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Host immune responses to rhinovirus: Mechanisms in asthma

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Abstract

Viral respiratory infections can have a profound effect on many aspects of asthma including its inception, exacerbations, and, possibly, severity. Of the many viral respiratory infections that influence asthma, the common cold virus, rhinovirus, has emerged as the most frequent illness associated with exacerbations and other aspects of asthma. The mechanisms by which rhinovirus influences asthma are not fully established, but current evidence indicates that the immune response to this virus is critical in this process. Many airway cell types are involved in the immune response to rhinovirus, but most important are respiratory epithelial cells and possibly macrophages. Infection of epithelial cells generates a variety of proinflammatory mediators to attract inflammatory cells to the airway with a subsequent worsening of underlying disease. Furthermore, there is evidence that the epithelial airway antiviral response to rhinovirus may be defective in asthma. Therefore, understanding the immune response to rhinovirus is a key step in defining mechanisms of asthma, exacerbations, and, perhaps most importantly, improved treatment.

Keywords

Asthma; exacerbation; rhinovirus; immune response to virus; pathogenesis

The role of respiratory infections in asthma has always been of clinical interest and importance, but their overall contribution to this disease has, until recently, been underappreciated. With the use of highly sensitive and specific molecular diagnostic and detection methods, the identification of infectious organisms has increased, and with these findings has come a greater and clearer understanding of the contributions of specific respiratory infections to asthma. From a wide variety of studies, the common cold virus, rhinovirus, has emerged as a key and perhaps central microorganism in many aspects of asthma. For example, recent studies have pointed to the importance and relevance of symptomatic infections with rhinovirus early in life as a major factor in recurrent wheezing and possibly even as a sentinel event in the pathogenesis of asthma.^{1,2} Equally important, and better characterized, is the demonstration that rhinovirus infections are the major cause of asthma exacerbations, accounting for 50% to 80% of all such attacks in both children and adults.^{3–5} Finally, recent observations have raised the possibility that the presence of rhinovirus in the lower airway may be a contributor to disease persistence and severity.⁶

To understand more fully how this apparently innocuous respiratory virus may lead to pathogenic events in asthma, and to develop more specific treatments, it is instructive to define, as well as possible, the immune response to rhinovirus and then translate this

information in terms of alterations in airway inflammation and asthma control. Furthermore, it is helpful to determine whether factors in the immune responses to rhinovirus are attenuated in some individuals with asthma and to ascertain whether these abnormalities increase their susceptibility to untoward effects of the virus.

In this review, we focus on what is known about the immune response to rhinovirus with *in vitro* models and observations from *in vivo* studies, and then discuss how these findings may relate to asthma exacerbations and possibly disease pathogenesis. In addition, we explore the possibilities that some patients with asthma may have abnormal antiviral responses to rhinovirus, and we consider how such deficiencies may play a role in the ability of this virus to exacerbate asthma. Finally, we discuss current treatment in terms of further understanding the immune response to virus, then speculate on the potential for novel interventions to regulate specifically and possibly more effectively the immune response to rhinovirus to thus prevent a loss of asthma control.

RHINOVIRUS

Rhinovirus is a genus of positive, single-stranded RNA viruses of the family Picornaviridae. Thus far, there are >100 rhinovirus serotypes identified, with serotype defined on the ability of a given serum to neutralize growth of a given strain of virus in cell culture.⁷ The rhinovirus capsid, which protects the central RNA core, is composed of 60 copies of each of 4 structural proteins. Virus protein 1 (VP1), VP2, and VP3 are located on the capsid surface and are responsible for its antigenic diversity.⁸ The fourth protein, VP4, is located inside the virus and anchors the RNA core to the viral capsid.⁹ The VP1 protein is the most surface-exposed of the rhinovirus capsid proteins, and it contains a number of major epitopes recognized by neutralizing antibodies.¹⁰ Analysis of genetic sequence variations in the *VP1* gene has shown close concordance with the known serotypes.¹⁰ Serotypes have classically been divided on the basis of susceptibility to antiviral agents into 2 groups—human rhinovirus (HRV)-A (susceptible) and HRV-B (not susceptible)—which have been found to correspond with *phylogenetic* analysis of the VP4/VP2 sequences.^{11,12} With the use of increasingly sophisticated techniques, a novel genetic cluster, HRV-C, has been identified in infants hospitalized with respiratory illness.^{12,13} The role and contribution of this new rhinovirus class to respiratory illnesses and asthma awaits further work.

Rhinovirus infections typically cause upper respiratory symptoms in the common cold, including rhinorrhea, sore throat, nasal congestion, sneezing, cough, and headache. In addition, rhinovirus is also the pathogen most commonly recovered in acute exacerbations of asthma. Moreover, it has been long recognized that hospital admissions for asthma correlate with the seasonal peaks of rhinovirus.³ In addition, rhinovirus is the most frequently identified virus in children hospitalized for wheezing episodes outside *respiratory syncytial virus (RSV)* season and especially after age 3 years.¹⁴

Rhinovirus was previously thought to infect primarily upper airway epithelium because optimal replication occurs between 33°C and 35°C, below the core temperature of the conducting airways and lung parenchyma.¹⁵ However, temperatures found throughout the lower airway lumen will also allow rhinovirus to replicate effectively.^{16,17} Rhinovirus also replicates equally well *ex vivo* in cultured epithelial cells (ECs) derived either from the upper or lower airway, and rhinovirus replication has been detected in lower airway ECs and secretions after experimental inoculation with rhinovirus.^{18,19} Finally, rhinovirus has been identified by *in situ hybridization* in the lower respiratory tract ECs in 45% of infants with recurrent respiratory symptoms when using a probe for just a single rhinovirus species.²⁰ Thus, infections from rhinovirus can occur throughout the airway and in the parenchyma as well.

