CHEST

Rhinovirus in the Pathogenesis and Clinical Course of Asthma

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In healthy individuals, human rhinovirus (HRV) infections are the major cause of the common cold. These are generally uncomplicated infections except for occasional cases of otitis media or sinusitis. In individuals with asthma, however, HRV infections can have a major impact on disease development and progression. HRV-induced wheezing illnesses in early life are a significant risk factor for subsequent development of asthma, and growing evidence supports a role of recurrent HRV infections in the development and progression of several aspects of airway remodeling in asthma. In addition, HRV infections are one of the most common triggers for acute exacerbations of asthma, which represent a major burden to health-care systems around the world. None of the currently prescribed medications for asthma are effective in preventing or reversing asthma development and airway remodeling or are ideal for treating HRV-induced exacerbations of asthma. Thus, a better understanding of the role of HRV in asthma is important if we are to develop more effective therapies. In the past decade, we have gained new insights into the role of HRV infections in the development and progression of airway remodeling as well as a new appreciation for the proinflammatory and host defense responses to HRV infections that may help to regulate susceptibility to asthma exacerbations. This article reviews the current understanding of the role HRV infections play in the pathogenesis of asthma and identifies possible avenues to new therapeutic strategies for limiting the effects of HRV infections in asthma. CHEST 2015; 148(6):1508-1516

ABBREVIATIONS: EGF = epidermal growth factor; HRV = human rhinovirus; IFN = interferon; ISG = interferon-stimulated gene; NO = nitric oxide

Human rhinovirus (HRV) is a single-strand, positive-sense RNA virus of the *Picornaviridae* family, with an approximately 7.2-kb genome enclosed in a protein capsid of roughly 27 nm in diameter. More than 160 strains of HRV have been identified and are classified into three genetic clades based on sequence homology.[1,2] Seventy-four strains are classified as HRV-A, whereas the HRV-B clade comprises 25 members. The remaining strains belong to the recently discovered HRV-C clade. HRV strains are also classified based on receptor usage. Eleven members of the HRV-A clade gain cellular entry through interaction with members of the low-density

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lipoprotein receptor family. The remaining strains of HRV-A and all members of the HRV-B clade bind to intercellular adhesion molecule 1.[1] The asthma susceptibility gene product cadherin-related family member 3 has been shown to mediate HRV-C binding and replication.[3] A number of studies have compared the association of the three HRV clades with severity of asthma outcomes. In children, studies have suggested that either HRV-C only or as a coinfection with HRV-C are more commonly associated with exacerbations of asthma requiring medical intervention.[4,5] This association has been less well studied in adults, but one study found that severity of disease in hospitalized adults was unrelated to viral genotype.[6]

The airway epithelium is the primary site of HRV infections in both the upper and the lower airways.[7,8] Because HRV infection does not cause overt epithelial cytotoxicity, alterations of epithelial biology are believed to be the initiating events in the pathogenesis of HRV infections. In healthy individuals, HRV infection of the upper airways is the major cause of the common cold, and spread of HRV infection to the lower airway epithelium generally is uneventful. In susceptible individuals, however, increases in asthma symptoms do not occur until several days after peak nasal symptoms, consistent with the concept that subsequent spread of HRV to infect the lower airway epithelium plays a role in triggering acute exacerbations of asthma. Moreover, recurrent HRV infections in early childhood are a risk factor for asthma development and may also contribute to the initiation and progression of airway remodeling. This article reviews the current state of knowledge regarding the role of HRV in each of these aspects of asthma.

HRV and Asthma Onset

Allergic sensitization and virus-induced wheezing are each independent risk factors for asthma development, and the combination of these two factors markedly enhances the likelihood of asthma development.[9-11] Spread of respiratory viral infections to the lower airway is the major trigger for episodic wheezing in children. With the advent of reverse transcription polymerase chain reaction techniques for improved virus detection, HRV-induced wheezing illnesses in early life have emerged as a greater risk factor for subsequent asthma development than previously appreciated.[11,12] In one birth cohort at high risk for asthma development, HRV-induced wheezing illnesses during the first year of life were the strongest predictor of subsequent wheezing in the third year of life. Moreover, children with HRV-induced wheezing illnesses during the first 3 years of life had an OR of 9.8 for development of asthma compared with those with no wheezing, whereas respiratory syncytial virus-induced wheezing illness was less strongly associated with asthma development (OR, 2.6).[9] Although a number of studies have shown HRV-induced wheezing as a particular risk factor for asthma development, a recent report found that it is the cumulative number of respiratory episodes in early life, rather than the particular viral trigger, that is associated with subsequent asthma development.[13] This may still be consistent with a dominant role of HRV infections, however, because HRV is the most common viral pathogen, and children experience recurrent respiratory illnesses due to serial HRV infections.[14]

HRV Infection and Genetic Susceptibility

Repeated HRV infections in early life are common in all children. The additional risk factors that determine which children are susceptible to developing wheezy bronchiolitis and subsequent asthma upon such infections remain unclear, although host genetic susceptibility and key environmental exposures are likely contributors.[10,11] Indeed, gene-environment interactions are recognized as critical for the development of asthma. Disease heritability has been estimated to range from 35% to 90%,[15] and genome-wide association studies have identified a number of candidate genes and loci associated with asthma development. Several such studies of childhood-onset asthma have identified a susceptibility locus on chromosome 17q21. The disease-linked variants at this locus are associated with the genes *GSDMB* (gasdermin B) and *ORMDL3* (orosomucoid like 3).[15,16] Chromosome 17q21 variants have been shown to be associated with asthma in children with HRV-induced wheezing illnesses (but not respiratory syncytial virus-induced wheezing illnesses) and with expression of *ORMDL3* and *GSDMB*.[17] Also of interest in terms of the role of HRV in asthma development is the recent description that *CDHR3* is a susceptibility locus for early childhood asthma with severe exacerbations. The single nucleotide polymorphism in *CDHR3* linked to increased exacerbations and hospitalizations leads to mutation of a cysteine residue at position 529 to a tyrosine residue.[18] This same mutation has been shown to be associated with increased binding and progeny yields for HRV-C strains.[3] Paradoxically, epithelial cells from subjects with asthma cultured ex vivo show lower gene expression of *CDHR3* than cells from normal subjects.[19]

Allergic Sensitization and HRV-Induced Wheezing

If genetic susceptibility factors contributing to asthma development are complex, the role of additional