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REVIEW

The role of human rhinovirus in immunology, COPD, and corresponding treatments

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Abstract **The common cold is most often a result of human rhinovirus (HRV) infection. Common cold symptoms including rhinorrhea and nasal obstruction frequently occur during HRV infection of the upper respiratory tract. Conversely, HRV may also infect the epithelial cells of the lower respiratory tract. Symptom severity associated with HRV infection ranges from mild to potentially serious depending on a person's susceptibility and pre-existing condition, such as chronic obstructive pulmonary disease. An over active host immune response is believed to be the primary contributor to HRV pathogenesis. Enhanced activity of various host cell cytokines and granulocytes mediate specific cellular pathways inducing many of the symptoms associated with HRV infection. There are over 100 serotypes of HRV which can be further categorized based on the specific characteristics of each type. The two main categories of HRV consist of the major and minor groups. The unique host cell receptor is the distinguishing factor between these two groups. Yet, these viruses may also differ in mechanism of infection and replication. Due to the high frequency of hospital and clinical visits and the corresponding economic burden, novel therapies are of interest. Several different treatment options varying from herbal remedies to anti-viral drugs have been studied. However, the vast number of HRV serotypes complicates the progress of developing a universal treatment for attenuating HRV infection.**

Keywords human rhinovirus, common cold, immunology, COPD

Introduction

Human rhinovirus (HRV) is a positive sense, single-stranded non-enveloped RNA virus belonging to the family *Picornaviridae* of the genus *Enterovirus* (Bochkov et al., 2011; Rollinger and Schmidtke 2011). The viral protein coat consists of 4 viral capsid proteins (Gavala et al., 2011). Over 100 serotypes have been classified and grouped based off of their unique antigenic properties, specific host cell receptors, and susceptibility to antiviral capsid binding compounds (Andries et al., 1990; Uncapher et al., 1991). Genome sequencing provided further methods of identification and corresponds with antiviral classification techniques which ultimately helped distinguish two general serotype groups, HRV-A and HRV-B (Bochkov et al., 2011). These advances in genome sequencing have led to the recent discovery of a new HRV-C group (Bochkov et al., 2011). However, the current understanding and information available regarding HRV-C is limited.

HRV infection is extremely prevalent during the change in seasons, mainly fall and spring, yet infection is diagnosed year-round (Turner 2001). The majority of common cold symptoms are a result of upper respiratory infection from HRV-A and HRV-B species (Bochkov et al., 2011; Kennedy et al., 2012). Rhinorrhea, nasal obstruction, sneezing, coughing, and sore throat are the most frequently observed symptoms (Tyrrell et al., 1993; Arruda et al., 1997; Turner 2001). Other symptoms may include headache, lethargy, and fever; fever being especially prevalent in children with upper respiratory infections (Harris and Gwaltney 1996; Pappas et al., 2008). Secondary bacterial infections are also observed in individuals infected with HRV. In these cases, acute otitis media (especially in children), pneumonia, and sinusitis are observed complications (Rollinger and Schmidtke, 2011). Patients may become symptomatic from as early as one day post infection and the symptoms usually subside after one week (Gwaltney et al., 1967).

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The primary host cell receptors for HRV infection are intercellular adhesion molecule-1 (ICAM-1) and low-density lipoprotein receptor (LDLR) (Bella and Rossmann 2000; Vlasak et al., 2005). After entry into the host cell, viral uncoating occurs freeing the viral RNA for virus replication and further symptom development. The more severe symptoms associated with HRV result from lower respiratory infections usually in asthmatic individuals and/or people suffering from other chronic lung diseases, such as chronic obstructive pulmonary disease (COPD) (McManus et al., 2008; Wat et al., 2008; Kennedy et al., 2012). For example, polymerase chain reaction (PCR) and reverse transcriptase (RT)-PCR techniques have detected a significant correlation between viral infection and asthma exacerbations (Message and Johnston, 2001). These HRV induced exacerbations contribute to airway restriction leading to diminished airflow and thus shortness of breath associated with wheezing (Kim and Gern, 2012). In addition, the severity of HRV related symptoms may be enhanced in patients with other underlying respiratory pathogenic conditions, such as pneumonia (Bochkov et al., 2011; Kennedy et al., 2012).

Although the symptoms of HRV infection are generally mild, the economic burden is extremely high (Turner and Hendley, 2005). Thus, many novel therapeutic strategies ranging from herbal and dietary treatments to antiviral agents have been considered (Turner, 2001). Furthermore, studies have also demonstrated the importance of preventative measures, such as hand washing, in attenuating transmission (Savolainen-Kopra et al., 2012).

HRV cell attachment and replication

HRV host cell attachment and replication occurs in epithelial cells of the upper and lower respiratory tract (Fuchs and Blaas, 2010). Major and minor group HRVs, of the HRV-A or HRV-B species, translocate into the cytosol via two different receptors pathways (Message and Johnston, 2001). Major group HRVs bind to ICAM-1 whereas minor group HRVs attach to LDLRs (Message and Johnston, 2001). To understand the differences between these pathways, studies have performed *in vitro* experiments utilizing human rhinovirus 14 (HRV14) for major group HRVs and human rhinovirus 2 (HRV2) for minor group HRVs. These serotypes provide a representative approach for understanding the pathway from HRV cell attachment to viral RNA release. Fuchs et al. provided an extensive review of these specific pathways. The following sections will provide a brief synopsis of these mechanisms (Fuchs and Blaas, 2010).

Major group human rhinovirus infection

Entry of major group HRVs, such as HRV14, via endosomal transport through upper and lower respiratory epithelial cells are mediated by ICAM-1, which is expressed primarily on non-ciliated cells (Winther et al., 1997; Winther et al., 2002; Fuchs and Blaas, 2010). Previous studies have shown that there is a significant correlation between the number of ICAM-1 receptors on the plasma membrane and susceptibility to infection (Winther et al., 1997; Lopez-Souza et al., 2004; Jakiela et al., 2008). Thus, the role of ICAM-1 during HRV entry is critical for understanding HRV replication. The viral capsid proteins VP1 and VP3 from the major group HRVs, contain highly conserved sequences that are recognized by the ICAM-1 receptor and these sequence motifs differ between HRV-A and HRV-B species (Olson et al., 1993; Laine et al., 2006; Fuchs and Blaas, 2010).