The intercellular adhesion molecule 1 (ICAM-1) is the major group rhinovirus receptor because it serves >90% of rhinovirus serotypes, whereas some of the remaining minor group rhinoviruses bind members of the low-density lipoprotein receptor family.^{21,22} ICAM-1 is a cell surface glycoprotein that normally regulates leukocyte trafficking and accumulation at sites of inflammation via engagement of lymphocyte function-associated antigen (LFA)-1 and macrophage-1 antigen (Mac-1) on the cell surface.²³ Rhinovirus attachment to ICAM-1 initiates entry into the host cell with insertion of the virus genome and thus infects the cell.

TARGETS FOR INFECTION AND IMMUNE RESPONSES

Epithelium

Rhinovirus, like most respiratory viruses, replicates primarily in airway ECs. In addition to attaching ICAM-1 to gain entry to the cell, rhinovirus infection induces expression of ICAM-1 to further the availability of receptors for rhinovirus to bind to and infect the cell.²⁴ Experimental infection of bronchial ECs with rhinovirus results in little cellular damage, a pattern of response that suggests that rhinovirus-induced asthma exacerbations occur through mechanisms other than direct cellular injury.¹⁸ The induction of gene expression in rhinovirus-infected ECs appears to involve a double-stranded RNA-mediated pathway, suggesting that active rhinovirus replication triggers production of cytokines and chemokines that are necessary for the recruitment of inflammatory cells as well as being part of the host antiviral response.²⁵ Rhinovirus infection of bronchial ECs induces the secretion of a wide variety of inflammatory cytokines and chemokines including *IL-1*, *IL-6*, *IL-8*, *GM-CSF*, *eotaxins*, and *regulated upon activation, normal T-cell expressed and secreted (RANTES)*.^{18,26–28} Thus, the epithelium not only serves as a target and possible reservoir for the infecting virus but also is the site and source of initial inflammatory response (Fig 1).

INNATE IMMUNE CELL RESPONSES TO RHINOVIRUS

Macrophages

Macrophages are the most numerous cell type found in the airway lumen. Rhinovirus can attach to airway macrophages but may have limited replication in this cell.^{29,30} More importantly, the interaction between rhinovirus and macrophages stimulates secretion of proinflammatory cytokines such as *IL-1*, *IL-8*, *TNF- α* , *IFN- γ* , and macrophage inflammatory protein (MIP)-1 α .^{29–33} *TNF- α* induction of EC expression of ICAM-1 allows for leukocyte trafficking to areas of infection but also increases the major rhinovirus receptor availability on the cells of primary rhinovirus replication.³⁴ *IL-8* is a potent chemokine for neutrophil recruitment. Rhinovirus infection also induces release of type I IFNs, including *IFN- α* , from airway macrophages, a process that may limit virus spread by inducing an antiviral state in ECs.³⁵

Neutrophils

Neutrophils are the predominant cell type recovered from sputum during acute asthma exacerbations.³⁶ In experimental rhinovirus infections of subjects with asthma or allergic rhinitis, *IL-8* and granulocyte colony-stimulating factor (G-CSF) levels increase rapidly in nasal lavage fluid and a day or 2 later in sputum samples. The generation of these particular cytokines parallels the increase in neutrophils, suggesting these factors are involved in recruitment of neutrophils to areas of rhinovirus infection.³⁷ In an experimental rhinovirus infection, peripheral blood neutrophils, but not total white blood cell counts, increase within 48 hours of inoculation. These findings correspond to changes in nasal lavage fluid G-CSF and *IL-8* concentrations.³⁸ In adults presenting with naturally occurring virus-induced asthma exacerbations, sputum neutrophils are increased as well as levels of neutrophil *elastase*, a marker of neutrophil degranulation.³⁹ Neutrophil activation and degranulation

likely contribute to airway obstruction and lower respiratory tract symptoms in asthma exacerbations or, at least in part, through neutrophil protease-induced mucus secretion by airway gland serous cells.⁴⁰

Eosinophils

Rhinovirus infection may also induce eosinophil infiltration and activation within the airway. Experimental rhinovirus infection increases bronchial eosinophilic infiltration in biopsies taken at the height of cold symptoms in both asthma and control subjects.⁴¹ However, only in asthma subjects does the eosinophilic infiltrate persist 6 to 8 weeks after infection.

