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Viral-associated exacerbations of asthma and COPD
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Exacerbations of asthma and chronic obstructive pulmonary disease are major burdens on the healthcare system, and contribute significantly to the mortality and morbidity associated with these diseases. Upper respiratory viral infections are associated with the majority of such disease exacerbations. The past few years have seen advances in the mechanisms by which viral infections induce pro-inflammatory chemokine production, and in our understanding of host antiviral and anti-inflammatory defence pathways that might regulate responses to infection. A more comprehensive understanding of the molecular basis of these processes could elucidate new therapeutic approaches to reduce the devastating impact that these exacerbations have on quality of life and healthcare costs.

Introduction
Exacerbations of asthma and chronic obstructive pulmonary disease (COPD) can be defined as ‘a worsening of the patient’s condition, beyond the day-to-day variability associated with the disease, that is sufficient enough to require a change in management, or to seek emergency medical intervention’ [1,2]. Exacerbations of both asthma and COPD represent a major financial burden on the healthcare system as a result of costs associated with hospitalizations, increased medication usage, and days lost from work and school. In the case of asthma, exacerbations are responsible for 50% of the total healthcare costs, and for the deaths of 5000 Americans each year [3]. Similarly in the case of COPD, exacerbations account for 70% of healthcare costs, as well as being a substantial cause of hospitalizations [3]. More importantly, recurrent exacerbations of COPD result in a loss of lung function, thus hastening the progression of a currently fatal disease [4].

In the current article, we discuss the evidence that common respiratory viruses are a major trigger factor for exacerbations of asthma and COPD. We also review the current state of our knowledge on the mechanisms by which viruses might trigger such disease exacerbations, as well as the factors that could regulate susceptibility to viral exacerbations. Finally, we consider the status of current therapies in the treatment of viral exacerbations of asthma and COPD, and discuss potential novel approaches to treatment.

Evidence for viral infections and exacerbations of asthma
The association between upper respiratory viral infections (URIs) and exacerbations of asthma has been recognized for decades, but it was not until the development of RT–PCR methods for improved detection of viruses that the extent of this association became clear [5,6]. Indeed, URIs are the principal risk factor associated with asthma exacerbations [3,7], and are associated with as many as 80–85% of asthma exacerbations in children and adolescents [5,8–10], and approximately 40–60% of exacerbations in adults [3,5]. There is a clear temporal relationship between URIs and asthma exacerbations in children. The peak of hospitalizations occurs in September, shortly after the return to school and at the peak time of year for human rhinovirus (HRV) infections [10,11]. Consistent with this, HRV is associated with approximately 60% of viral-triggered exacerbations [6,10,12]. Other viral types associated with asthma exacerbations include influenza, coronaviruses, parainfluenza and respiratory syncytial virus. Epidemiological evidence suggests that viruses may also interact with other causal factors linked to asthma exacerbations, such as allergens and pollution. Studies of the interaction between experimental allergen exposure and experimental virus infection, however, have generated mixed results. In a murine model, influenza infection aids allergen sensitisation and enhances airway inflammation [13]. In humans, however, chronic low-dose allergen provocations did not alter subsequent lower airway responses to HRV infection [14] whereas, in the upper airways, acute allergen challenge delayed onset and shortened the duration of common colds.

Evidence for viral infections and exacerbations of COPD
By 2020, COPD is predicted to become the third most common cause of death worldwide and the fifth leading cause of disability [15]. Exacerbations of COPD occur more commonly in patients in the advanced GOLD II or III stages [16]. (GOLD stands for the Global Initiative for Chronic Obstructive Lung Disease, and ranks disease in...
Mechanisms of viral-associated exacerbations

The specific mechanisms by which viruses invoke exacerbations of asthma and COPD remain unclear. Growing evidence, however, suggests direct infection of the lower respiratory tract, leading to a robust host inflammatory response, and an increase in bronchial hyperresponsiveness [6]. Because HRV is the major viral type associated with exacerbations, we focus on this virus as a prototype for the mechanisms by which viruses exert their effects. HRV infects both the upper and lower respiratory tracts, with the principal site of infection being the airway epithelial cell [22]. Although it has been reported that some strains of HRV can cause epithelial cell death in cultures grown at low density [23], the majority of studies found no overt cytotoxicity either in vitro or in vivo. Epithelial cells are clearly the major site of HRV infection and sustain prolonged replication [24,25]. Although HRV can bind to, and enter, a variety of other cell types in vitro, including fibroblasts, monocytes and macrophages [25,26], the contribution of these individual cell types to pathogenesis in vivo is still unclear.