Endocytosis of HRV is triggered by HRV binding to ICAM-1. However, the entry mechanism and transfer route to early endosomes, where the uncoating process takes place, differs depending on cell type (Fuchs and Blaas, 2010). Low pH of the endosomal environment along with the help of ICAM-1 likely aid in the viral uncoating process (Fuchs and Blaas, 2010). Yet, sensitivity to ICAM-1 and low pH induced uncoating varies among HRVs (Skern et al., 1991; Giranda et al., 1992; Khan et al., 2007). Thus, the uncoating requirements for major group HRVs have not been fully elucidated. Yet, the overwhelming data suggesting endosomal rupture is a highly likely theory (Fuchs and Blaas, 2010). It has been proposed that this rupture is mediated by the viral capsid protein VP4 which interacts with ICAM-1leading to membrane destabilization and consequently endosomal rupture and release of viral RNA (Xing et al., 2000; Xing et al., 2003).

Minor group human rhinovirus infection

The receptors for minor group HRVs are expressed on the apical surface of ciliated upper respiratory epithelial cells and include the low-density lipoprotein family of receptors (Fuchs and Blaas, 2010). In contrast to the ICAM-1 receptors of major group HRVs, minor group receptors are mostly localized on the endosomal membrane and are frequently recycled back to the plasma membrane (Strickland et al., 2002; Schneider and Nimpf, 2003). Another difference between the pathways of these two HRV groups is that translocation via LDLR is clathrin dependent, whereas ICAM-I is believed to be clathrin independent (Snyers et al., 2003). Nevertheless, once the virus is internalized, it is transported to an early endosome where the virus dissociates and the receptor is recycled. Consistent with the major group HRV pathway, uncoating of minor group HRVs is likely due to the acidic pH of endosomes; however there are several studies that provide evidence for the release of viral RNA into the cytosol via endosomal pore formation (Brabec et al., 2005; Prchla et al., 1995; Brabec-Zaruba et al., 2009). Determining the exact mechanism of viral RNA release is difficult due to the expansive number of HRV serotypes and various pH values required for HRV RNA translocation to the cytosol.

Viral replication

Once the viral RNA is translocated to the host cell cytosol, the RNA is translated into a 250 kDa polyprotein via cellular ribosomes (Gavala et al., 2011; Rollinger and Schmidtke, 2011). This polyprotein is cleaved by the HRV proteases 2A and 3C into structural and non-structural proteins (Gavala et al., 2011; Rollinger and Schmidtke, 2011). The 2A and 3C proteases not only cleave the viral polyprotein into proteins necessary for viral replication, but also the 2A protease cleaves host cell transcription factors needed for normal protein and RNA synthesis (Liebig et al., 1993; Sommergruber et al., 1994; Haghighat et al., 1996; Rollinger and Schmidtke, 2011). Thus inhibition of these proteases, as discussed later, may provide for development of new antiviral drugs. Interestingly, other studies have observed HRV's ability to inhibit the host's antiviral properties by cleaving the intracellular viral mediators RIG-1 and IPS-1, thus impeding the viral recognizing immune response (Barral et al., 2009; Drahos and Racaniello, 2009). One key non-structural protein of HRV is viral RNA polymerase 3D, which forms a structure with other viral and cellular proteins constituting the RNA replication complex (Rollinger and Schmidtke, 2011). This complex is required for HRV RNA synthesis (Rollinger and Schmidtke, 2011).

The HRV immune response

The clinical symptoms associated with HRV infection are derived from the host's own immune response. There are several mediators, including cytokines and granulocytes, which initiate the common inflammatory symptoms demonstrated in HRV infected individuals. The human immune response to HRV infection begins with innate immune system activation subsequently followed by an adaptive or humoral response. Symptoms of mucous hypersecretion and inflammation are a result of an over activated immune response stimulated by HRV infection.

Innate immune response

The epithelial cell layer of the upper and lower respiratory system is susceptible to HRV infection. During acute infection, the innate immune response is initiated by HRV binding to a pattern recognition receptor (PRR) on the surface of the respiratory epithelium or after cellular entry, inducing an intracellular signaling cascade (Fig. 1) (Fuchs and Blaas, 2010; Triantafilou et al., 2011). The specific receptors for HRV immune recognition include: Toll-like receptors (TLR), and RIG-like receptors (RLRs), including the helicases; retinoic acid inducible gene-I (RIG-I), and melanoma differentiation associated gene-5 (MDA-5) (Wang et al., 2009; Kennedy et al., 2012).

Currently, there is extensive research demonstrating the importance of TLRs regarding innate immune activity associated with HRV infection. TLRs are located on both plasma and endosomal membranes (Wang et al., 2009). The location of the TLR corresponds with the part of the HRV that stimulates its activation. For instance, Triantafilou et al. observed that TLR-2 responds specifically to the HRV6 capsid and not to the virus's ssRNA (Triantafilou et al., 2011). Conversely, the researchers observed that TLR7 and TLR8, which are both localized on the endosome membrane, are activated by the ssRNA of HRV6. One study utilizing BEAS-2B epithelial cells demonstrated that upon HRV16 infection, TLR3 expression was upregulated (Hewson et al., 2005). The role of TLR3 in HRV16 infection was further supported by the finding that transfection of human kidney cells with TLR3 enhanced the expression of HRV-induced interleukin (IL)-8 (Sajjan et al., 2006).

RLRs are another class of PRRs that are important for triggering innate immunity. For example, MDA-5 responds to dsRNA resulting from intracellular virus replication (Kato et al., 2005; Yoneyama et al., 2005). Studies have shown that when HRV replicates, elevated activity of MDA-5 was observed about 4 h post infection, which is the approximate time for HRV RNA synthesis, further verifying the specificity of MDA-5 to dsRNA of HRV during replication (Triantafilou et al., 2011). However, the mechanism for MDA-5/HRV interaction has not been fully elucidated. Wang et al. have observed that RIG-I, another type of RLR, cannot initiate a proper immune response when MDA-5 expression or activity is reduced (Wang et al., 2009). Additionally, TLR3 activation has been shown to mediate the induction of RIG-1 and MDA-5, which are all involved in the increased expression of HRV-induced interferons (IFNs) during the innate response (Slater et al., 2010; Gavala et al., 2011). Together these findings suggest that these receptors may cooperate synergistically during the HRV stimulated innate immune response. These receptor initiated pathways result is the generation of a variety of cytokines including, IL-8, IL-6, IL-12, IL-15, and INFs (Fig. 1) (Turner, 2001; Wang et al., 2009; Kennedy et al., 2012). Several of these cytokines contribute to virus eradication. For instance, IL-12 and IL-15 are needed for natural killer (NK) cell recruitment and activation as well as INF, specifically IFNγ, generation (Fehniger and Caligiuri 2001; Kennedy et al., 2012). INFs mitigate viral replication and can also promote T cell differentiation and macrophage activation (Kelly and Busse, 2008; Kennedy et al., 2012). Conversely, IL-8 and IL-6 initiate a pro-inflammatory response inducing the recruitment and activation of granulocytes which are associated with the clinical symptoms of the common cold (Wang et al., 2009; Triantafilou et al., 2011). IL-8 correlates with an increase in neutrophil levels in the blood of HRV infected patients (Kennedy et al., 2012). In addition, HRV infected individuals displayed these pro-inflammatory mediators in nasal lavage fluid (Turner, 2001; Kennedy et al., 2012). Therefore, the production of these signaling molecules corresponds to neutrophil accumulation in the nasal exudate, which is frequently seen in symptomatic

patients with HRV infection (Turner, 2001). It is worth noting that peripheral white blood cell count does not increase in asymptomatic infected individuals (Turner, 2001).

