Allergy and Infectious Diseases-sponsored Inner City Anti-IgE Therapy of Asthma trial provide further evidence of the relevance of this pathway; the group of children who received omalizumab experienced a near-complete elimination in the fall increase in asthma exacerbations, a seasonal increase known to be associated with the fall peak in rhinovirus infections.⁵³ Taken together, these studies suggest that pathways involving IgE, Fc ϵ RI, allergens, and viral-induced IFN- α may play critical roles in the allergen-viral interplay in asthma pathogenesis. The role of dendritic cells and monocytes in this and other potential mechanisms underlying allergen and viral-associated exacerbation of asthma is illustrated in **Fig. 1** and has been reviewed elsewhere.⁵⁴

IgE-mediated effects on monocytes and antigen-presenting cells present in high numbers within lung tissues may also contribute to inflammatory responses relevant to respiratory viral infections associated with allergic disease. Pyle and colleagues⁵⁵ demonstrated that monocytes exposed to IgE cross-linking conditions secreted high concentrations of the inflammatory cytokines tumor necrosis factor (TNF)- α and IL-6; this effect was greatest in individuals with elevated serum IgE. Furthermore, monocyte function was critically impaired by this allergic activation, resulting in significant disruption of phagocytosis. Phagocytosis of apoptotic epithelium represents a major component in the resolution of inflammatory responses; crippling of this monocyte function could thus prolong inflammatory responses (see **Fig. 1**). In the setting of aeroallergen sensitization/exposure, coupled with viral-induced apoptosis of respiratory epithelium, cross-linking of allergen-specific IgE on monocytes represents another potential mechanism whereby allergens and viruses may synergistically promote exacerbations of allergic disease.

Enhanced T-Helper 2 Responses

Deficient type I interferon antiviral responses, as demonstrated in epithelial cells,²⁸ whole blood cultures,^{56,57} PBMCs,³⁰ and purified pDCs³¹ isolated from patients with asthma, may indirectly promote the enhancement of Th2 environment through loss of this negative regulatory effect of IFN. Deficient IFN- α/β responses in the context of viral infections could thus promote increased Th2 CD4 inflammatory responses.

Using genomic profiling of PBMC subpopulations isolated from asthmatic patients, Subrata and colleagues⁵⁸ demonstrated increased Fc ϵ RI expression and Th2-promoting functions in monocytes and DCs during viral exacerbations of asthma. Of