Rhinovirus-associated eosinophil activation correlates with changes in airway hyperresponsiveness and is reflected by an increase in eosinophilic cationic protein in the sputum supernatants.⁴² RANTES, a potent chemotactic cytokine and activator of eosinophils, is produced by ECs in response to rhinovirus infection¹⁸ and can be found in higher concentrations in nasal washings from children with wheezing compared with individuals with cold symptoms alone.⁴³ Collectively, these findings imply that RANTES is an important factor in the activation of eosinophils in rhinovirus-induced asthma exacerbations.

Properties of the eosinophil also suggest an innate antiviral role. Eosinophils produce and secrete ribonucleases, including eosinophil-derived neurotoxin and eosinophilic cationic protein, which have antiviral properties.⁴⁴ In a murine model using RSV, another single-stranded RNA respiratory virus, increased numbers of eosinophils improve viral clearance and reduce airway dysfunction.⁴⁵ In experimental rhinovirus infection after nasal allergen challenge, elevated percentages of eosinophils in nasal lavage before inoculation correlated with a delayed onset and reduced severity of cold symptoms.⁴⁶ These outcomes suggest eosinophil products have antiviral effects in rhinovirus infections. In contrast, elevated sputum eosinophil counts predict the likelihood for an asthma exacerbation, a finding that implies the presence of eosinophils may enhance susceptibility for a rhinovirus infection.⁴⁷

Eosinophils may also act as antigen-presenting cells in human viral respiratory infections. Murine models have demonstrated that eosinophils serve as antigen-presenting cells under conditions of allergic inflammation as well as parasitic infection.^{48,49} As further support for this concept, human eosinophils express surface molecules necessary for activation of naive CD4⁺ T cells—that is, MHC class II proteins—when stimulated with cytokines including IFN- γ , GM-CSF, *IL-3*, *IL-4*, and *IL-5*.^{50–52} In addition, eosinophils expressing MHC II proteins are present in sputum from subjects with asthma as well as in bronchoalveolar lavage fluid after allergen challenge.^{53,54} CD40, a costimulatory surface molecule sufficient for activation of CD4⁺ T cells, is also expressed on eosinophils.⁵⁵ When eosinophils are pretreated with GM-CSF to express ICAM-1, they can bind rhinovirus and present viral antigen to rhinovirus-specific T cells in an MHC-restricted manner, resulting in T-cell proliferation and IFN- γ secretion.⁵⁶ However, compared with macrophages, eosinophils are capable of but less efficient at inducing CD4⁺ T-cell proliferation and IFN- γ production in the presence of bacterial superantigens, and appear unable to present efficiently antigens that require intracellular processing⁵⁷ (Fig 2).

ADAPTIVE IMMUNE CELL RESPONSES TO RHINOVIRUS

T cells

Bronchial biopsies of subjects with asthma and control subjects with an experimental rhinovirus infection show T-cell infiltration of the airway epithelium and submucosa.⁴¹ Peripheral blood lymphopenia also occurs during a rhinovirus infection, possibly reflecting

vigorous T-cell recruitment to the lung.⁵⁸ Both airway lymphocyte infiltration and peripheral blood lymphopenia correlate inversely with changes in bronchial hyperresponsiveness during rhinovirus infection and revert to baseline levels during convalescence (unlike airway eosinophilia in subjects with asthma). These findings suggest that T cells may also contribute to lower respiratory tract symptoms during rhinovirus infection.⁴¹

The recruitment of T cells may also contribute to the clearance of virus through production of T_H1 cytokines including IFN- γ and IL-2. Rhinovirus-infected ECs secrete RANTES and IFN- γ -inducible protein (IP)-10, which promote T-cell chemotaxis.⁵⁹ IP-10 induces chemotaxis through engagement of a highly expressed receptor on activated CD4⁺, CD8⁺, and natural killer T cells, chemokine receptor (CXCR) 3.⁶⁰ Expression of IP-10 appears to require active rhinovirus replication, possibly in response to double-stranded RNA.⁶¹ IP-10 expression is increased in asthma exacerbations because of rhinovirus and other viruses, and the level of expression can discriminate between virus-induced and nonvirus-induced asthma exacerbations.⁵⁹ A vigorous T_H1 response to viral infection may be hampered in asthma by the presence of large numbers of airway eosinophils. IFN- γ induces indoleamine 2,3-dioxygenase production by eosinophils, which in turn induces T_H1-cell-specific apoptosis.⁶²

B cells

After virus inoculation, B-cell responses to infection can be detected in the generation of mucosal IgA by day 3, followed by IgM, and finally IgG after 7 to 8 days.⁶³ Rapid induction of specific preformed neutralizing IgG to rhinovirus serves to prevent or limit the extent of reinfection. Elevated serum titers of serotype-specific IgG neutralizing antibody correlate with attenuated cold symptoms and reduced viral shedding.⁶⁴ In RSV infection in infants, RSV-specific IgE titers in nasopharyngeal secretions were significantly higher in subjects with wheezing and correlated with the degree of hypoxia.⁶⁵ Experimental rhinovirus infection of subjects with allergic rhinitis induced a rapid increase in serum IgE without evidence of elevation in antigen-specific IgE.⁶⁶ Whether IgE or rhinovirus-specific IgE plays a role in lower airway responses to rhinovirus infection remains to be demonstrated.

