

Immune responses to rhinoviruses and asthma: Are we 3 steps closer to the door?



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Rhinoviruses (RVs) cause respiratory illnesses that are closely linked to asthma in all age groups. RV infections that cause wheezing in infants are strong risk factors for developing asthma, and once asthma is established, RV infections are major contributors to exacerbations of asthma in children and adults. The RVs are well characterized—they have been sequenced, their structures have been solved, their cellular receptors are known, and new discoveries about the replication cycle and interaction with host subcellular structures are unfolding. Despite these advances, anti-RV drugs have not been successful due to a high mutation rate of the virus, the sheer number of RV types (more than 160), and problems with off-target effects and toxicity. Novel approaches are being tested, but obstacles remain daunting.

Although the door that leads to the cure for the common cold (and RV wheezing illnesses) is currently closed, perhaps the identification of susceptibility factors opens other doors for reducing the risk of RV wheezing illnesses (Fig 1).¹ Age is important—the very young and very old are more susceptible to RV lower respiratory tract illnesses, as are individuals with low lung function. In early childhood, polymorphisms in *CDHR3* (which encodes the receptor for RV-C) and 17q12-21 (eg, *GSDMB*) can influence RV wheezing and the progression to asthma. In addition, viral species is important: RV-A and RV-C are more likely than RV-B to cause wheezing illnesses. Modifiable factors that increase the risk of more severe RV illnesses include exposure to pollutants and allergens (for those with allergies), and colonization with pathogenic bacteria in the upper airway (eg, *Moraxella catarrhalis*).²

Another factor that is potentially modifiable is the immune response to the virus. Type 2-biased immune systems and allergy have been associated with RV-induced wheezing in clinical studies³ and in studies of experimental RV infection.⁴ In addition, there is evidence that the susceptibility to viral illnesses in asthma is associated with reduced virus-induced IFN synthesis by blood or airway cells,⁵ but this concept is

controversial. In fact, some studies have reported that IFN responses *in vivo* correlate with more severe clinical illness.⁶ More information is needed to understand the immune response to RV infection, how it is determined, and how RV-induced immune responses relate to illness.

In this issue, 3 articles shed more light on these important research goals. Han et al⁷ used a mouse model of RV infection to better understand how age and sequential RV infections affect the establishment of antiviral immune responses and illness characteristics. The age of the initial infection was important; mice infected at age 6 days exhibited a type 2 response together with a goblet cell hyperplasia and mucin hypersecretion. In contrast, a first infection at age 13 days induced a more mature antiviral response and less airway remodeling. However, sequential infection with 2 different RV types at age 6 and then 13 days amplified the T2-biased responses and goblet cell hyperplasia observed after a single early infection. There are some caveats with mouse models of RV infection that are acknowledged by the authors; RV is not a natural pathogen in mice, and patterns of immune development can be species-specific. Even so, these data indicate that age and maturity of the immune system at the time of first infection have the potential to mold (or imprint) the immune response to subsequent infections. Additional clinical studies are needed to test these interesting concepts.

In the second article, Heymann et al⁸ used an experimental RV inoculation model to define how asthma and IgE influence the severity of illness and spread to the lower airway. Experimental inoculation has the advantage of allowing detailed studies of the immune and clinical responses to a well-defined virus. There are also a few limitations to this approach. For reasons of safety, the study volunteers were required to have relatively mild asthma that was stable at the time of inoculation, with no recent respiratory illnesses in the last 6 weeks. Thus, these volunteers were unlikely to develop exacerbations, and information about exacerbations needs to be extrapolated from observations related to symptoms and lung function. The investigators used 2 different study designs to (a) compare RV inoculation of individuals without asthma to those with allergic asthma, and (b) determine effects of omalizumab versus placebo on RV-induced symptoms and immune responses of volunteers with allergic asthma.

