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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.

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

phosphatidylinositol 3-kinase and mitogen activated protein kinase pathways have been implicated in viral induction of chemokines [47–49], the early signaling events induced by virus remain poorly elucidated. Similarly, while the viral replication intermediate, double-stranded RNA, and the rhinovirus 3C protease both have been implicated as mediators of late, replication dependent events [23,50,51], the pathways by which such products induce responses are not well defined. Moreover, while it is clear that viral induction of some cytokines and chemokines occurs via transcriptional pathways involving NF-κB and/or interferon regulatory factor [23,52], our understanding of the control of transcriptional and post-transcriptional regulation of epithelial cytokine and chemokine production in response to viral infection also is limited and requires further study. Delineating those aspects of signaling that may be unique for viral induction of chemokines may provide a rational basis for targeted interventions, while studies with selective chemokine or chemokine receptor antagonists will be required to provide a definitive answer on which are the key epithelial mediators involved in disease pathogenesis.

Once viral infection of the epithelium initiates a proinflammatory process, subsequent production of other mediators that are not of epithelial origin may further contribute to the inflammatory status of the airways. These mediators may be derived from plasma or from other cell types within the airway mucosa. Of the mediators assessed thus far, some are relatively virus-specific, while others are observed with colds induced by multiple viral types. For example, while RSV infections have been reported to be associated with the generation of virus-specific IgE and increased release of histamine into nasal secretions [53], levels of histamine are not increased in airway secretions during HRV infections [22]. Moreover, while older antihistamines that display anticholinergic and sedative properties do reduce rhinorrhea during colds, second generation antihistamines lacking these side effects are ineffective [54]. By contrast, other mediators, such as kinins and leukotrienes have been associated with infections due to more than one type of common respiratory virus [22,55–57]. Defining the role of each of these mediators in disease pathogenesis will, again, require studies with effective and selective antagonists.

3. Host defense responses

Several factors are likely to play a role in determining the severity of the clinical outcome to upper airway viral responses, including the susceptibility of patients with asthma or COPD to experience lower airway exacerbations. Such factors include pre-existing immunity to a particular viral strain and, in the case of lower airways, the degree of disease control at the time of infection. Another important factor is likely to be the variability of the individual host immune and antiviral response to infection. Although both innate and specific immunity contribute to the host response to infection, it appears

as though the innate response is dominant early after infection and is more likely to help regulate the symptomatic response. For example, while HRV infections elicit antigen-specific humoral and cellular immune responses, these are usually not detectable until after disease symptoms have resolved [58].

As may be expected based on its central role in viral infection, the epithelial cell is a significant contributor to the innate response to infection. As noted above, infected cells release several cytokines and chemokines that can recruit, and activate, cells of the immune system to the airways. In addition, epithelial production of nitric oxide (NO) appears to play an important role in host antiviral responses [59]. Infection of cultured epithelial cells with any of several common respiratory viruses leads to marked upregulation of inducible nitric oxide synthase (iNOS) and increased generation of NO. A similar response occurs during experimental HRV infections *in vivo*, in that levels of epithelial iNOS induction correlate with levels of exhaled NO. Interestingly, in this study, subjects with the highest levels of exhaled NO cleared virus more rapidly and had lower symptoms [60]. A rationale for this is provided by several studies showing that NO exerts direct antiviral activity against several common respiratory viruses, in part by nitroslyating key thiol residues in viral proteases. Moreover, it has been shown that NO also inhibits virally induced generation of several cytokines and chemokines from epithelial cells [59].

It also should be noted that infection of epithelial cells with HRV induces the production of human β-defensin-2 (HBD-2) and HBD-3 [61]. These peptides are chemotactic for immature dendritic cells expressing CCR6, as well as other cell types contributing to the immune response, and likely play an important role in linking innate and specific immunity to HRV [62]. HBD-3 also can reduce the extent of influenza infections by blocking the fusion of the virus with cell membranes [63].

As viral replication progresses, and intact virus is released into airway secretions, it can interact with other cell types that may further contribute to the immune response. Presumably, for example, dendritic cells initiate antigen presentation to T cells in the airways or lymph nodes to initiate the specific immune response. In addition, monocytes and macrophages may release additional cytokines, including interferons that can stimulate a variety of interferon (IFN)-stimulated genes (ISGs) that collectively limit virus replication and spread.