Adaptive immune response

T cell infiltration and recruitment is associated with HRV infected airway epithelium and lung tissue, respectively (Levandowski et al., 1986; Fraenkel et al., 1995). It has been suggested that T cell recruitment may eliminate HRV through the activity of T-helper 1 (TH1) cell cytokines, such as IL-2 and IFN-γ (Kelly and Busse, 2008). IL-2 contributes to T cell proliferation whereas IFN-γ, as described previously, functions as an anti-viral agent (Kelly and Busse, 2008). Moreover, T cell recruitment is induced from HRV infected epithelial cells by the chemotaxic factor IP-10, which recognizes a specific receptor on helper and cytotoxic T cells as well as NK cells (Rabin et al., 1999). Activated helper T cells may facilitate a humoral response resulting in antibody (Ab) production; however, the exact role of cytotoxic T cells in HRV elimination is not completely understood (Kennedy et al., 2012).

Ab activity, specifically Immunoglobulin (Ig)A, IgM, and IgG, are observed 3, ~5, and ~7 days post HRV infection, respectively (Message and Johnston, 2001; Kennedy et al., 2012). Although IgA declines with time, serum IgGs, that recognize a specific viral serotype, may remain throughout life (Message and Johnston, 2001). This IgG retention is vital for neutralizing HRV from subsequent infection (Alper et al., 1998). There are a variety of ways for Abs to neutralize and eliminate a viral pathogen. Abs can opsonize the virus for phagocytosis, block the virus from adhering to cellular attachments, and/or stimulate NK cell activation (Kennedy et al., 2012). These beneficial effects reduce the symptoms associated with viral infection and attenuate viral shedding (Alper et al., 1996).

HRV pathogenesis

HRV enters through the nasal or conjunctiva mucosa and eventually localizes in the nasopharynx with the assistance of epithelial cell ciliary movement of mucous (Rollinger and Schmidtke, 2011). HRV will bind to specific host cell receptors on both ciliated and non-ciliated (primarily) epithelial cells and replicate extensively within the first 2 days of infection (Rollinger and Schmidtke, 2011). Researchers have observed that during experimental HRV infection, common HRV symptoms may occur as early as 10–12 h post intranasal administration (Harris and Gwaltney, 1996). HRV can infect both the upper and lower respiratory epithelial tissue. However, non-asthmatic individuals usually only exhibit the symptoms of the upper respiratory tract (Kennedy et al., 2012). Interestingly, biopsies collected and examined from HRV infected nasal epithelium did not consistently reveal cellular damage, thus the complete mechanism of pathogenesis is still not thoroughly understood (Turner et al., 1982; Turner, 2001; Rollinger and Schmidtke, 2011). Yet, as mentioned earlier, these findings suggest that the host immune response may be the key contributor in producing the symptoms often seen in patients with HRV infection. Common cold symptoms including rhinorrhea and nasal obstruction, are a result of mucous hypersecretion, vasodilation, and increased vascular permeability due to enhanced neutrophilic activity at the site of infection (Kennedy et al., 2012). Immunological assays demonstrated a correlation between IL-6 and IL-8 concentration in nasal secretions and severity of symptoms in HRV-induced upper and lower

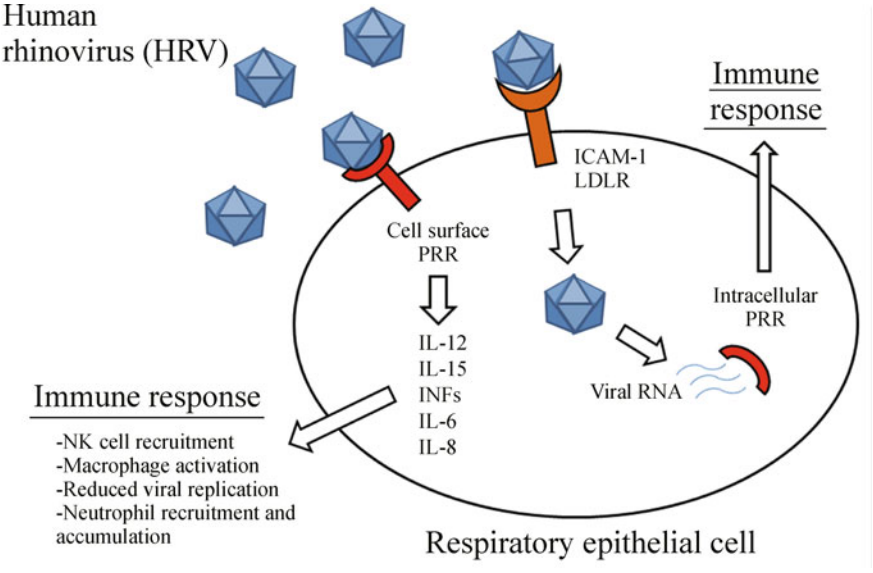

Figure 1 The schematic demonstrates a likely immune response to HRV infection in a respiratory epithelial cell.

respiratory infections (Papadopoulos et al., 2000; Turner et al., 1998). Neutrophilic activity in symptomatic individuals may be due specifically to the increase in IL-8 (Rollinger and Schmidtke, 2011). Douglass et al. reported that IL-8 intranasal administration in non-HRV infected subjects displayed symptoms of the common cold, which suggested an important role of IL-8 in HRV infection (Douglass et al., 1994). The transcription of IL-8 in different cell lines may require the activation of nuclear factor-κB (NF-κB) (Mukaida et al., 1994; Kim et al., 2000). Previous research has shown that HRV16 binding to epithelial cells activate the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway, which ultimately induces NF-κB (Newcomb et al., 2005). Upon activation, this transcription factor will localize to the nucleus and induce the transcription of inflammatory cytokines including IL-8 (Edwards et al., 2007).