In the first study, RV infection caused increased lower respiratory tract symptoms and airway obstruction in the asthma group. Although this was an expected finding, it was interesting that these changes were greatest 14 to 22 days after inoculation, which is well after acute infection has subsided. These results raise the possibility that acute infection damages the airways and/or induces inflammation that lingers following resolution of the acute infection. Whether this is due to compromised epithelial barrier function, changes to the airway microbiome, or some other mechanism remains to be determined. Understanding this mechanism is of obvious clinical significance because the risk of

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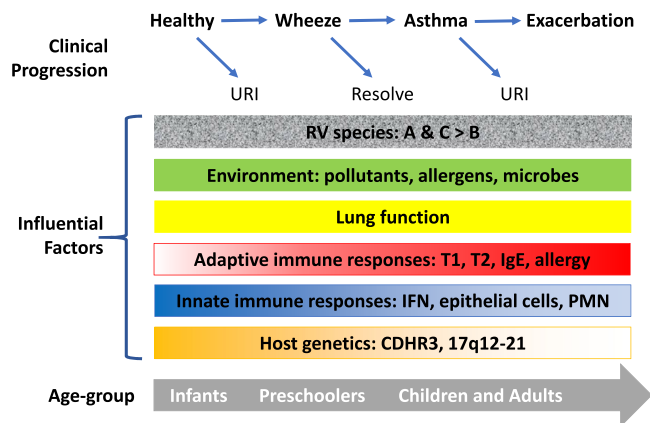


FIG 1. Factors that influence the probability of RV wheezing illnesses and exacerbations of asthma. URI, Upper respiratory infection.

having an exacerbation of asthma is greatly enhanced by a recent exacerbation.

In the omalizumab interventional trial, RV increased airway obstruction during the acute phase of the illness in the volunteers with asthma. Omalizumab prevented this reduction in lung function, providing direct evidence that IgE-mediated inflammation contributes to RV-induced airway obstruction in patients with allergic asthma. The likely mechanism is that omalizumab also reduced baseline airway inflammation, which underlines the importance of controlling allergic inflammation to reduce the risk for virus-induced exacerbations.

In the third article, Muehling et al⁹ used state-of-the-art tetramer analysis to describe effects of RV infection on circulating virus-specific and allergen-specific T cells during the 2 experimental inoculation studies described above. T cells were analyzed before and after inoculation using RV- and allergen-specific tetramers. One interesting finding in the preinoculation blood samples was that virus-specific T cells, induced by previous infections, were increased in asthma and their numbers were inversely associated with lower lung function. These cells had a memory T_H1 phenotype and expressed the PD1 antigen, which has been associated with cell activation and fibrosis in previous studies. These results raise the possibility that RV-specific memory T_H1 cells contribute to chronic airway inflammation, even in the absence of acute infection. One caveat is that causality cannot be determined in this observational study. It is also possible, for example, that a dysfunctional airway epithelium in asthma leads to more severe RV infections and a stronger T-cell antiviral response, but the virus-specific T cells do not contribute to airway obstruction or clinical symptoms.

In addition, experimental RV infection increased circulating virus-specific T_H1 cells, and to a lesser extent, increased allergen-specific T_H2 cells through a “bystander” effect. One week after inoculation, both RV-specific and allergen-specific T cells were inversely related to the FEV₁/forced vital capacity ratio. These results suggest that RV infections coordinately

activate virus-specific and allergen-specific T cells, and that both T_H1 and T_H2 inflammatory mechanisms contribute to RV-induced airways dysfunction in asthma.

Similarly, analysis of nasal cell transcriptional response in another recent report¹⁰ found that virus-induced increases in type 2 inflammatory genes and exaggerated type I IFN responses were both associated with progression from upper respiratory infection to asthma exacerbation. Moreover, in baseline samples, the ratio of these 2 indicators (type 2 inflammation/type I IFN response) was related to a significantly shorter time to exacerbation. Thus, the kinetics of the IFN response may be important: cells with greater baseline expression may be able to mount a brisk response during the early stages of infection to prevent viral replication and secondary induction of a stronger IFN response with associated adverse clinical effects.

In conclusion, these 3 innovative studies provide new and much-needed information about immune responses to RV and their relationship to RV wheezing episodes and exacerbations of asthma. Although we are still a long way from developing a safe, effective, and affordable antiviral for RV, insights into host immune responses to the virus are likely to identify new therapeutic strategies and targets to reduce the severity of RV illnesses and prevent exacerbations in patients with asthma. We are 3 steps closer to that goal.

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