4. Therapeutic approaches

Traditional approaches to mitigate the effects of URI have focused on symptomatic relief, although such approaches have generally had modest success. The topical anticholinergic, ipratropium bromide reduces rhinorrhea, an effect mimicked to some degree, as noted above, by older "first generation" antihistamines that are known to also have anticholinergic properties. Similarly oral adrenergic

drugs have modest benefit in terms of reducing nasal blockage, while topical agents have a greater efficacy but suffer from issues of rebound [54]. A somewhat greater reduction in total symptoms was observed in experimental HRV infections when a combination of IFN-α2b, together with the first generation antihistamine, chlorpheniramine, and ibuprofen was administered beginning 24 h after viral challenge [64]. Although this represents an important proof of concept regarding the effectiveness of combining an antiviral compound with conventional compounds for symptomatic relief, the practical utility of this combination is limited by cost factors.

There is also a growing literature on the use of "natural' remedies for the treatment of colds. Although the rationale for the use of zinc in the treatment of colds is not well established, multiple studies have evaluated the effectiveness of various zinc salts in this regard. Overall, the results of these studies have been inconclusive. A recent, well-controlled trial, however, found that zinc salts had an extremely modest effect in reducing symptoms of experimental HRV infections and was ineffective in natural colds [65]. Similarly, echinacea and ginseng have been widely reported as herbal remedies for colds. Most of the trials to evaluate such agents have been small and have generated conflicting data. Recent randomized trials with relatively large number of subjects reported modest efficacy of a ginseng extract in reducing the frequency of natural colds [66], but found no significant effect of an extract of echinacea in experimental HRV infections [67]. A major issue in regard to trials of herbal remedies, of course, is that there is no standardization of extracts used across studies. Indeed, given that the identity of any proposed "active" ingredient is unknown, it is impossible to know what to standardize.

All of the above trials have been limited to analyzing effects on nasal symptoms, and have never evaluated effects on viral exacerbations of asthma or COPD. Given the data reported, however, it seems unlikely that they will provide any major benefit. Indeed, an interesting question is whether drugs that are currently used for the treatment of asthma and COPD have any beneficial effects during viral exacerbations. There is no doubt that the use of corticosteroids, long acting β-agonists, or leukotriene receptor antagonists, alone or in combination, to maintain optimal asthma control has proven efficacious in reducing number of asthma exacerbations, and the use of oral corticosteroids early in exacerbations helps prevent relapses. Effects on basal inflammation, however, may not necessarily translate to effects on viral-specific inflammation, and there have been no defined studies of the effects of these medications during asthma or COPD exacerbations of known viral origin. Corticosteroids have little efficacy in HRV-induced colds [68], and it is of interest that asthmatics who display prominent sputum neutrophilia, perhaps indicative of viral etiology, are poorly responsive to inhaled corticosteroids [29]. Because of these limitations, alternative therapeutic approaches to virally induced airway disease continue to be sought.

An obvious strategy is to use antiviral approaches. Influenza vaccine is clearly effective in reducing upper airway symptoms, and in preventing lower disease exacerbations, induced by this virus during the winter months. Unfortunately, vaccination approaches are not feasible for HRV, given the large number of viral serotypes, and have, thus far, proven unsuccessful in the case of RSV infections. Neutralizing antibody prophylaxis has proven effective in preventing RSV-induced bronchiolitis but cost factors limit a broader utility and, again, major feasibility issues would arise with using this approach for HRV. Selective antiviral approaches have shown more promise. In the case of influenza, neuraminidase inhibitors have been available for several years and have proven clinical efficacy in reducing development and severity of symptoms. At least two approaches also have been used to develop potential antiviral agents against HRV. The novel capsid-binding inhibitor, pleconaril, prevents viral uncoating. In natural colds, oral pleconaril (400 mg) administered three times daily led to a significant, but modest reduction in symptoms and also shortened the reported duration of colds [69]. Concerns regarding effects on cytochrome P450 3A4, however, precluded further development as an oral treatment. The alternative antiviral approach used for HRV infections has targeted inhibition of the viral 3C protease, which is necessary for cleavage of the viral polyprotein and, thus, replication. Topical administration of one 3C inhibitor, ruprintrivir, significantly inhibited symptoms in experimental HRV infections even when administered beginning 24 h after infection, although multiple daily dosing was required [70]. Neither of these drugs has been evaluated for their ability to limit HRV-induced exacerbations of lower airway diseases.

5. Conclusions

Upper respiratory tract viral infections and their complications lead to a significant burden on health care systems throughout the world. Current treatments are less than ideal, and a greater insight into the molecular basis by which common viruses induce both upper and lower airway symptoms is needed if alternative therapeutic approaches are to be developed rationally. The delineation of which specific cytokines and chemokines are key contributors to disease pathogenesis, and elucidation of signaling pathways selective for viral modulation of epithelial cell function may identify novel targets for therapy. Alternatively, endogenous enhancement of key host antiviral and host defense molecules, or the topical administration of such molecules may provide alternative approaches to reduce the sequelae of viral infection.

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