HRV induced oxidative stress has been reported as another method for enhancing IL-8 activity. Since the activity of endogenous antioxidants including superoxide dismutase, catalase, and glutathione peroxidase, do not decrease during HRV infection, reactive oxygen species (ROS), such as hydrogen peroxide, over-accumulation is the likely cause of oxidative stress induced IL-8 overexpression (Turner, 2001). Studies involving the alteration or inhibition of the enzyme NADPH-oxidase, a known ROS generator, resulted in decreased levels of HRV induced IL-8 (Kaul et al., 2000; Turner, 2001). These results suggest that this enzyme may be partially responsible for the excessive production of IL-8 via ROS signaling after HRV infection. Moreover, intracellular xanthine oxidase, a common source of superoxide, is active during HRV infection (Gavala et al., 2011). Since superoxide, a type of ROS, is believed to induce expression of ICAM-1, as well as activation of NF-κB, xanthine oxidase is a likely contributor to HRV induced oxidative damage (Papi et al., 2002; 2008). Although the intracellular signaling events initiated by HRV infection are complex, these findings suggest that oxidative stress plays a substantial role in HRV pathogenesis.

Transmission and treatment

Transmission

HRV can be spread by small and large particle aerosols, direct person to person contact, such as hand shaking, or via inanimate objects including door handles and furniture (Turner and Hendley, 2005; Winther et al., 2007). Although the spread of HRV may occur through sneezing and coughing, the efficacy of this type of transmission is relatively low. Therefore, touching contaminated surfaces and subsequent self-inoculation is a more frequent mode of transmission (Turner and Hendley, 2005). This involves rubbing the conjunctiva or the nose with HRV covered fingertips allowing the virus to enter the upper respiratory tract (Hendley and Gwaltney, 1988).

Symptomatic treatments

Treating HRV infection is primarily based on limiting the symptoms. Over-the-counter decongestants and non-steroidal anti-inflammatory drugs have revealed beneficial effects in reducing nasal edema, coughing, and sneezing (Fashner et al., 2012). Zinc has been proposed as a possible treatment option because of its ability to provide protection against respiratory syncytial virus, another common respiratory virus, and inhibit the replication of the rhinovirus 3C protease, which is needed for virus replication (Turner, 2001; Science et al., 2012). However, the results from studies since 1984 have been controversial as to whether zinc treatment can substantially limit the symptoms associated with respiratory virus infections (Science et al., 2012).

Herbal remedies have also been explored. The alkamides of *E. angustifolia* and *E. purpurea* of the plant genus *Echinacea* have demonstrated anti-inflammatory characteristics which may attenuate the over-active immune response frequently seen in HRV infected patients (Müller-Jakic et al., 1994). Conversely, the polysaccharides of *Echinacea* may propagate non-specific immune responses, such as the complement system and cytokines, increasing T cell, macrophage, and NK cell activation (Di Pierro et al., 2012). Therefore, *Echinacea* plants have also been proposed as a possible preventative treatment against HRV infection. However, it is worth noting that if *Echinacea* is to be used as a prophylactic, the alkamide levels during drug preparation must be kept low so as to not interfere with the immunostimulatory properties necessary for protection from infection (Di Pierro et al., 2012).

Vitamin C enhances the immune response by increasing INF generation and proliferation of T lymphocytes (Hemilä, 1996, 1997). Accordingly, its application as a prophylactic against HRV infection has been suggested as well. In a double-blind, 5-year randomized controlled trial conducted by Sasazuki et al., a significant decrease in the occurrence of the common cold in vitamin C treated patients was observed (Sasazuki et al., 2006). However, in this study the definition of the common cold was not adequately described and the results relied on the patients' own interpretation of a common cold. In contrast, another study by Douglas et al. concluded that vitamin C does not reduce the incidence of colds in adults but may have a prophylactic effect in children (Douglas et al., 2007). Thus, the effectiveness of vitamin C as a preventative measure against HRV infection should be explored in future studies.

Antiviral treatments

Blockade of the ICAM-1 receptor was one of the first approaches for developing antiviral treatments against HRV infection (Turner, 2001). Previous *in vitro* studies have demonstrated the inhibition of HRV binding to ICAM-1 using monoclonal antibodies (Colonno et al., 1986). Initially, this

concept was promising from the observation that when intranasal administrations of anti-ICAM-1 antibodies were applied to human volunteer subjects, symptoms and viral shedding were decreased. Unfortunately, marked increases in viral shedding, as well as more severe symptoms, were observed after antibody treatment was suspended (Hayden et al., 1988). Other studies targeted the ICAM-1 receptor, but instead of blocking the attachment of HRV with antibodies, the researchers altered the structure of the ICAM-1 receptor by eliminating the intracellular and transmembrane subunits of the protein (Marlin et al., 1990). When applied to human studies, these soluble ICAMs (sICAM) reduced HRV symptoms. The researchers also observed a reduction in HRV concentration in nasal secretions and IL-8 concentration in nasal lavage fluid from treated subjects (Turner et al., 1999). Yet, treatment with sICAM in this study did not decrease the incidence of infection and the dosing regimen was impractical. Alternatively, viral capsid binding agents have been developed as a way of inhibiting virus attachment. The drug pleconaril binds to the small hydrophobic pocket of VP-1 which is located beneath the ICAM-1 binding canyon on HRV (Rollinger and Schmidtke, 2011). Studies on HRV3 and HRV14 have shown that binding in this way changes the conformation of the HRV canyon and thus inhibits the attachment of the virus to ICAM-1. However, HRV1A attachment was not inhibited by pleconaril, suggesting that this drug may not act universally among different viral serotypes (Rollinger and Schmidtke, 2011).

The HRV 3C protease is a highly conserved, among different HRV serotypes, enzyme required for HRV replication (Turner, 2001). Antiviral therapies targeting this enzyme have been considered a promising area of focus. One *in vitro* study demonstrated the antiviral effects of the 3C protease inhibitor, rupintrivir (Binford et al., 2005). The researchers collected nasal lavage fluid from human volunteers and observed complete inhibition of viral replication in all isolates tested with rupintrivir. Other studies have reported this drug's ability to not only inhibit HRV replication, but also limit HRV-induced IL-6 and IL-8 in a human respiratory cell line (Zalman et al., 2000). The first clinical study of intranasal rupintrivir administration demonstrated decreased illness, reduced viral load, and mild adverse effects (De Palma et al., 2008). However, in a later study involving natural infection, rupintrivir did not display these same beneficial effects, and consequently further development of this inhibitor was discontinued (Patick et al., 2005). Nevertheless, because of the highly conserved region of the 3C protease among many HRV serotypes and its effectiveness *in vitro*, further research into the development of these inhibitors should continue.

Due to the large number of serotypes (>100), creating a drug that displays universal inhibitory effects has remained a challenge (Binford et al., 2005; Rollinger and Schmidtke, 2011). The most efficient method for producing broad spectrum anti-HRV drugs should focus on highly conserved regions among different serotypes. Due to the generally mild symptoms and the self-limiting nature of HRV, prospective drugs must be safe and display very little adverse side effects as well as eliminate the possibility of viral resistance.

