Host response to human rhinovirus infection: toward targeted treatment strategies

Editorial Future Virology

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“Approximately 50% of (chronic obstructive pulmonary disease) exacerbations are associated with viral infections, and (the human rhinovirus) is, again, the dominant viral pathogen...”

Human rhinoviruses (HRVs) are responsible for up to 50% of common colds experienced annually [1]. Although these infections are usually mild and self-limiting, complications of HRV infections cause substantial morbidity in susceptible individuals. In addition to complications such as sinusitis or otitis media [2–5], respiratory viral infections are a major trigger for exacerbations of lower airway diseases, such as chronic obstructive pulmonary disease (COPD) and asthma [6]. Acute exacerbations of asthma and COPD cause significant morbidity and mortality, and account for over half of the total healthcare costs for each disease [7,8]. HRV infections account for approximately 60% of virally induced exacerbations of asthma [9–12]. Approximately 50% of COPD exacerbations are associated with viral infections, and HRV is, again, the dominant viral pathogen [13,14]. COPD exacerbations triggered by viral infections are more severe, and have longer recovery times than those linked solely to bacteria [13]. Thus, HRV-induced exacerbations of lower airway diseases are a major healthcare burden.

There have been few studies in adults examining treatment of exacerbations of known viral etiology, but studies in children with viral bronchiolitis suggest that current therapies used to treat asthma and COPD are of limited benefit in virally induced disease. Bronchodilators produce modest, short-term improvement but do not affect rates or duration of hospitalization [15,16]. Corticosteroids are ineffective in the treatment of HRV-induced colds [17,18], and asthmatics with prominent sputum neutrophils, suggestive of viral etiology, are poorly responsive to inhaled corticosteroids [19]. In addition, inhaled corticosteroids did not significantly reduce the increased lower airway inflammation in asthmatic subjects

after HRV infection [20]. Moreover, administration of prednisolone to children hospitalized with viral bronchiolitis did not reduce the duration of hospitalization [21]. Thus, while corticosteroids may reduce exacerbation frequency by helping to maintain better asthma control, there is little evidence that they are effective in combating virally induced exacerbations of asthma once they occur. Similarly, there is mixed evidence regarding the ability of inhaled corticosteroids to reduce exacerbations of COPD [22,23]. Although a pilot study suggested that the leukotriene receptor antagonist, montelukast, might have efficacy in reducing symptoms of postviral bronchiolitis, a larger study failed to confirm this effect [24].

Conventional treatments targeting specific symptoms of colds have consistent, but modest, effects on the symptom being targeted. Thus, topical anticholinergic drugs [25], or older antihistamines with anticholinergic effects [26], tend to reduce rhinorrhea by approximately 25–30%, and oral adrenergic agents have modest effects on nasal congestion. Overall, however, modest efficacy and, in some instances, troublesome side effects limit the usefulness of these approaches [27]. Clearly, therefore, new approaches to control the pathogenesis of HRV infections are required.

One strategy that has been explored is to target HRV binding, replication and spreading. The majority of HRV serotypes utilize intercellular adhesion molecule (ICAM)-1 as a cell-surface receptor [28], while the remainder of serotypes use members of the low-density lipoprotein (LDL) receptor family to gain cell entry. A soluble form of ICAM-1 (sICAM-1) administered intranasally, six times daily, to subjects beginning either 7 h before or 12 h after experimental HRV infection reduced symptom scores

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and nasal secretion weights, and reduced viral titer [29]. A similar proof-of-concept was also established using soluble fragments of the LDL receptor, which inhibited infection [30]. Practical issues of dosing and cost, however, have limited the clinical utility and development of these biological inhibitors of receptor binding. Capsid-binding drugs that bind to the hydrophobic pocket at the bottom of the canyon region of the viral capsid to modulate attachment of the virus to its receptor and/or subsequent uncoating, and cell entry of the viral genome, have also been studied. One such compound, pleconaril, modestly reduced the duration of HRV infections and symptom scores, but concerns arose, as this compound was found to induce cytochrome P450 enzymes [31]. Inhibitors of the picornavirus 3C protease, which is essential for viral replication owing to its role in cleavage of the viral polyprotein, have also been studied. One compound, rupintrivir, was tested as an intranasal spray, and reduced viral titer and significantly inhibited symptom scores by one-third [32]. This suggests that inhibition of 3C protease is a viable approach for therapy, and development of such compounds continues. At present, however, no antiviral agents are approved for the treatment of HRV infections or their complications.