CONSEQUENCE OF RHINOVIRUS INFECTIONS ON AIRWAY INFLAMMATION

What are the products generated?

Products generated in response to rhinovirus infection by structural and immune cells have both effector and regulatory functions. The chemotactic cytokines, IL-8, RANTES, and MIP-1 α , are increased with rhinovirus infection and correlate with the severity of cold symptoms.^{18,26,67–69} IL-8 is produced by ECs and macrophages and serves primarily as a chemoattractant for neutrophils. RANTES attracts eosinophils and can induce eosinophil degranulation.⁶⁹ MIP-1 α is a chemokine for lymphocytes including both T cells and B cells.⁷⁰ Acute inflammatory cytokines such as IL-6 are also elevated during rhinovirus infection and likely reflect an acute-phase inflammatory response.

Inducible elevations in leukotrienes have also been demonstrated in rhinovirus infection and may contribute to airway dysfunction and cell attraction. For example, *leukotriene (LT) C₄* levels are elevated in nasal lavage fluid during rhinovirus infection.⁷¹ In addition, rhinovirus infection in bronchial ECs induces expression of proteins in the biosynthetic pathway for *LTB₄* and *LTC₄*.⁷² The possible importance of the leukotrienes is further noted in therapeutic trials to be discussed later in the section on leukotriene receptor antagonists.

Cell recruitment, cellular inflammation

The acute neutrophilic response with a rhinovirus infection correlates with the severity of cold symptoms. What role neutrophils play in the clearance of rhinovirus is not fully known but may be dualistic. Neutrophils can aid in clearance of cellular debris through phagocytosis, although the inflammation associated with rhinovirus infections has limited cytopathic effects. Conversely, activated airway neutrophils can contribute to the pathophysiology of asthma exacerbations. For example, neutrophil proteases induce airway edema, trigger airway smooth muscle bronchoconstriction, and induce mucus gland secretion, all cardinal features of asthma exacerbations. However, because both asthma and control subjects respond to rhinovirus infection with sputum neutrophilia, it appears that factors other than, or in addition to, neutrophilic inflammation are necessary for asthma exacerbation.⁶⁹

Eosinophil recruitment also occurs with rhinovirus infection,⁴¹ although this is not uniformly noted. One study of patients hospitalized for asthma exacerbation found a suppression of sputum eosinophils during the acute exacerbation from rhinovirus, with sputum eosinophils returning with recovery from exacerbation.⁶⁹ In this particular study, **IL-10** emerged as a key factor in eosinophil regulation because its detection varied inversely with sputum eosinophil numbers. Leukotrienes are produced by activated eosinophils and can contribute to features commonly found in asthma exacerbations, including airway edema, plasma leakage, chemotaxis of inflammatory cells, and airway smooth muscle contraction.

As discussed, T lymphocytes are recruited to the lung in rhinovirus infections and likely participate in many phases of the response to infection—inflammation, antiviral activity, and regulation of the immune responses to rhinovirus. The end result, inflammation versus antiviral activity, is likely highly variable among individuals with asthma and likely determines whether the patient wheezes or has a rapid resolution of the viral illness (Fig 3).

Why are some patients with asthma more susceptible to rhinovirus lower respiratory tract infection?

Not all patients with asthma have an exacerbation with a cold. To explain this observation, investigators have begun to evaluate the antiviral response to rhinovirus in at-risk groups. An impaired innate antiviral response, particularly a reduction in IFN production, has been observed in some subjects with asthma. The clinical impact and relevance of these defects have been explored during experimental rhinovirus infections where the degree of deficiencies in IFN production contributes to the occurrence and severity of lower respiratory tract symptoms. Compared with bronchial ECs cultured *ex vivo* from normal subjects, samples from asthma subjects have a significantly impaired production of **IFN- β** , a type I IFN. This abnormality is also reflected in a reduction of EC apoptosis in response to rhinovirus infection, an impairment of innate antiviral activity that results in increased rhinovirus replication in bronchial ECs from subjects with asthma. These findings provide an explanation for why patients with asthma are susceptible to lower respiratory tract rhinovirus infection and have a more severe illness.⁷³ The induction of **IFN- λ** , a type III IFN also involved in innate antiviral responses, is compromised in response to rhinovirus infection in primary bronchial EC cultures from subjects with asthma.⁷⁴ Collectively, these asthma-associated defects will lead to impaired rhinovirus clearance, more severe infections, and a greater persistence of this virus in the lower airway.

