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MINIREVIEW

Understanding the Association of Human Rhinovirus with Asthma

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Human rhinoviruses are ubiquitous seasonal pathogens. They have known associations with first onset of wheezing illnesses in children and with asthma exacerbations in patients of all ages. It is not yet certain whether human rhinoviruses play a direct role in the pathogenesis of asthma by activating deleterious inflammatory responses or if they only serve as a catalyst to accelerate the disease in genetically predisposed individuals. There have been previously demonstrated reductions in the development of the asthmatic phenotype with passive immunization against respiratory syncytial virus; however, in the case of rhinovirus, there are barriers to effective vaccine development, such as the lack of a common antigenic target due to alterations of surface markers among subtypes. It remains to be determined whether certain subtypes of human rhinovirus are more asthmagenic and therefore worthy of greater attention as vaccine candidates, but several studies have suggested that RV-C and certain RV-A strains may be more strongly linked with asthma.

Human rhinoviruses (RVs), which are among the most ubiquitous viral pathogens in humans, were originally discovered in the 1950s. RVs produce disease in all parts of the world and typically have seasonal peaks in spring and fall in geographic regions with temperate climates. RVs typically infect the upper respiratory tract, and the most common clinical manifestations include rhinitis or nasal congestion, although up to 15% of patients infected with RVs may be asymptomatic (1). More recently, RVs have been implicated in more serious respiratory disease, including dyspnea, laryngotrachobronchitis, exacerbations of chronic obstructive pulmonary disease (COPD), bronchitis, pneumonia, and bronchopneumonia. For example, infant bronchiolitis has historically been attributed to respiratory syncytial virus (RSV) infection (2, 3), but recent studies implicate rhinovirus as another important cause of bronchiolitis (2, 4–6). Papadopoulos et al. demonstrated that RSV and RV were recovered from 72% and 29%, respectively, of virologically confirmed cases of acute bronchiolitis in infants and that RVs were associated with more severe disease than RSV in this population (7). RVs have also been detected outside the respiratory tract in patients with symptoms including fever, febrile convulsion, otitis media, gastroesophageal reflux disease, pericarditis, dyspnea, apnea, and a variety of other potentially life-threatening conditions.

RVs are nonenveloped viruses with capsids that express four viral proteins (VPs), VP1, VP2, VP3, and VP4. These proteins are arranged in overlapping fashion to form an icosahedral structure, with VP1, VP2, and VP3 expressed on the surface of the capsid and VP4 somewhat hidden beneath, just overlying the viral genome. Three genetically distinct RV species, RV-A, RV-B, and RV-C, have been described. RV-A and RV-B were distinguished from one another in the early 1990s based on the activities of antiviral compounds (8), and these distinctions were further refined through molecular analysis; RV-C has only been recognized since 2009 (9). There are currently 74 known subtypes of RV-A, 26 subtypes of RV-B, and at least 50 subtypes of RV-C (10). Assignment of an RV to a given species is based on sequences of the VP4/VP2 or VP1 proteins (11). In most RVs, binding and fusion of the viral particle are mediated by attachment to ICAM-1 (12), which binds to a pocket groove of the VP-1 protein (13). Other subtypes of RVs bind to LDL receptor family receptors. There are additional receptors for RV-C that are currently unknown which appear to be distinct from the other known receptors (14), but one of them appears to be CDHR3, a cadherin-related family member protein identified in a genome-wide association study as being strongly associated with severe asthma exacerbations (15). Upon attachment to the cell, the virion particle is internalized in an endosome, where the subsequent drop in pH causes uncoating of the virus's positive-sense strand of RNA and release of that RNA from the endosome, leading to translation of viral proteins, replication of viral RNA via formation of negative-sense complementary strands that allow for transcription of further mRNA-like positive strands, and assembly of new viral particles. Newly assembled virus is released through epithelial cell lysis, shedding viral particles onto neighboring cells (10).

In general, RV-A and RV-C are the dominant species found circulating among humans and are significantly more common than RV-B. RV-A and RV-C generally do not peak during the same season, suggesting that these species could interfere with one another's activities or that there is cross-protection from previous infection (16).

HUMAN RHINOVIRUSES AND ASTHMA

More than 80% of pediatric asthma is diagnosed before 5 years of age (17), and a consensus statement from the Environmental and Occupational Respiratory Diseases Interest Section of the American Academy of Allergy, Asthma, and Immunology identified five crucial host factors that could increase the probability of developing asthma in infants and remain areas for further inquiry. These are (i) lower lung volumes at birth, (ii) the presence of atopic disease, (iii) greater intensity of mucus secretion when infected with a viral pathogen during infancy, (iv) neutrophilic pathways that induce airway hyperresponsiveness to infection, and (v) differential production of type I and III interferons (IFNs) in re-

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sponse to a variety of viral infections, including RVs, during infancy (18, 19).