Influences on COPD

COPD exacerbations account for most COPD healthcare expenditures, particularly those requiring hospitalization, and are also associated with decreased quality of life and reduced lung function (Donaldson et al., 2002). Acute exacerbations of COPD are a major cause of mortality, morbidity, and contribute to amplified healthcare costs (Sullivan et al., 2000). According to the US Department of Health and Human Services, in 2010 the United States expenditures were estimated at over $49 billion in direct costs alone. Aside from financial burden, exacerbations are also associated with clinically debilitating symptoms such as increased airway and systemic inflammation, airway edema, mucus plugging, and bronchoconstriction. Treatments for these symptoms may require hospitalization and can lead to costly interventions such as mechanical ventilation.

Studies of COPD exacerbations have estimated that ~ 50% are caused by viruses; HRV is numerically the most prevalent viral type (Papi et al., 2006; Ko et al., 2008). Several researchers have explored viral infections detected at increased frequency during COPD exacerbations (Papi et al., 2006; Wilkinson et al., 2006). Various models of viral exacerbation have been described in COPD subjects. An infective dose of rhinovirus was administered by nebulized inhalation route to stimulate an acute exacerbation with reduced pulmonary function (Mallia et al., 2006). However, a more recent viral exacerbation model by the same research group found increases in respiratory symptoms in COPD subjects as compared to their healthy counterparts (Mallia et al., 2011). COPD patients in the study exhibited increased airflow obstruction, systemic and prolonged airway inflammation, and increased neutrophil count following rhinovirus inoculation. The researchers concluded that experimental rhinovirus inoculation produced upper and lower respiratory symptoms thereby supporting a causal relationship between virus infection and COPD exacerbation (Mallia et al., 2011). Moreover, two studies suggested that greater susceptibility to rhinovirus infection is due to upregulation of adhesion molecule ICAM-1 receptors in patients with COPD. Retamales et al. related this to latent expression of adenoviral E1A in alveolar epithelial cells of patients with emphysema (Retamales et al., 2001). Sajjan et al. associated chronic bacterial colonization in bronchial epithelial cells to increasing the expression of ICAM-1 and TLR-3 for HRV in these cells (Sajjan et al., 2006). Others related increased exacerbations with inflammatory response mechanisms and suggested transcription factors controlling production of the anti-inflammatories become a target of novel anti-microbials (Potena et al., 2007). Current treatment for COPD exacerba-

tion includes pharmacotherapy (bronchodilators and oral/inhaled corticosteroids), supplemental oxygen, and sometimes mechanical ventilation, depending on severity. Treatments described in the literature have demonstrated limited efficacy, as shown to be partially effective, which has unfavorable side effects, and may not address underlying mechanisms. For example, the therapeutic effect of steroid administration reduced the absolute treatment failure rate by only 10% and shortened length of hospital stay by only 1 or 2 days (Niewoehner, 2002). Similarly disappointing therapeutic effects are noted in the prevention of COPD exacerbation. Optimum therapy combining long-acting bronchodilators (beta-2 agonists or anticholinergics) and inhaled corticosteroids are only able to decrease the frequency of exacerbation by approximately 20% (Casaburi et al., 2002; Calverley et al., 2003). Current therapeutic interventions for viral COPD exacerbation have not been found to be effective in the prevention or treatment of these exacerbations. Therefore, it is important to develop effective anti-HRV therapeutic programs to halt HRV induced COPD exacerbations. Aforementioned strategies such as hand-washing and preventative efforts to reduce modes of transmission should be encouraged in this high-risk population. Although current therapeutic interventions for viral COPD exacerbation have not been found to be effective in the prevention or treatment of these exacerbations, the continued discovery explores the mechanism of virus-induced COPD exacerbation, targeting mediators in the pathogenesis of viral infection will subsequently ensue.

Summary

The complete mechanism of HRV attachment, uncoating, and replication is complex and still not completely understood. The different antigenic characteristics of the varying HRV serotypes make it difficult to map a universal mechanism. Although there are a wide variety of HRV serotypes, the potential for serious respiratory complications is quite low. Some individuals, such as asthmatics or COPD subjects, may display more severe symptoms from HRV infection. This difference in illness may be due to the varying susceptibility to HRV infection and immune system sensitivity between different individuals. Current treatment options focus primarily on limiting HRV symptoms and specific molecular mechanism of HRV attachment and replication, which will aid in the development of antiviral drugs. However, the most effective method to avoid the common cold symptoms of HRV infection is to limit the efficacy of transmission, especially during the change in seasons.

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Compliance with ethics guidelines

William J. Roberts, Georgianna G. Sergakis, and Li Zuo declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

Alper C M, Doyle W J, Skoner D P, Buchman C A, Cohen S, Gwaltney J M (1998). Prechallenge antibodies moderate disease expression in adults experimentally exposed to rhinovirus strain hanks. Clin Infect Dis, 27(1): 119–128

Alper C M, Doyle W J, Skoner D P, Buchman C A, Seroky J T, Gwaltney J M, Cohen S A (1996). Prechallenge antibodies: moderators of infection rate, signs, and symptoms in adults experimentally challenged with rhinovirus type 39. Laryngoscope, 106(10): 1298–1305

Andries K, Dewindt B, Snoeks J, Wouters L, Moereels H, Lewi P J, Janssen P A (1990). Two groups of rhinoviruses revealed by a panel of antiviral compounds present sequence divergence and differential pathogenicity. J Virol, 64(3): 1117–1123

Arruda E, Pitkäranta A, Witek T J Jr, Doyle C A, Hayden F G (1997). Frequency and natural history of rhinovirus infections in adults during autumn. J Clin Microbiol, 35(11): 2864–2868

Barral P M, Sarkar D, Fisher P B, Racaniello V R (2009). RIG-I is cleaved during picornavirus infection. Virology, 391(2): 171–176

Bella J, Rossmann M G (2000). ICAM-1 receptors and cold viruses. Pharm Acta Helv, 74(2–3): 291–297

Binford S L, Maldonado F, Brothers M A, Weady P T, Zalman L S, Meador J W 3rd, Matthews D A, Patick A K (2005). Conservation of amino acids in human rhinovirus 3C protease correlates with broad-spectrum antiviral activity of rupintrivir, a novel human rhinovirus 3C protease inhibitor. Antimicrob Agents Chemother, 49(2): 619–626

Bochkov Y A, Palmenberg A C, Lee W M, Rathe J A, Amineva S P, Sun X, Pasic T R, Jarjour N N, Liggett S B, Gern J E (2011). Molecular modeling, organ culture and reverse genetics for a newly identified human rhinovirus C. Nat Med, 17(5): 627–632

Brabec M, Schober D, Wagner E, Bayer N, Murphy R F, Blaas D, Fuchs R (2005). Opening of size-selective pores in endosomes during human rhinovirus serotype 2 *in vivo* uncoating monitored by single-organelle flow analysis. J Virol, 79(2): 1008–1016