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A second, largely unexplored potential therapeutic approach is to modulate the host response to HRV infection. The airway epithelial cell is the primary site of HRV infection [33,34], and it is known that HRV can spread to the epithelium of the lower respiratory tract [35]. By contrast to other viral types, however, HRV causes no overt epithelial toxicity either *in vitro* or *in vivo* [36,37]. Thus, it is likely that viral alterations of epithelial cell biology trigger the inflammatory changes that initiate the pathogenic response to the virus, and that it is the host response to HRV, rather than the virus itself, that is responsible for symptomatic outcomes. In support of this, HRV infection has been shown to induce epithelial production of a number of individual proinflammatory cytokines and chemokines [36,38–41], as well as molecules associated with host antiviral and immune responses [42,43]. Several of these molecules have also been detected in airway secretions during *in vivo* HRV infections [38,40,42–44]. Although these studies implicated individual proteins in the response to HRV, a better understanding of the pathogenesis of HRV infections has recently been achieved as a result of a comprehensive assessment of epithelial gene expression changes in response to HRV infection *in vivo*. Nasal epithelial scrapings were

obtained before and 2 days after inoculation with HRV or medium without virus, and total RNA was extracted. Microarray chips were used to analyze changes in the expression of more than 47,000 transcripts. After infection, 11,887 transcripts representing 6530 genes were found to be significantly different between the infected and placebo-inoculated groups [45]. Using an arbitrary threshold of a twofold change, 471 transcripts showed at least a twofold increase in expression, whereas 201 transcripts were decreased to levels of 0.5-fold or less, relative to control. There were few obvious functional groupings in the genes that were downregulated, but a substantial number of highly induced genes fell into discrete functional categories. These included genes for a number of chemokines of both the C–C and C–X–C families. Although some of these genes were anticipated based on prior literature, some were unexpected and are candidates for further study. Other groups included signaling molecules, molecules involved in adhesion and airway remodeling, and interferon-inducible genes. Overlapping with this latter category were a variety of gene products with known or potential antiviral functions. These data provide the first complete ‘roadmap’ of the host response to HRV infections, and identify several novel genes that require further study to evaluate their roles. The data also suggest several potential therapeutic approaches. One would be to target key proinflammatory chemokines to limit the airway inflammation induced by HRV infection. However, this approach requires a clear understanding of which mediators and inflammatory cell populations are inducing excessive inflammation, and which are essential for inducing antiviral immune responses. As neutrophil numbers correlate with symptom severity, both in simple colds and during viral exacerbations of asthma [46,47], one may suggest that inhibitors of neutrophil chemoattractants, such as CXCL8 and CXCL5, provide a therapeutic approach. Given the complexity of the proinflammatory response, however, targeting individual chemokines or chemokine receptors may be both time consuming and relatively ineffective. Other strategies could involve targeting HRV-specific epithelial signaling pathways. Perhaps the most promising approach, however, is to enhance the endogenous expression of, or to exogenously supplement, key host antiviral defense pathways. For example, the two genes most upregulated among the antiviral products in the gene array were viperin and type II nitric oxide synthase (iNOS). The same study demonstrated for the

first time that viperin is, indeed, a component of the host antirhinovirus response, as knock-down of viperin led to a threefold increase in viral replication [45]. Interestingly, in subjects with experimental HRV infections, both epithelial iNOS and levels of airway-exhaled nitric oxide (NO) increase [43,48]. Importantly, subjects who show the greatest exhaled NO levels had the lowest symptoms and cleared the virus more rapidly [48]. Consistent with this effect, NO inhibits HRV replication in epithelial cells and can also inhibit HRV-induced chemokine production independently of its effects on replication [49–51]. Inhibition of chemokine production by NO in HRV-infected epithelial cells is due to NO-mediated inhibition of activation and nuclear translocation/binding of the transcription factors nuclear factor- κ B and interferon response factor-1 [51]. The broad-ranging inhibition of HRV-induced epithelial chemokine production by NO, together with

its effects on HRV replication, clearly suggests a potential therapeutic utility of NO donors in HRV infections.

In summary, therefore, recent insights into the pathogenesis of HRV infections strongly support the concept that modulating aspects of the host response to HRV represents a rational approach to identify new therapeutic strategies for the treatment of HRV infections and their lower airway complications.

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