HRV infection of cultured human airway epithelial cells results in production of several pro-inflammatory cytokines and chemokines, including interleukin (IL)-1, IL-6, IL-8, interferon (IFN)-inducible protein of 10 kDa (IP-10), regulated on activation normal T-cell expressed and secreted (RANTES), granulocyte macrophage-colony stimulating factor and eotaxin [24–26]. This profile of mediators could enhance airway inflammation via the recruitment and retention of a wide range of inflammatory cells (Figure 1) that contribute to the pathogenesis of exacerbations [25]. Moreover, some of these chemokines have also been detected in airway secretions during viral infections [27]. Despite the potential for epithelial chemokines to recruit multiple cell types to the airways, experimental HRV infections and viral exacerbations of asthma and COPD are dominantly associated with selective recruitment of neutrophils and lymphocytes [4]. This implies that mechanisms must exist to limit the cell types recruited, but these mechanisms are not well understood. It has recently been reported that increased IL-10 gene expression is observed during viral exacerbations of asthma, suggesting that immunoregulatory effects of IL-10 include suppression of eosinophil influx [28].

Viral infections might also contribute to disease exacerbations by enhancing mucus production. HRV infection of epithelial cells has been shown to result in increased mRNA expression for MUC2, MUC3, MUC5AC, MUC5B and MUC6. Importantly, concentrations of MUC5AC and total mucin were also increased in supernatants and lysates from epithelial cells [29].

Although viral infection modulates epithelial cell function, the viral-induced signalling mechanisms involved are just beginning to be elucidated. Induction of chemokines such as IL-8 occurs early after HRV binding and does not require viral replication, but instead depends upon activation of both phosphatidylinositol 3-kinase and the p38 mitogen-activated protein kinase pathway [30]. Given that intercellular adhesion molecule-1 (ICAM-1), the receptor for the majority of HRV serotypes, has no inherent kinase activity or recognition motifs for receptor-associated kinases, it was unclear how viral binding initiated this signalling cascade. However, it has recently been shown that HRV binding to ICAM-1 leads to an association with the spleen tyrosine kinase Syk. This association is mediated via the cytoskeletal linker protein ezrin, which binds both ICAM-1 and Syk. Formation of this complex leads to activation of Syk, with subsequent downstream activation of the p38 mitogen-activated protein kinase pathway and increased expression of IL-8. Thus, Syk is an important signalling component in early virus responses [31**].

In contrast to the rapid generation of IL-8, other responses to viral infection, such as generation of RANTES or IP-10, do not occur until several hours after viral exposure and are absolutely dependent upon viral replication. This has led to intense investigation of the role of viral replication products, particularly double-stranded RNA (dsRNA), in cell responses. It is known that dsRNA mimics several responses to viral infection and triggers host anti-viral responses. Initially, dsRNA was thought to be recognized exclusively by Toll-like receptor (TLR)3 [32], but genetic deletion of TLR3 did not alter viral pathogenesis or host adaptive antiviral responses to several viruses [33]. This apparent conundrum was resolved with the demonstration that two intracellular RNA helicases — retinoic
acid inducible gene (RIG-I) \cite{34,35} and melanoma-differentiation-associated gene 5 (mda-5) \cite{35} — can also bind to dsRNA. The helicase domain of these proteins binds dsRNA, while a caspase activation and recruitment domain (CARD) permits binding of a downstream adaptor protein. This downstream mitochondrial-associated protein was identified independently by four groups and is known by the names CARDIF (CARD adapter inducing interferon-β), MAVS (mitochondrial antiviral signalling), IPS-1 (interferon-β promoter stimulator-1) and VISA (virus-induced signalling adapter) \cite{36}. CARDIF binds to several proteins and induces both classical nuclear factor-κB (NF-κB) pathway activation and IKKe/Tank-binding kinase 1-mediated activation of interferon response factors \cite{36}. These pathways are also activated when dsRNA binds to TLR3 (Figure 2). Controversy now exists regarding the relative roles of TLR3, RIG-I and mda-5 in viral recognition. It has been suggested that different viral types may preferentially utilize one of these three recognition proteins. To further complicate this picture, RIG-I also recognizes single-stranded RNA (ssRNA) containing 5′-phosphates. Indeed, it has been reported that influenza A does not generate dsRNA but, rather, activates RIG-I via binding of genomic viral ssRNA bearing 5′-phosphates \cite{37,38}. Further studies are needed to clarify the preferential utilization of different intracellular recognition molecules by different viral types, and to determine if this also varies with cell type.
Susceptibility to exacerbation