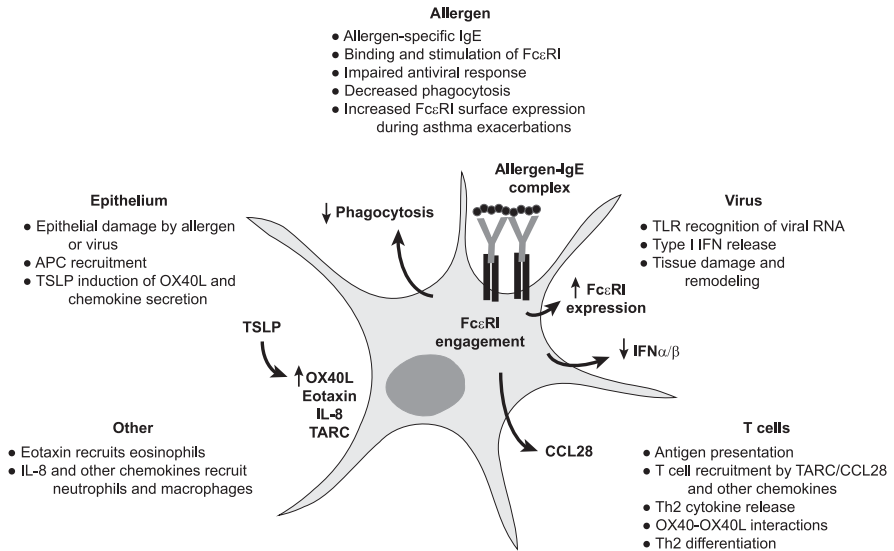


Fig. 1. Antigen-presenting cells (APCs) are key mediators of viral-allergen effects in asthma pathogenesis. Epithelial damage by virus or allergen results in APC recruitment to the lung (myeloid dendritic cells [mDCs], plasmacytoid dendritic cells [pDCs], and monocytes). Virus effects specifically result in type I interferon (IFN) release from APCs, and tissue damage and remodeling of the epithelium. Epithelial thymic stromal lymphopoietin (TSLP) release mediates upregulation of OX40L on DCs and release of multiple chemokines (eotaxin, interleukin [IL]-8, and thymus and activation-regulated chemokine [TARC]). FcεRI engagement by immunoglobulin E (IgE)-allergen complex has multiple downstream effects including inhibition of toll-like receptor (TLR)-mediated antiviral responses (type I IFN secretion from pDCs) and phagocytosis (by monocytes). Chemokines induced by either TSLP- or FcεR-mediated pathways recruit other critical immune cells including eosinophils, macrophages, and T cells. APCs present antigen to T cells either in the tissue or draining lymph node, and drive T-helper 2 (Th2) cell differentiation through OX40L-OX40 interactions.

note, more than 95% of the patients who experienced a severe viral-associated asthma exacerbation were also atopic, adding to the body of evidence linking these 2 factors in asthma.

Viral proteases can also contribute to Th2 inflammatory responses relevant to asthma. Intranasal administration of recombinant RV 2A, a protease of RV, enhanced ovalbumin-induced Th2 inflammation in a murine model.⁵⁹ Such enhancement of Th2 responses may further contribute to asthma pathogenesis, promoting the production of IgE, eosinophilic inflammation, and goblet-cell hyperplasia.

Mechanisms Involving the Respiratory Epithelium

Epithelial integrity

Both the integrity of the respiratory epithelium⁶⁰ and the mediators released during allergen and viral stimulation may contribute to enhanced disease driven by the synergy of these factors in allergic asthma. Increased airway epithelial damage has been reported in children with allergic sensitization and asthma, and correlated with diminished immune responses to RV infection.⁶¹ This underlying compromise of the epithelial barrier, the site where the host first encounters allergens and viruses, may promote a more rapid loss of epithelial integrity during immune responses to viral infection.

Epithelial mediators: thymic stromal lymphopoietin, interleukin-33, interleukin-25

Mediators secreted by the respiratory epithelium on virus and allergen exposure may also contribute to the pathogenesis of synergistic disease. Thymic stromal lymphopoietin (TLSP), an epithelial-derived cytokine induced by both allergen and viral exposure,^{62,63} activates dendritic cells to promote Th2 inflammatory responses. Elevated levels of TLSP have been reported in the airway epithelium of atopic asthmatics.^{64,65} The amplification of TLR-3-induced TLSP secretion by IL-4 provides evidence that viral infection coupled with the recruitment of Th2 cytokine-producing cells to the airway may further enhance allergic inflammation in the airways of atopic asthmatics.⁶²

IL-33, another cytokine that enhances Th2 inflammation, is also increased in lung epithelium from asthmatics.⁶⁶ Both allergens⁶⁷ and viruses⁶⁸ promote increased expression of IL-33. IL-25 also promotes Th2 cytokine release from immune cells and has been detected in lung tissue from asthmatics.⁶⁹ The findings that IL-25 is enhanced by viral infection and that Th2 inflammatory responses are reduced by IL-25 blockade and IL-25 receptor knockout (IL-17RB^{-/-}) in a murine model of RSV-induced asthma suggests a potential role for IL-25 in viral allergen-induced asthma exacerbations.⁷⁰

Altered Purinergic Receptor Activation and Signaling

Purines including adenosine triphosphate (ATP) have been implicated in the pathogenesis of allergic inflammation associated with asthma. Both airway allergen challenge and viral exposure result in increased extracellular ATP concentrations in lung tissues, which can lead to activation of purinergic signaling with resulting inflammatory responses.⁷¹ Recently P2X7, a purinergic receptor expressed on epithelial cells and innate immune cells, has been shown to play a role in allergic sensitization and viral-induced asthma exacerbations in both children and adults,⁷² suggesting yet another potential mechanism by which viruses and allergens contribute to asthma pathogenesis.

Other mechanisms involving dysregulation of regulatory T-cell and innate lymphoid cell responses,³⁴ altered IL-15 secretion,²⁹ and indoleamine 2,3-deoxygenase,⁵⁴ a tryptophan-regulating enzyme, are reviewed elsewhere.