There is substantial evidence linking RVs to wheezing illness, bronchiolitis, and exacerbations of asthma in adults, children, and infants (18, 20–28). One group linked RVs and asthma epidemiologically based on an association between the development of bronchiolitis during RV season and a subsequent diagnosis of childhood asthma; significantly, however, this study did not include virologic testing (29). Iwane et al. studied children <5 years of age hospitalized with acute respiratory illnesses compared to healthy clinic control patients and demonstrated RV-A detection rates among children >24 months old of 8.1% in the hospitalized group and of 2.2% in the control group ($P = 0.009$) and RV-C detection rates among children >6 months old of 8.2% and 3.9%, respectively ($P = 0.002$), with hospitalization diagnoses of asthma or wheezing being more common among patients with RVs than among patients with other viruses (30). Piotrowska et al. found that infection with RV was an important determinant for the likelihood of children <2 years of age being hospitalized for wheezing illness, at rates similar to RSV (31).

Importantly, acute RV-induced wheezing during infancy has been associated with increased risk for recurrent wheezing and subsequent childhood asthma (3, 32). Jackson et al. (3) demonstrated that infants of atopic families who wheeze with RVs in the first 3 years of life are more likely to develop asthma by 6 years of age than those who wheeze with RSV (odds ratio [OR] for RV, 9.8; OR for RSV, 2.6). Further, 90% of children who wheezed with RV in the third year of life developed asthma by 6 years of age (3, 28). The association of RVs with bronchiolitis (25, 33, 34), wheezing in infancy and in later childhood (35), and asthma exacerbations suggests that RVs may be associated with the pathogenesis of asthma. Having shown earlier that RV-induced wheezing predicts subsequent asthma development, Jackson et al. have more recently hypothesized that initial allergic sensitization leads to the propensity for RV-related wheezing to occur. In a sequentially monitored birth cohort, they showed that children transitioned from allergic sensitization to wheezing illness at higher ratios if they were exposed to rhinoviruses in between (36).

RISK FACTORS FOR SEVERE RHINOVIRUS INFECTION

There are several epidemiologic risk factors known to predict the likelihood of having a more severe outcome with rhinovirus infection. The presence of bronchopulmonary dysplasia has been noted to increase the incidence of severe rhinovirus infection in very-low-birth-weight infants, whereas breastfeeding decreases the incidence (37). Active smoking is known to increase the likelihood of severe asthma exacerbation caused by rhinovirus in adults (38); in children, prenatal and postnatal secondhand smoke exposure has long been known to predispose to increased respiratory infections and increased hospitalizations for lower respiratory tract infections (39, 40). A history of maternal atopy and asthma also increases the risk of severe rhinovirus infection in the offspring (41). Finally, more frequent exposure to pathogens in settings such as day care leads to increased infection rates of all types of respiratory pathogens (42), and rhinoviruses are more commonly associated with severe outcomes than most other viruses acquired in day care (43).

HOST-PATHOGEN INTERACTIONS AND THE ONSET OF WHEEZING AND ASTHMA

Evidence supports the concept that certain individuals are predisposed to the development of wheezing illness by genetic and environmental factors (44) and that viral infections acquired during early infancy and childhood are often the initial triggers for these illnesses (35). For example, studies of RSV using genetic variance and direction of causation models in twins demonstrated that wheezing illness may reflect genetic susceptibilities of the host (45). Elevated total IgE level (46) and sensitization to dust mites (47) or other allergens (48) have been shown to influence the likelihood of wheezing with rhinovirus, adding evidence that allergic individuals may have a different response to infection.

In mouse models of allergic airway inflammation, RV infection has been demonstrated to induce increased levels of eotaxin, interleukin 4 (IL-4), and IL-13. Bronchoalveolar lavage performed in these animals also showed increased infiltration of the respiratory tract with eosinophils, macrophages, and neutrophils compared to controls (49). RVs have also been shown to stimulate the synthesis of a variety of factors that can influence airway remodeling, such as vascular endothelial growth factor (50), nitric oxide (51), and transforming growth factor beta (52) during *in vitro* experiments with cultured human epithelial cells (53). Human volunteers with allergic disease and mild asthma who were experimentally inoculated with human RV-16 had a reduced forced expiratory volume in 1 s (FEV1) and potentiated airway inflammation after provocation (54).

RHINOVIRUSES, ASTHMA, AND DIFFERENTIAL INTERFERON PRODUCTION BY THE HOST

There is a debate on the role of production of interferons, specifically type III interferons, in the development of wheezing in response to upper respiratory infections. Some groups have shown impaired Th1 responses and deficient IFN-γ production in human patients with asthma and went on to suggest that deficient antiviral defenses might play a role in the pathology of RV-initiated asthma (55–57). Baraldo et al. noticed that, compared to healthy controls, asthmatics showed decreases in both type I and type III interferons when challenged with RV-16, regardless of atopic status; they also noted that there was a correlation of decreases in IFN-λ with increased serum IgE (58, 59).