A consequence of these defective antiviral responses can lead to an enhanced likelihood of rhinovirus replication in the airway during acute infection, causing greater airway inflammation. Among children evaluated for an asthma exacerbation, rhinovirus RNA was

present in 82% of nasal aspirates at the initial visit and persisted in greater than 44% of the subjects 6 weeks after the initial visit without new symptoms of a cold.⁷⁵ Naturally occurring rhinovirus infections lead to decrements in peak expiratory flow as well as both more severe and longer-lasting lower respiratory tract symptoms in asthma compared with controls.⁷⁶ A reduction of the IFN- γ /IL-5 mRNA ratio, presumably representing a shift toward T_H2 activity, in airway cells of subjects with asthma correlates with higher symptom scores as well as greater detection of rhinovirus RNA. Conversely, those subjects with higher IFN- γ /IL-5 mRNA ratios presumably shifted more toward a T_H1 profile, had lower symptom scores, and had less detectable virus RNA at convalescence.³⁷ These observations suggest that an imbalance of T_H1 versus T_H2 cytokine responses to rhinovirus infection may explain the persistence of rhinovirus in the airway and level of symptom scores. Support for this concept also comes from a study of rhinovirus-stimulated PBMCs in which atopic subjects with asthma had reduced production of IFN- γ and IL-12, with increased IL-4 and IL-10 compared with control subjects.⁷⁷

Last, new evidence has shown the presence of rhinovirus in subjects with asthma without cold symptoms or an exacerbation. Rhinovirus antigen was identified in bronchial biopsies of some subjects with asthma and control subjects without exacerbation in the previous 2 weeks or cold symptoms in the previous 3 weeks.⁶ The detection of rhinovirus correlated with increased peripheral blood neutrophil counts and a greater degree of airflow obstruction in all subjects, as well as increased blood eosinophil counts in subjects with asthma. Rhinovirus was found significantly more often in subjects with asthma compared with controls, and subjects with asthma with rhinovirus present had lower FEV₁ values. Whether rhinovirus infection can become persistent and contribute to asthma severity has yet to be established, however.

Does allergic sensitization play a role in rhinovirus-associated asthma exacerbations?

Atopy is a common condition in asthma, with allergic rhinitis occurring in as many as 80% of patients with asthma.⁷⁸ The impact allergic sensitization may have in the asthmatic airway response to viral infection has generated much interest and research. Elevated IgE antibodies to airborne allergens have been suggested as a marker for patients at increased risk for lower respiratory tract symptoms with viral infections such as rhinovirus. For example, in children presenting for emergency care because of wheezing, the presence of airborne allergen specific IgE and high total IgE appeared to be a risk factor for wheezing with viral infections.^{79,80} In addition, a *post hoc* analysis of experimental rhinovirus infections in adult subjects with mild asthma revealed a subset of subjects with total IgE >300 who experienced significantly increased upper and lower respiratory tract symptoms compared with controls, although no asthma exacerbations occurred.⁸¹

Allergic sensitization may increase the susceptibility to rhinovirus infection. For example, IL-13 and other T_H2 cytokines have been shown to increase expression of ICAM-1 on an EC line *in vitro*, which resulted in increased viral titers after experimental rhinovirus infection.⁸² Moreover, ECs recovered from nasal brushings of atopic subjects express significantly higher ICAM-1 levels than those from healthy controls, and increased ICAM-1 expression with allergen exposure was inducible only in the ECs from atopic subjects.⁸³ Thus, allergic sensitization with allergen exposure may increase the likelihood of infection by rhinovirus by increasing ICAM-1 expression on ECs. This is supported clinically in a case-controlled study of children admitted for asthma exacerbations—the risk factor combination of detectable virus, allergic sensitization, and high allergen exposure was significantly higher in the hospitalized asthma group versus children with stable asthma.⁸⁴ These results should be interpreted with some caution because the exacerbation group had significantly fewer subjects regularly using inhaled corticosteroid (ICS) compared with the

stable asthma group. Further evidence for atopy increasing susceptibility to rhinovirus comes from a study of experimental rhinovirus infection in atopic and nonatopic subjects. Although there were no differences found in cold symptom scores or viral shedding between the groups, a subset of subjects in this study developed virus-specific neutralizing antibodies between screening and inoculation with the experimental rhinovirus.⁸⁵ The atopic subjects in this subset developed severe colds, whereas those without atopy did not have colds.

In contrast with these findings, experimental rhinovirus cold symptoms were significantly delayed in onset and of shorter duration in subjects with allergic rhinitis after intranasal allergen challenge compared with those with placebo challenge. In addition, there was no difference between the 2 groups in rhinovirus titer recovered from postinoculation nasal lavage.⁴⁶ Moreover, in a study of subjects with mild atopic asthma, allergen challenge before experimental rhinovirus infection did not alter cold symptom scores, asthma symptom scores, peak expiratory flow, FEV₁, airway hyperresponsiveness, or exhaled nitric oxide despite increases in sputum eosinophils, neutrophil elastase, and IL-8 levels⁸⁶ (Fig 4).

What are the effects of treatment on virus-provoked asthma, and what may their effect tell us about immune response to the virus?