Brabec-Zaruba M, Pfanzagl B, Blaas D, Fuchs R (2009). Site of human rhinovirus RNA uncoating revealed by fluorescent in situ hybridization. J Virol, 83(8): 3770–3777

Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C, and the TRial of Inhaled STeroids ANd long-acting beta2 agonists study group (2003). Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet, 361(9356): 449–456

Casaburi R, Mahler D A, Jones P W, Wanner A, San P G, ZuWallack R

L, Menjoge S S, Serby C W, Witek T Jr (2002). A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J, 19(2): 217–224

Colonno R J, Callahan P L, Long W J (1986). Isolation of a monoclonal antibody that blocks attachment of the major group of human rhinoviruses. J Virol, 57(1): 7–12

De Palma A M, Vliegen I, De Clercq E, Neyts J (2008). Selective inhibitors of picornavirus replication. Med Res Rev, 28(6): 823–884

Di Pierro F, Rapacioli G, Ferrara T, Togni S (2012). Use of a standardized extract from Echinacea angustifolia (Polinacea) for the prevention of respiratory tract infections. Altern Med Rev, 17(1): 36–41

Donaldson G C, Seemungal T A, Bhowmik A, Wedzicha J A (2002). Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax, 57(10): 847–852

Douglas R M, Hemilä H, Chalker E, Treacy B (2007). Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev, (3): CD000980

Douglass J A, Dhami D, Gurr C E, Bulpitt M, Shute J K, Howarth P H, Lindley I J, Church M K, Holgate S T (1994). Influence of interleukin-8 challenge in the nasal mucosa in atopic and nonatopic subjects. Am J Respir Crit Care Med, 150(4): 1108–1113

Drahos J, Racaniello V R (2009). Cleavage of IPS-1 in cells infected with human rhinovirus. J Virol, 83(22): 11581–11587

Edwards M R, Hewson C A, Laza-Stanca V, Lau H T, Mukaida N, Hershenson M B, Johnston S L (2007). Protein kinase R, IkappaB kinase-beta and NF-kappaB are required for human rhinovirus induced pro-inflammatory cytokine production in bronchial epithelial cells. Mol Immunol, 44(7): 1587–1597

Fashner J, Ericson K, Werner S (2012). Treatment of the common cold in children and adults. Am Fam Physician, 86(2): 153–159

Fehniger T A, Caligiuri M A (2001). Interleukin 15: biology and relevance to human disease. Blood, 97(1): 14–32

Fraenkel D J, Bardin P G, Sanderson G, Lampe F, Johnston S L, Holgate S T (1995). Lower airways inflammation during rhinovirus colds in normal and in asthmatic subjects. Am J Respir Crit Care Med, 151(3 Pt 1): 879–886

Fuchs R, Blaas D (2010). Uncoating of human rhinoviruses. Rev Med Virol, 20(5): 281–297

Gavala M L, Bertics P J, Gern J E (2011). Rhinoviruses, allergic inflammation, and asthma. Immunol Rev, 242(1): 69–90

Giranda V L, Heinz B A, Oliveira M A, Minor I, Kim K H, Kolatkar P R, Rossmann M G, Rueckert R R (1992). Acid-induced structural changes in human rhinovirus 14: possible role in uncoating. Proc Natl Acad Sci USA, 89(21): 10213–10217

Gwaltney J M Jr, Hendley J O, Simon G, Jordan W S Jr (1967). Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. JAMA, 202(6): 494–500

Haghighat A, Svitkin Y, Novoa I, Kuechler E, Skern T, Sonenberg N (1996). The eIF4G-eIF4E complex is the target for direct cleavage by the rhinovirus 2A proteinase. J Virol, 70(12): 8444–8450

Harris J M 2nd, Gwaltney J M Jr (1996). Incubation periods of experimental rhinovirus infection and illness. Clin Infect Dis, 23(6): 1287–1290

Hayden F G, Gwaltney J M Jr, Colonno R J (1988). Modification of experimental rhinovirus colds by receptor blockade. Antiviral Res, 9 (4): 233–247

Hemilä H (1996). Vitamin C and common cold incidence: a review of studies with subjects under heavy physical stress. Int J Sports Med, 17(5): 379–383

Hemilä H (1997). Vitamin C intake and susceptibility to the common cold. Br J Nutr, 77(1): 59–72

Hendley J O, Gwaltney J M Jr (1988). Mechanisms of transmission of rhinovirus infections. Epidemiol Rev, 10: 243–258

Hewson C A, Jardine A, Edwards M R, Laza-Stanca V, Johnston S L (2005). Toll-like receptor 3 is induced by and mediates antiviral activity against rhinovirus infection of human bronchial epithelial cells. J Virol, 79(19): 12273–12279

Jakiela B, Brockman-Schneider R, Amineva S, Lee W M, Gern J E (2008). Basal cells of differentiated bronchial epithelium are more susceptible to rhinovirus infection. Am J Respir Cell Mol Biol, 38(5): 517–523

Kato H, Sato S, Yoneyama M, Yamamoto M, Uematsu S, Matsui K, Tsujimura T, Takeda K, Fujita T, Takeuchi O, Akira S (2005). Cell type-specific involvement of RIG-I in antiviral response. Immunity, 23(1): 19–28

Kaul P, Biagioli M C, Singh I, Turner R B (2000). Rhinovirus-induced oxidative stress and interleukin-8 elaboration involves p47-phox but is independent of attachment to intercellular adhesion molecule-1 and viral replication. J Infect Dis, 181(6): 1885–1890

Kelly J T, Busse W W (2008). Host immune responses to rhinovirus: Mechanisms in asthma. J Allergy Clin Immunol, 122: 671–682; quiz 683–674

Kennedy J L, Turner R B, Braciale T, Heymann P W, Borish L (2012). Pathogenesis of rhinovirus infection. Curr Opin Virol, 2(3): 287–293

Khan A G, Pichler J, Rosemann A, Blaas D (2007). Human rhinovirus type 54 infection via heparan sulfate is less efficient and strictly dependent on low endosomal pH. J Virol, 81(9): 4625–4632

Kim J, Sanders S P, Siekierski E S, Casolaro V, Proud D (2000). Role of NF-kappa B in cytokine production induced from human airway epithelial cells by rhinovirus infection. J Immunol, 165(6): 3384–3392

Kim W K, Gern J E (2012). Updates in the relationship between human rhinovirus and asthma. Allergy Asthma Immunol Res, 4(3): 116–121

Ko F W, Ip M, Chan P K, Ng S S, Chau S S, Hui D S (2008). A one-year prospective study of infectious etiology in patients hospitalized with acute exacerbations of COPD and concomitant pneumonia. Respir Med, 102(8): 1109–1116