Other groups have suggested a different viewpoint: that type III interferons, such as IFN-λ, increase Th2-type responses. One group studied school-aged children with underlying asthma and upper respiratory symptoms and found that increased wheezing and wheezing severity were associated with elevated, not depressed, levels of nasal wash IFN-λ_1. Moreover, the association between wheezing and RV infections disappeared when levels of IFN-λ_1 were accounted for in the statistical analysis as a covariate (60). Pritchard et al. have noted that type I interferons, IFN-α and IFN-β, secreted by plasmacytoid dendritic cells, are an important brake in controlling RVs and in preventing a deleterious Th2 response (61). The same group recently reported an increase in Th2 cytokines, specifically IL-5 secretion, by peripheral blood mononuclear cells (PBMCs) when both RV and the type III interferon IFN-λ were present and attenuation of Th2 secretion when IFN-β was present (62). They went on to check the PBMCs of 22 asthmatic patients and noted multiple abnormalities in the expression of type I interferons via pathways of reduced expression of intracellular signaling molecules, including interferon regulatory fac-

tors (IRFs; e.g., IRF1, IRF7), NF-κB family members (p50, p52, p65, and IκKα), and STAT1, and via reduced responsiveness to Toll-like receptor 7 (TLR7)/TLR8 activation (63). Their hypothesis is that failure of type I interferon function, either by deficient production or by poor receptor and downstream performance, leads to failure of suppression of the Th2 phenotypic response from RV-specific memory T cells (63). Taking this hypothesis one step further, Djukanović et al. have noted in randomized controlled trials that, by administering the type I interferon IFN-β via nebulization, response to viral upper respiratory infections does not progress to wheezing disease in asthmatics (64).

Progress toward rhinovirus vaccination. Studies with RSV have shown that passive immunization with monoclonal antibodies can reduce the probability of developing asthma (65). Given the strong association between early RV infection and subsequent wheezing illness and asthma, the concept of developing an RV vaccine that would similarly reduce the likelihood of developing asthma has attracted considerable attention. Unfortunately, there are over 150 RV subtypes (66), and little cross-protection is afforded among subtypes after infection (67). The amino acid sequences of antigenic sites expressed on VP1 and other surface proteins have high intraspecies variability, but vaccination of mice with either VP2 plus VP4 antigens and adjuvant or VP1 antigens and adjuvant has produced cross-species neutralizing IgG antibodies (68, 69). It is known that high homotypic antibody levels reduce symptoms on reexposure to a previously experienced strain (70), but it has been very difficult to generate cross-reactive neutralizing antibodies in humans up to this point. Interest remains in vaccination as a strategy if certain RV subtypes can be consistently shown to be more asthmagenic, similar to the way that targeted human papillomavirus (HPV) vaccination has been implemented (71).

Closing comments. The association of rhinovirus infection with the onset of wheezing illness in children and exacerbations of asthma continues to be an important area for research in host-pathogen interactions. Certain features of infection with rhinovirus—including stimulation of IL-4, IL-13, and eotaxin production; immigration of inflammatory cells, such as eosinophils, macrophages, and neutrophils; and subsequent increases in factors thought to be important for airway remodeling, such as vascular endothelial growth factor, nitric oxide, transforming growth factor beta, and fibroblast growth factor—all point to the possibility that rhinovirus infection is an asthmagenic infection.

Host factors that predispose to an asthmatic response, such as impaired Th1 responses and variations in host interferons expressed in response to rhinovirus infection, have been observed in subjects with subsequent asthma. When coupled with clinical knowledge that children with lower lung volumes and atopic phenotypes are more likely to develop asthma, it can sometimes seem that rhinovirus infection is simply the revelation of an inevitable progression for certain children. Perhaps, though, rhinovirus infection and the subsequent response to it are a modifiable risk factor.

Although creating a universal RV vaccine is currently quite difficult to achieve, due to the wide variety of RV subtypes and poor cross-protection from prior heterologous infections, ongoing research in rhinovirus subtypes and subsequent risk of asthma development, as well as in treatments aimed toward patients with alterations in interferon response to viral infection, may be fruitful pathways toward rational interventions that could impact the development of asthma in early childhood and reduce the overall disease burden. Given the enormous economic impact of caring for patients with asthma, estimated at $56 billion per year in 2007 (72), there is substantial financial and social incentive to identify the pathogenic mechanisms leading to the development of asthma and to develop better approaches for preventing and treating this disease.

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