Corticosteroids—Corticosteroids are the backbone of therapy for persistent asthma and are also efficacious in treatment of childhood wheezing episodes. ICSs reduce asthma exacerbations among subjects with persistent asthma but do not eliminate these events completely.⁸⁷ In a recent cohort of adults with asthma, the absence of ICS treatment was identified as a risk factor for exacerbations related to rhinovirus infection.⁸⁸ However, although ICS therapy before experimental rhinovirus infection improved airway hyperresponsiveness and reduced bronchial eosinophil numbers, this treatment did not inhibit the recruitment of other inflammatory cells, including T cells.⁸⁹

In selected situations, corticosteroid therapy in early childhood has been shown to reduce the frequency of recurrent wheezing. For example, treatment of an initial wheezing episode in childhood with oral corticosteroids reduces recurrent wheezing events for as long as 1 year.⁹⁰ In children with an initial rhinovirus-associated wheezing, the reduction in recurrent wheezing was greatest in the first 2 months. In children with asthma, oral corticosteroid bursts given early in viral respiratory infections limit the severity and duration of asthma exacerbations but do not alter cold symptoms.⁹¹

Corticosteroids suppress inflammation through multiple mechanisms, with their greatest effect on eosinophil-associated processes. They suppress gene expression of proinflammatory cytokines through binding to the elements of the gene promoter region. For example, pretreatment with corticosteroids reduces rhinovirus-induced IL-6 production by bronchial ECs.⁹² The suppression of rhinovirus-induced IL-6 requires the presence of a negative glucocorticoid response element in the promoter sequence of the IL-6 gene. Corticosteroids also suppress inflammation through the production of anti-inflammatory molecules, the formation of transcription factor inhibitors, and the inhibition of intracellular signaling pathways.^{93–95} The production of IL-8 by ECs in response to IL-1 β requires intact nuclear factor- κ B.⁹⁶ Corticosteroids suppress IL-1 β -induced IL-8 production; this suppression does not require an intact glucocorticoid response element in the IL-8 promoter region, indicating the inhibition occurs before transcription.⁹⁶ Other cytokines appear to be suppressed through transrepression, a process in which activated glucocorticoid receptors interact with transcription factors, including nuclear factor- κ B and activator protein-1, to prevent translocation to the nucleus and binding to DNA, thereby preventing transcription of inflammatory products.⁹³ Therefore, although corticosteroids are effective in asthma and diminish the frequency of wheezing with a cold, the effects are not uniform. These clinical observations suggest that although components of the immune response to viruses that

promote asthma are sensitive to the corticosteroid effects, other aspects of the response to viruses are not modulated by this treatment.

Leukotriene receptor antagonists—In young children, the use of montelukast over the course of a year reduced the number of exacerbations by ~30% but did not reduce the use of oral corticosteroids presumably prescribed for severe exacerbations.⁹⁷ In a cohort of predominantly school-age children, the addition of montelukast to usual therapy during the “September asthma epidemic” (presumably the time of rhinovirus-induced asthma exacerbations) significantly reduced the number of days of increased asthma symptoms. Finally, in children with a history of virus-induced asthma symptoms, short courses of montelukast initiated at the first indications of a cold or asthma symptoms significantly lowered the use of health care units and symptom scores, but did not change need for oral corticosteroids or rescue inhaler medication.⁹⁸ Taken together, these studies indicate that leukotriene receptor antagonists taken prophylactically or therapeutically may mildly ameliorate, but do not eliminate, asthma exacerbations in children, including those induced by rhinovirus infection. Collectively, these findings also suggest that respiratory viral provocation of asthma involves the generation of leukotriene products, which, when blocked, can reduce the increase in asthma symptoms with a cold.

Antiviral agents—Given the ubiquity of the common cold, the optimal choice for the prevention of a rhinovirus infection and related asthma exacerbations would be the development of a vaccine. However, because of the antigenic diversity of the >100 serotypes of rhinovirus, a vaccine is not likely to be immediately forthcoming. The antiviral agent research involving rhinovirus to date has focused on the prophylaxis and treatment of upper respiratory infections but not asthma exacerbations per se. Still, what is known about the efficacy and limitations of these approaches provides insight on potential therapies for asthma exacerbations.

IFNs reduce host cell susceptibility to viral infections and have been studied as therapeutic agents for rhinovirus infections. Intranasal IFN- α 2 has been effective in reducing transmission of rhinovirus-related colds among family members.⁹⁹ It has also been shown to be fully effective compared with placebo in the prevention of rhinovirus-related colds among office workers when given during the fall rhinovirus season.¹⁰⁰ However, symptoms of nasal obstruction, discomfort, and nasal bleeding limit its usefulness for long-term prophylaxis. Under *in vitro* conditions, IFN- β serine has antiviral activity to rhinovirus similar to that of IFN- α 2.¹⁰¹ Although intranasal IFN- β serine appears to be better tolerated than IFN- α 2, attempts at prophylaxis of natural rhinovirus colds using intranasal IFN- β serine have been ineffective.¹⁰²

Pleconaril is an orally absorbed viral capsid-function inhibitor that blocks replication of ~90% of rhinovirus serotypes.¹⁰³ Clinical trials have demonstrated a modest benefit in reducing the severity and duration of colds caused by picornaviruses when pleconaril was started within 24 hours of the onset of cold symptoms.¹⁰⁴ However, the US Food and Drug Administration has not approved pleconaril because of concerns of emergence of viral resistance and the reduced effectiveness of oral contraceptives for women using pleconaril through its rapid induction of cytochrome P450 3A4.¹⁰⁵

Imiquimod is an immune modulator capable of activating macrophages and other PBMCs, inducing production of IFN- α , TNF- α , and IL-12.¹⁰⁶ It is used topically for the treatment of human papilloma virus infections including genital warts and molluscum contagiosum. Intranasal application in primates induces rapid production of IFN- α and TNF- α , suggesting it may provide local antiviral response to rhinovirus.¹⁰⁷ In a rat model of respiratory infection with Sendai virus, treatment with imiquimod suppresses viral titers and reduces

neutrophil and eosinophil numbers in the bronchoalveolar lavage fluid.¹⁰⁸ There have been no published studies to date involving imiquimod and the treatment of or prophylaxis for human rhinovirus infection.

