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Review

Upper airway viral infections

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Abstract

Upper airway viral infections (URI) are a major cause of absence from school and work. Although morbidity is low in most of the subjects, the complications of URI, including otitis media, sinusitis and exacerbations of asthma and chronic obstructive pulmonary disease (COPD) have an enormous health impact. Despite the major health care consequences associated with these complications, our understanding of how URI trigger upper airway symptoms and cause exacerbations of lower airway diseases remains limited. This article reviews our current understanding of the pathogenesis of URI, and of viral exacerbations of asthma and COPD, and considers host defense parameters that may regulate susceptibility to disease exacerbations. We will also consider current and potential therapeutic approaches for the treatment of URI and their lower airway complications.

Keywords: Common cold; Host defense; Epithelial cells; Asthma; COPD; Rhinovirus

Contents

1. Introduction: Upper respiratory viral infections (URI) and their complications

URI, manifesting as the clinical syndrome we refer to as the common cold, is the most frequent acute respiratory illness experienced by humans. Adults will experience 2 to 4 colds each year, while children experience 6 to 10. As a result of this, according to the Centers for Disease Control and Prevention, 22 million school days are lost annually in the United States due to colds. Although common colds can be caused by a variety of different virus types, including coronaviruses, parainfluenza virus and respiratory syncytial virus (RSV), the predominant viral pathogens, particularly in the autumn season, are human rhinoviruses (HRV) [1–3].

Although simple colds in healthy individuals are associated with little morbidity, it has long been known that rhinovirus infections can precipitate or exacerbate other diseases, including otitis media [4], and sinusitis [5,6]. More recently, growing evidence also has implicated URI as the predominant risk factor associated with exacerbations of both asthma and chronic obstructive pulmonary disease (COPD).

In the case of asthma, there is a clear temporal relationship between increase in hospitalizations for

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asthma exacerbations and outbreaks of URI [7,8], with a major spike in early September, which is the peak time for HRV infections. Moreover, prospective studies using RT-PCR to assist in viral detection have demonstrated that common respiratory viruses are associated with up to 60% of asthma exacerbations in adults and over 80% of exacerbations in children [9,10]. Although several viral types were found during these exacerbations, the dominant pathogen detected was HRV. HRV also was the most common viral pathogen associated with asthma attacks in young children over 2 years of age presenting in the emergency room [11,12].

There also has been a growing appreciation regarding the important role of URI in triggering exacerbations of COPD [13]. Recent studies indicate that about half of all COPD exacerbations are associated with viral infections, and that HRV is, again, the dominant viral pathogen [14,15]. Interestingly, respiratory viral infections are associated with COPD exacerbations that are more frequent, severe and have longer recovery times [14].

The ability of URI to serve as precipitants for exacerbations of asthma and COPD has enormous consequences in terms of both health care costs and patient's quality of life. The total health care costs for asthma in the United States for the year 2000 was estimated at $12.1 billion [16], and acute exacerbations account for half of the total health care costs for the disease [17,18]. Similarly, acute exacerbations of COPD are a major cause of hospitalizations and death, and account for 70% of health care costs for the disease [19]. Moreover, exacerbation frequency is a major determinant of health status and quality of life for COPD patients [20].

Despite the high incidence and serious complications of URI, the mechanisms by which viruses induce upper airway symptoms, or cause exacerbations of lower airway diseases, remain poorly understood. Although it is possible that different viral types may induce these outcomes via variable mechanisms, it seems more likely that common aspects of viral pathogenesis dominate. Given that HRV is the major viral pathogen associated with colds and exacerbations of asthma and COPD, we will focus on the current status of our knowledge of the response to HRV infection as representative of viral pathogenesis, indicating differences with other viral types when appropriate.

2. Viral infection and airway inflammation

It is clear that URI are associated with increased airway inflammation. In particular, HRV infections lead to increased numbers of neutrophils and lymphocytes in the upper airways [21–23]. HRV infections also induce neutrophilic recruitment to the lower airways in subjects with asthma [24,25]. Consistent with this virally induced pattern, many acute asthma exacerbations seen in the clinical setting are characterized by increased levels of neutrophils and lymphocytes in the airways [26–28]. Asthmatics who display this neutrophilic profile show a poor response to inhaled corticosteroids [29]. Similarly, while stable COPD is associated with a characteristic infiltration of the bronchial mucosa with $CD8^+$ T lymphocytes and macrophages, severe exacerbations of COPD are associated with increased neutrophilic and lymphocytic influx [30,31]. It seems reasonable, therefore, to infer that viruses may trigger exacerbations of asthma and COPD by enhancing already existing inflammation in the lower airways.

The mechanisms by which viral infections are able to enhance upper, and lower, airway inflammation are not fully defined, but growing evidence supports the concept that viral modulation of epithelial function may initiate the inflammatory response.

The airway epithelial cell is the primary target for inhaled pathogens and expresses receptors for several viral types. Indeed, the epithelial cell is the only cell type in which HRV has been detected, thus far, by *in situ* hybridization [32,33], during *in vivo* infections. Moreover, there is now strong evidence that, upon experimental nasal inoculation with HRV, virus spreads to infect epithelial cells in the lower airways [34,35], suggesting that epithelial infection may also directly initiate lower airway inflammatory responses. In contrast to viruses such as influenza and RSV, HRV infections do not cause overt epithelial toxicity [36,37]. Thus, while the cytotoxic effects of influenza and RSV may contribute to the severity of symptoms, it seems reasonable to assume that alterations of epithelial biology represent a common pathway of symptom development by multiple virus types. In support of this concept, infection of epithelial cells by HRV has been shown to generate a wide variety of proinflammatory chemokines and cytokines, including IL-8 (CXCL8), ENA-78 (CXCL5), IP-10 (CXCL10), RANTES (CCL5), IL-1, IL-6 and IL-11 [23,37–42]. Given that several of these products also are detected in airway secretions during HRV infections *in vivo* [23,38,42–44], it is likely that they contribute to recruitment and activation of inflammatory cells during infections. The ability to induce proinflammatory cytokine production from epithelial cells is also shared by other viruses. For example, influenza infection induces epithelial production of IL-6, IL-8 and RANTES [45], while RSV infections induce expression of a wide range of chemokine genes [46].

Although there is a clear potential for these chemokines and cytokines to induce inflammation, the profile of products described clearly has the capacity to recruit a plethora of inflammatory cell types to the airways. Despite this, a relatively selective cellular profile is seen during infections *in vivo*. It is unclear what other parameters regulate this limited pattern of inflammatory cell recruitment. It also must be acknowledged that our understanding of the mechanisms by which virally induced chemokine production occurs remains limited. In the case of HRV infections, some chemokines are induced quickly after viral exposure and do not seem to require viral replication [41,47], while other genes are not induced until several hours post-infection and are absolutely dependent upon replicating virus [23,39]. Although both