What determines susceptibility of a given individual to experience disease exacerbation upon viral infection is not clear but multiple factors are probably involved. Those subjects whose underlying disease is well controlled are less likely to experience an acute viral-mediated exacerbation. Similarly, pre-existing specific immunity to a given pathogen will reduce the likelihood of that pathogen triggering an exacerbation. Epithelial contributions to host innate antiviral immunity might also play a role. Recent reports suggest that bronchial epithelial cells from asthmatic subjects show impaired production of both IFNβ and type 3 IFNs [39**,40**], and that this plays a role in the increased susceptibility of asthmatic subjects to lower airway disease. Additional studies are needed to confirm these data and to put such defects in the context of why specific asthmatic subjects experience exacerbations. Moreover, although type 1 and type 3 IFNs contribute to host defence mainly via induction of numerous IFN-stimulated genes (ISGs) that collectively limit virus replication and spread, there is a precedent for several viruses, including HRV, to induce ISGs independently of IFN induction [24,41].
Nitric oxide (NO) also appears to be an important component of the host antiviral response because it exerts direct antiviral activity against several viruses associated with exacerbations of asthma and COPD, and also inhibits the viral-induced generation of several cytokines/chemokines from epithelial cells [42]. Viral infection of epithelial cells increases expression of inducible NO synthase (iNOS) and, during in vivo HRV infections, epithelial iNOS induction correlates with levels of exhaled NO. Moreover, subjects with the highest levels of exhaled NO cleared virus more rapidly and had fewer symptoms than those who exhaled lower levels [43].

**Treatment of exacerbations**

Corticosteroids are crucial in the treatment of asthma [44] and, when used alone or in combination with long-acting β-agonists or leukotriene receptor antagonists, they are known to improve asthma control and, thereby, reduce the number of exacerbations.

Acute asthma exacerbations tend to be treated with oxygen, inhaled short-acting β2-adrenoceptor agonists, and intravenous or oral corticosteroids [44]. Although use of oral corticosteroids early in exacerbations can reduce subsequent relapse [44], there have been few studies looking specifically at exacerbations of known viral etiology. Corticosteroids are ineffective in the treatment of HRV-induced colds and current evidence would suggest that they are of limited efficacy in viral-induced exacerbations of asthma. Asthmatics with prominent sputum neutrophilia, perhaps indicative of viral etiology, are poorly responsive to inhaled corticosteroids [45], and inhaled corticosteroids did not significantly reduce lower airway inflammation induced by HRV infection of asthmatic subjects [46]. Moreover, administration of prednisolone to children hospitalized for viral-induced episodes of wheezy bronchiolitis did not reduce the duration of hospital stay [47]. Combination therapies of inhaled anticholinergic agents with short-acting β2-adrenoceptor agonists have been reported to be more effective against exacerbations in school children [44]; furthermore, a leukotriene receptor antagonist decreased asthma exacerbations in 2- to 5-year-old patients with intermittent asthma [48]. Nedocromil sodium and inhaled corticosteroids might also be of limited benefit in asthma exacerbations in children [49]. It must be noted, however, that most of these studies did not discriminate between exacerbations of viral and non-viral origin.

Although there is conflicting evidence over whether inhaled corticosteroids reduce exacerbations of COPD, oral corticosteroids appear to hasten recovery from certain exacerbations [17]. Combined therapy with corticosteroids and long-acting β-adrenoceptor agonists has been shown to reduce the number of exacerbations in patients with COPD, presumably by improving baseline control [50]. Again, however, there have been no studies specifi-

cally examining the effects of corticosteroids, alone or in combination with long-acting β-adrenoceptor agonists, during COPD exacerbations of known viral etiology. Similarly, although antibiotic therapy is widely used in exacerbations of COPD, their utility in virally triggered exacerbations is questionable.

Antiviral approaches appear to be a logical alternative to the treatment of viral exacerbations of asthma and COPD, and influenza vaccine is clearly effective in preventing exacerbations triggered by this virus. Vaccination approaches have not been successful for respiratory syncytial virus, however, and are not feasible for HRV, given the large number of viral serotypes. Antiviral agents are available for influenza, and neuraminidase inhibitors have proven clinical efficacy in reducing the severity of symptoms during influenza infections. By contrast, antiviral approaches targeting HRV are still in development and have not yet been applied to viral exacerbations of asthma or COPD.

If the assumption that an over-exuberant host inflammatory response to viral infection plays a key role in disease exacerbation is valid, several potential therapeutic approaches can be suggested. The first would be to identify specific viral signaling pathways that would be targets for intervention. These could include, for example, specific early signaling pathways involving the spleen tyrosine kinase Syk, or pathways triggered by viral interactions with the intracellular RNA helicases. Although targeting specific chemokines or chemokine receptors, such as CXCR3 or CXCR1/2, might also prove an attractive target, it remains to be determined which chemokine/chemokine-receptor systems are particularly important in disease pathogenesis. Finally, enhancement of endogenous host antiviral pathways, or topical administration of drugs such as nitric oxide donors, could provide alternative approaches to reduce virally induced inflammation.

**Conclusions**

There is an urgent need for additional therapeutic approaches to combat viral exacerbations of asthma and COPD. Although the past few years have seen a significant increase in our understanding of how viruses cause exacerbations, much remains to be learned. The complex signalling pathways triggered upon viral infection are not completely understood but, once delineated, could provide novel therapeutic targets. In addition, better understanding of host innate antiviral mechanisms could provide an alternative therapeutic approach if such pathways can be stimulated.

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