Attempts at limiting rhinovirus cell entry through blockade of its cell receptor have met with some experimental success. Because ICAM-1 serves as the receptor for >90% of rhinovirus serotypes, it is a logical therapeutic target. The use of monoclonal anti-ICAM-1 antibodies neither modified rhinovirus infection rates nor altered the clinical course of experimental infections of healthy subjects.¹⁰⁹ However, use of multivalent anti-ICAM-1 antibodies blocks rhinovirus infection of EC cell lines *in vitro*.¹¹⁰ In addition, intranasal tremacamra, a recombinant soluble ICAM-1 molecule, reduces symptom scores, IL-8 levels, and viral titers in experimental rhinovirus infections of subjects without allergy.¹¹¹ Although no adverse effects were observed in the trials with tremacamra, the need for frequent dosing (5–6 times per day) will likely limit tremacamra development.¹¹²

Another target for inhibition of viral replication is the rhinovirus 3C protease. After insertion into the host cell, the rhinovirus RNA undergoes translation into a precursor polypeptide, which requires 3C protease for cleavage into structural and enzymatic proteins essential for viral replication.^{113,114} Sequencing of the 3C protease from different rhinovirus serotypes reveals a high degree of homology within the coding region, which makes it a sensible target for therapy. Rupintrivir (formerly AG7088) is a 3C protease inhibitor that shows an *in vitro* ability to reduce viral titers as well as production of IL-6 and IL-8 in ECs infected with rhinovirus.¹¹⁵ In a phase II clinical trial of intranasal rupintrivir, the treatment group demonstrated reduced viral titers and lower symptom severity scores versus placebo, even though prophylactic administration before inoculation did not affect infection frequency.¹¹⁶ Side effects include blood-tinged mucus and nasal irritation.¹¹⁶

Given the strong link between symptom severity and neutrophilic recruitment, IL-8 is another logical target for therapy. Limiting neutrophil infiltration in this manner may ameliorate many of the central features of asthma exacerbations. There are no candidate anti-IL-8 compounds available currently. In addition, inhibition of the proinflammatory signal transduction cascade may prove fruitful. This proposed inhibition would optimally be specific enough to preserve IFN responses, for example, to allow rapid clearance of viral titers (Fig 5).

Summary

Defining the immune response to rhinovirus has provided insight to our understanding of the unique features of the inflammation associated with colds. Furthermore, the discovery of an increased susceptibility of patients with asthma to the adverse effects of a respiratory infection, which may stem from deficient antiviral responses to rhinovirus infection, has helped to define better the immune response to viruses, and to rhinovirus in particular. From these observations has emerged a clearer picture of the immune response and which components are beneficial and which are detrimental. We now have a better understanding of the inflammatory cytokine response to rhinovirus infection as well as the profile of cellular infiltrates involved, including neutrophils, eosinophils, and lymphocytes. What remains to be explained is how cellular recruitment and activation result in the symptoms of asthma exacerbations. Investigation into the next steps to identify specific cellular responses as intervenable targets for therapy will be key in ameliorating, and perhaps preventing, the most common cause of a loss of asthma control. It still remains unknown what factors contribute to early-onset asthma or whether this is simply a marker of susceptibility to rhinovirus. Finally, the evidence of persistent rhinovirus antigen within the lower airway

during periods of asthma stability and its relation to chronic inflammation further solidify the intertwining relationship of rhinovirus and asthma as a clinical disease entity.

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Abbreviations used

EC	Epithelial cell
ICAM-1	Intercellular adhesion molecule 1
ICS	Inhaled corticosteroid
IP	Inducible protein
LT	Leukotriene
MIP	Macrophage inflammatory protein
RANTES	Regulated upon activation, normal T-cell expressed and secreted
RSV	Respiratory syncytial virus

GLOSSARY

ELASTASE	A component of neutrophil azurophilic granules, elastase is a serine protease that degrades outer membrane proteins on Gram-negative bacteria and prevents the escape of <i>Shigella</i> from the phagosome. Mutations in the elastase-2 gene are responsible for autosomal-dominant cyclic neutropenia and congenital neutropenia. α -1-Antitrypsin inhibits elastase, and this may be a mechanism for loss of inflammation control and pulmonary damage in patients with α -1-antitrypsin deficiency
GM-CSF, EOTAXIN, REGULATED UPON ACTIVATION, NORMAL T-CELL EXPRESSED AND SECRETED (RANTES)	All are factors that promote survival, proliferation, and chemotaxis of eosinophils. Eotaxins and IL-5 work together to promote eosinophil activation and degranulation. GM-CSF promotes chemotaxis and survival of mast cells. Eotaxin-1 and eotaxin-2 are important in eosinophil recruitment to the lung; eotaxin-3 promotes esophageal eosinophil accumulation
<i>IN SITU</i> HYBRIDIZATION	The technique whereby a labeled probe is incubated with a tissue sample for direct visualization of the target RNA or DNA; this is used on chromosomes in a fluorescent <i>in situ</i> hybridization assay
IFN-α, IFN-β, IFN-λ, IFN-γ	IFNs were originally named for their ability to interfere with viral function. IFN- α and IFN- β have similar functions, are produced by macrophages, inhibit viral replication, and increase MHC I expression. IFN- γ is made by T cells, is stimulated by IL-12, and increases the production of IL-1 and TNF- α . INF- λ (also known as IL-29) is part of the IL-10 superfamily, is induced by viral