Additional Mechanistic Insights from Animal Models

Animal models utilizing mouse pneumovirus I or Sendai virus (SeV) infection provide further insight. SeV infection of mice, which closely mimics the pathology of acute RSV in humans, culminates in chronic airway inflammation, including airway remodeling, increased mucous secretion, and airway reactivity.⁷³ This model, combined with murine allergen models, provides clues in the complex interaction between viruses and allergens. Infection of the respiratory epithelium leads to epithelial-specific cytokine and chemokine release.^{74,75} This initial inflammatory response recruits IgE receptor (FcεRI)-expressing dendritic cells, eosinophils, and CD4 T cells to the lung,⁷⁶ resulting in IL-13 release and an “allergic” Th2-mediated response. Paralleling *in vivo* clinical observations, the antiviral response is critical in controlling viral-induced pathology, as the absence of TLR-7, a critical component of IFN- α/β signaling, results in disease exacerbation.⁷⁵ Following viral infection, reexposure to allergen recapitulates components of human asthma pathology including airway remodeling, mucous cell hyperplasia, and airway reactivity,⁷⁷ demonstrating that viral infection can induce an allergic state. These findings, including the role of FcεR expression,^{76,77} complement data from human studies, shedding light on potential mechanisms underlying the synergism between the allergic responses and viral infections in asthma (see **Fig. 1**).

FUTURE CONSIDERATIONS AND SUMMARY

The interplay between respiratory viruses and atopy contributes significantly to the development and exacerbation of asthma, thus suggesting that therapeutic strategies aimed at interrupting either the viral or allergic components of disease pathogenesis may provide clinical benefits.

Targeting Viral Infection

Preventing initial viral infection is one approach to halting disease development in high-risk children. For example, treatment of infants with palivizumab, an anti-RSV antibody, decreases infection severity⁷⁸ and wheezing episodes during infancy and early childhood.^{79,80} Because repetitive, prolonged wheezing increases the risk of developing asthma, these findings suggest that palivizumab treatment in select, high-risk infants might prevent asthma development. Though effective in nonatopic children, palivizumab-mediated reduction in asthma was limited in atopic children.⁸¹ At present there is no approved antiviral treatment of rhinovirus, which plays a more significant role in asthma development. By contrast, effective vaccine and antiviral therapies are available for influenza virus. Influenza vaccination is effective in reducing steroid use, clinic and hospital visits, and exacerbations associated with asthma.^{82,83} Furthermore, administration of oseltamivir, an influenza neuraminidase inhibitor, to asthmatic children during acute influenza infection improved lung function over the duration of disease.⁸⁴ Despite recommendations from the Centers for Disease Control and Prevention for widespread influenza vaccination in this population, vaccination coverage remains low (~50%) in asthmatic individuals.⁸⁵ These studies highlight the importance of promoting both vaccination and continued development of new antiviral agents as strategies to improve asthma-associated morbidity.

Even simple nutritional changes may have effects on prevention of virus-induced disease. A meta-analysis indicates that vitamin D supplementation reduced the incidence of upper respiratory tract infections,⁸⁶ and a small trial suggests a positive effect on virus-induced asthma exacerbations in children.⁸⁷ Furthermore, targeting the mucosal immune system through the use of probiotics also demonstrated protection from upper respiratory infections.⁸⁸ Further analysis revealed a decrease in IgE levels and atopy in children treated with probiotics, but a limited effect on asthma and wheezing.⁸⁹

Targeting Allergic Inflammation

Targeting allergic inflammation represents another therapeutic strategy for preventing virus-induced atopic disease. Although guidelines-based asthma therapy including inhaled corticosteroids and β -agonists do help control exacerbations during seasonal rhinovirus infections,⁹⁰ there is a limited effect on viral replication and cytokine release in vitro.⁹¹ Additional therapies, such as targeting IgE with omalizumab, have already been shown to be effective.⁵³ Development of additional IgE/Fc ϵ RI signaling inhibitors that dampen IgE pathways and potentially restore viral-induced IFN- α / β responses may prove useful in preventing allergic airway inflammation associated with viral infections. Additional biologics targeting multiple pathways, including IL-5, IL-4, IL-13, TNF- α , TLR-7 and -9, and Th2 development are being evaluated in clinical trials.⁹² Other pathways, such as IL-33, have also been proposed as potential therapeutic targets.⁹³

In summary, asthma pathogenesis is complex and multifactorial, and affected by genetic and environmental factors. The interplay between respiratory viral infection and allergic responses dramatically affects disease outcome. While components of

the mechanisms underlying these associations are known, many questions remain. Additional research is needed to translate new ideas into effective therapies.

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