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