IL-1, IL-6, IL-8

infections, and can downregulate IL-13. IFNs have clinical uses including the treatment of hepatitis and hypereosinophilic syndrome (IFN- α), multiple sclerosis (IFN- β), and chronic granulomatous disease (IFN- γ)

ILs are involved in the inflammatory response, especially a neutrophilic response. IL-1 is produced by neutrophils, epithelial cells, and endothelial cells following stimulation by endotoxin, bacteria, and viruses. IL-1 increases ICAM-1 (increased rhinovirus binding) and TNF- α expression, IL-1 (positive feedback), IL-6, IL-8, and GM-CSF (neutrophil survival) production. IL-6 stimulates the production of acute-phase reactants and class-switch to IgG₁, whereas IL-8 induces neutrophil migration into target tissues. Glucocorticoids, IL-4, and IL-13 inhibit IL-6; IL-8 inhibits IL-4-induced IgE production

IL-3, IL-4, IL-5

IL-3 and IL-5 promote the survival, activation, and chemotaxis of mast cells and eosinophils. IL-4 increases the production of IL-5 and IgE while decreasing IL-1, IL-6, and IL-8. IL-5 and IL-3 share a common β -chain in their receptors, whereas IL-4 and IL-13 bind a common α -chain on their receptors. IL-4 increases expression of vascular cell adhesion molecule 1 on endothelial cells, allowing trafficking of eosinophils

IL-10

Associated with dampening immune responses, for example, after successful immunotherapy. IL-10 can be produced by CD25-positive regulatory T cells, and levels can be elevated in viral infections such as rhinovirus, respiratory syncytial virus, enterovirus, and influenza. IL-10 suppresses eosinophilia by inhibiting IL-5 and GM-CSF

LEUKOTRIENE (LT) C₄, B₄

Products of inflammatory cells such as eosinophils and mast cells, LTC₄ is a cysteinyl leukotrienes (along with LTD₄ and E₄), whereas LTB₄ is produced by LTA₄ hydrolase and binds to the BLT_{1,2} receptors rather than the cysteinyl leukotriene (cysLT) receptors. Both are potent bronchoconstricting agents, especially LTB₄, which also acts as a chemoattractant for neutrophils. The variability in clinical response to cysLT receptor antagonists is a result, in part, of differences in promoters in genes such as 5-lipoxygenase (pharmacogenomics)

**NEGATIVE
GLUCOCORTICOID
RESPONSE ELEMENT**

Glucocorticoid receptors are nuclear steroid receptors that dimerize and bind to the glucocorticoid response element to activate or repress transcription. Glucocorticoid receptor-mediated transcriptional repression can use a number of mechanisms, including (1) direct binding to negative glucocorticoid response element consisting of a consensus sequence ATYACnnTnTGATCn, (2) direct interference with binding of other transcription factors because of overlapping DNA binding sites, or (3) DNA-

binding independent repression caused by competition for mutual coactivators or direct binding to other transcription factors

PHYLOGENETICS

Phylogenetics is the study of evolutionary relationship among organisms, such as plants and viruses

RESPIRATORY SYNCYTIAL VIRUS (RSV)

The most common cause of pneumonia and bronchiolitis in infants; repeated RSV infections commonly occur over a lifetime. RSV is a single-stranded, negative sense RNA paramyxovirus. Although RSV has been thought to be associated with the development of asthma, recent studies show that rhinovirus may be a more robust predictor of asthma in children than RSV. Premature infants with chronic lung disease are treated with palivizumab, a humanized mAb to RSV, during the appropriate season

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FIG 1. EC response to rhinovirus infection. ECs secrete cytokines that attract neutrophils, eosinophils, and lymphocytes. Macrophages may be infected in part by rhinovirus released from the epithelium.

FIG 2.

Immune cell response to rhinovirus. Innate immune response from macrophages includes secretion of cytokines, which recruit additional innate and adaptive immune cell responses. *ECP*, Eosinophilic cationic protein; *EDN*, eosinophil-derived neurotoxin.

FIG 3.
Consequences of immune response to rhinovirus and altered airway responses in asthma.

FIG 4.
Antiviral response to rhinovirus in a healthy subject versus a subject with asthma.

FIG 5. Interface and interactions between antirhinovirus therapeutic agents and regulation of the immune response to rhinovirus. Experimental agents in *boldface*; proposed therapies in *italics*.