Laine P, Blomqvist S, Savolainen C, Andries K, Hovi T (2006). Alignment of capsid protein VP1 sequences of all human rhinovirus prototype strains: conserved motifs and functional domains. J Gen Virol, 87(Pt 1): 129–138

Levandowski R A, Ou D W, Jackson G G (1986). Acute-phase decrease of T lymphocyte subsets in rhinovirus infection. J Infect Dis, 153(4): 743–748

Liebig H D, Ziegler E, Yan R, Hartmuth K, Klump H, Kowalski H, Blaas D, Sommergruber W, Frasel L, Lamphear B, et al (1993). Purification of two picornaviral 2A proteinases: interaction with eIF-4 gamma and influence on in vitro translation. Biochemistry, 32(29): 7581–7588

Lopez-Souza N, Dolganov G, Dubin R, Sachs L A, Sassina L, Sporer H, Yagi S, Schnurr D, Boushey H A, Widdicombe J H (2004). Resistance of differentiated human airway epithelium to infection by

rhinovirus. Am J Physiol Lung Cell Mol Physiol, 286(2): L373–L381

Mallia P, Message S D, Gielen V, Contoli M, Gray K, Kebadze T, Aniscenko J, Laza-Stanca V, Edwards M R, Slater L, Papi A, Stanciu L A, Kon O M, Johnson M, Johnston S L (2011). Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. Am J Respir Crit Care Med, 183(6): 734–742

Mallia P, Message S D, Kebadze T, Parker H L, Kon O M, Johnston S L (2006). An experimental model of rhinovirus induced chronic obstructive pulmonary disease exacerbations: a pilot study. Respir Res, 7(1): 116

Marlin S D, Staunton D E, Springer T A, Stratowa C, Sommergruber W, Merluzzi V J (1990). A soluble form of intercellular adhesion molecule-1 inhibits rhinovirus infection. Nature, 344(6261): 70–72

McManus T E, Marley A M, Baxter N, Christie S N, O'Neill H J, Elborn J S, Coyle P V, Kidney J C (2008). Respiratory viral infection in exacerbations of COPD. Respir Med, 102(11): 1575–1580

Message S D, Johnston S L (2001). The immunology of virus infection in asthma. Eur Respir J, 18(6): 1013–1025

Mukaida N, Okamoto S, Ishikawa Y, Matsushima K (1994). Molecular mechanism of interleukin-8 gene expression. J Leukoc Biol, 56(5): 554–558

Müller-Jakic B, Breu W, Pröbstle A, Redl K, Greger H, Bauer R (1994). *In vitro* inhibition of cyclooxygenase and 5-lipoxygenase by alkamides from *Echinacea* and *Achillea* species. Planta Med, 60 (1): 37–40

Newcomb D C, Sajjan U, Nanua S, Jia Y, Goldsmith A M, Bentley J K, Hershenson M B (2005). Phosphatidylinositol 3-kinase is required for rhinovirus-induced airway epithelial cell interleukin-8 expression. J Biol Chem, 280(44): 36952–36961

Niewoehner D E (2002). The role of systemic corticosteroids in acute exacerbation of chronic obstructive pulmonary disease. Am J Respir Med, 1(4): 243–248

Olson N H, Kolatkar P R, Oliveira M A, Cheng R H, Greve J M, McClelland A, Baker T S, Rossmann M G (1993). Structure of a human rhinovirus complexed with its receptor molecule. Proc Natl Acad Sci USA, 90(2): 507–511

Papadopoulos N G, Bates P J, Bardin P G, Papi A, Leir S H, Fraenkel D J, Meyer J, Lackie P M, Sanderson G, Holgate S T, Johnston S L (2000). Rhinoviruses infect the lower airways. J Infect Dis, 181(6): 1875–1884

Papi A, Bellettato C M, Braccioni F, Romagnoli M, Casolari P, Caramori G, Fabbri L M, Johnston S L (2006). Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med, 173(10): 1114–1121

Papi A, Contoli M, Gasparini P, Bristot L, Edwards M R, Chicca M, Leis M, Ciaccia A, Caramori G, Johnston S L, Pinamonti S (2008). Role of xanthine oxidase activation and reduced glutathione depletion in rhinovirus induction of inflammation in respiratory epithelial cells. J Biol Chem, 283(42): 28595–28606

Papi A, Papadopoulos N G, Stanciu L A, Bellettato C M, Pinamonti S, Degitz K, Holgate S T, Johnston S L (2002). Reducing agents inhibit rhinovirus-induced up-regulation of the rhinovirus receptor intercellular adhesion molecule-1 (ICAM-1) in respiratory epithelial cells. FASEB J, 16(14): 1934–1936

Pappas D E, Hendley J O, Hayden F G, Winther B (2008). Symptom profile of common colds in school-aged children. Pediatr Infect Dis J, 27(1): 8–11

Patick A K, Brothers M A, Maldonado F, Binford S, Maldonado O, Fuhrman S, Petersen A, Smith G J 3rd, Zalman L S, Burns-Naas L A, Tran J Q (2005). *In vitro* antiviral activity and single-dose pharmacokinetics in humans of a novel, orally bioavailable inhibitor of human rhinovirus 3C protease. Antimicrob Agents Chemother, 49 (6): 2267–2275

Potena A, Caramori G, Casolari P, Contoli M, Johnston S L, Papi A (2007). Pathophysiology of viral-induced exacerbations of COPD. Int J Chron Obstruct Pulmon Dis, 2(4): 477–483

Prchla E, Plank C, Wagner E, Blaas D, Fuchs R (1995). Virus-mediated release of endosomal content in vitro: different behavior of adenovirus and rhinovirus serotype 2. J Cell Biol, 131(1): 111–123

Rabin R L, Park M K, Liao F, Swofford R, Stephany D, Farber J M (1999). Chemokine receptor responses on T cells are achieved through regulation of both receptor expression and signaling. J Immunol, 162(7): 3840–3850

Retamales I, Elliott W M, Meshi B, Coxson H O, Pare P D, Sciurba F C, Rogers R M, Hayashi S, Hogg J C (2001). Amplification of inflammation in emphysema and its association with latent adenoviral infection. Am J Respir Crit Care Med, 164(3): 469–473

Rollinger J M, Schmidtke M (2011). The human rhinovirus: human-pathological impact, mechanisms of antirhinoviral agents, and strategies for their discovery. Med Res Rev, 31(1): 42–92

Sajjan U S, Jia Y, Newcomb D C, Bentley J K, Lukacs N W, LiPuma J J, Hershenson M B (2006). H. influenzae potentiates airway epithelial cell responses to rhinovirus by increasing ICAM-1 and TLR3 expression. FASEB J, 20(12): 2121–2123

Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Hayashi M, Tsugane S (2006). Effect of vitamin C on common cold: randomized controlled trial. Eur J Clin Nutr, 60(1): 9–17

Savolainen-Kopra C, Korpela T, Simonen-Tikka M L, Amiryousefi A, Ziegler T, Roivainen M, Hovi T (2012). Single treatment with ethanol hand rub is ineffective against human rhinovirus—hand washing with soap and water removes the virus efficiently. J Med Virol, 84(3): 543–547

Schneider W J, Nimpf J (2003). LDL receptor relatives at the crossroad of endocytosis and signaling. Cell Mol Life Sci, 60(5): 892–903

Science M, Johnstone J, Roth D E, Guyatt G, Loeb M (2012). Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials. CMAJ, 184(10): E551–E561

Skern T, Torgersen H, Auer H, Kuechler E, Blaas D (1991). Human rhinovirus mutants resistant to low pH. Virology, 183(2): 757–763

Slater L, Bartlett N W, Haas J J, Zhu J, Message S D, Walton R P, Sykes A, Dahdaleh S, Clarke D L, Belvisi M G, Kon O M, Fujita T, Jeffery P K, Johnston S L, Edwards M R (2010). Co-ordinated role of TLR3, RIG-I and MDA5 in the innate response to rhinovirus in bronchial epithelium. PLoS Pathog, 6(11): e1001178

Snyers L, Zwickl H, Blaas D (2003). Human rhinovirus type 2 is internalized by clathrin-mediated endocytosis. J Virol, 77(9): 5360–5369

Sommergruber W, Ahorn H, Klump H, Seipelt J, Zoephel A, Fessl F, Krystek E, Blaas D, Kuechler E, Liebig H D, Skern T (1994). 2A proteinases of coxsackie- and rhinovirus cleave peptides derived from eIF-4 gamma via a common recognition motif. Virology, 198 (2): 741–745

Strickland D K, Gonias S L, Argraves W S (2002). Diverse roles for the LDL receptor family. Trends Endocrinol Metab, 13(2): 66–74

Sullivan S D, Ramsey S D, Lee T A (2000). The economic burden of COPD. Chest, 117(2 Suppl): 5S–9S

Triantafilou K, Vakakis E, Richer E A, Evans G L, Villiers J P, Triantafilou M (2011). Human rhinovirus recognition in non-immune cells is mediated by Toll-like receptors and MDA-5, which trigger a synergetic pro-inflammatory immune response. Virulence, 2(1): 22–29

Turner R B (2001). The treatment of rhinovirus infections: progress and potential. Antiviral Res, 49(1): 1–14

Turner R B, Hendley J O (2005). Virucidal hand treatments for prevention of rhinovirus infection. J Antimicrob Chemother, 56(5): 805–807

Turner R B, Hendley J O, Gwaltney J M Jr (1982). Shedding of infected ciliated epithelial cells in rhinovirus colds. J Infect Dis, 145(6): 849–853

Turner R B, Wecker M T, Pohl G, Witek T J, McNally E, St George R, Winther B, Hayden F G (1999). Efficacy of tremacamra, a soluble intercellular adhesion molecule 1, for experimental rhinovirus infection: a randomized clinical trial. JAMA, 281(19): 1797–1804

Turner R B, Weingand K W, Yeh C H, Leedy D W (1998). Association between interleukin-8 concentration in nasal secretions and severity of symptoms of experimental rhinovirus colds. Clin Infect Dis, 26(4): 840–846

Tyrrell D A, Cohen S, Schlarb J E (1993). Signs and symptoms in common colds. Epidemiol Infect, 111(1): 143–156

Uncapher C R, DeWitt C M, Colonno R J (1991). The major and minor group receptor families contain all but one human rhinovirus serotype. Virology, 180(2): 814–817

Vlasak M, Roivainen M, Reithmayer M, Goesler I, Laine P, Snyers L, Hovi T, Blaas D (2005). The minor receptor group of human rhinovirus (HRV) includes HRV23 and HRV25, but the presence of a lysine in the VP1 HI loop is not sufficient for receptor binding. J Virol, 79(12): 7389–7395

Wang Q, Nagarkar D R, Bowman E R, Schneider D, Gosangi B, Lei J, Zhao Y, McHenry C L, Burgens R V, Miller D J, Sajjan U, Hershenson M B (2009). Role of double-stranded RNA pattern recognition receptors in rhinovirus-induced airway epithelial cell responses. J Immunol, 183(11): 6989–6997

Wat D, Gelder C, Hibbitts S, Cafferty F, Bowler I, Pierrepoint M, Evans R, Doull I (2008). The role of respiratory viruses in cystic fibrosis. J Cyst Fibros, 7(4): 320–328

Wilkinson T M, Hurst J R, Perera W R, Wilks M, Donaldson G C, Wedzicha J A (2006). Effect of interactions between lower airway bacterial and rhinoviral infection in exacerbations of COPD. Chest, 129(2): 317–324

Winther B, Arruda E, Witek T J, Marlin S D, Tsianco M M, Innes D J, Hayden F G (2002). Expression of ICAM-1 in nasal epithelium and levels of soluble ICAM-1 in nasal lavage fluid during human experimental rhinovirus infection. Arch Otolaryngol Head Neck Surg, 128(2): 131–136

Winther B, Greve J M, Gwaltney J M Jr, Innes D J, Eastham J R, McClelland A, Hendley J O (1997). Surface expression of intercellular adhesion molecule 1 on epithelial cells in the human adenoid. J Infect Dis, 176(2): 523–525

Winther B, McCue K, Ashe K, Rubino J R, Hendley J O (2007). Environmental contamination with rhinovirus and transfer to fingers of healthy individuals by daily life activity. J Med Virol, 79(10): 1606–1610

Xing L, Casasnovas J M, Cheng R H (2003). Structural analysis of human rhinovirus complexed with ICAM-1 reveals the dynamics of receptor-mediated virus uncoating. J Virol, 77(11): 6101–6107

Xing L, Tjarnlund K, Lindqvist B, Kaplan G G, Feigelstock D, Cheng R H, Casasnovas J M (2000). Distinct cellular receptor interactions in poliovirus and rhinoviruses. EMBO J, 19(6): 1207–1216

Yoneyama M, Kikuchi M, Matsumoto K, Imaizumi T, Miyagishi M, Taira K, Foy E, Loo Y M, Gale M Jr, Akira S, Yonehara S, Kato A, Fujita T (2005). Shared and unique functions of the DExD/H-box helicases RIG-I, MDA5, and LGP2 in antiviral innate immunity. J Immunol, 175(5): 2851–2858

Zalman L S, Brothers M A, Dragovich P S, Zhou R, Prins T J, Worland S T, Patick A K (2000). Inhibition of human rhinovirus-induced cytokine production by AG7088, a human rhinovirus 3C protease inhibitor. Antimicrob Agents Chemother, 44(5): 1236–1241