HHS Public Access

Author manuscript

Curr Allergy Asthma Rep. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Curr Allergy Asthma Rep. 2016 April ; 16(4): 30. doi:10.1007/s11882-016-0608-7.

Rhinoviruses and Their Receptors: Implications for Allergic Disease

Yury A. Bochkov[a,#] and **James E. Gern**[a,b]

[a]Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA

[b]Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA

Abstract

Human rhinoviruses (RVs) are picornaviruses that can cause a variety of illnesses including the common cold, lower respiratory tract illnesses such as bronchitis and pneumonia, and exacerbations of asthma. RVs are classified into three species, RV-A, B and C, which include over 160 types. They utilize three major types of cellular membrane glycoproteins to gain entry into the host cell: intercellular adhesion molecule 1 (ICAM-1) (the majority of RV-A and all RV-B), low density lipoprotein receptor (LDLR) family members (12 RV-A types) and cadherin-related family member 3 (CDHR3) (RV-C). CDHR3 is a member of cadherin superfamily of transmembrane proteins with yet unknown biological function, and there is relatively little information available about the mechanisms of RV-C interaction with CDHR3. A coding single nucleotide polymorphism (rs6967330) in CDHR3 could promote RV-C infections and illnesses in infancy, which could in turn adversely affect the developing lung to increase the risk of asthma. Further studies are needed to determine how RV infections contribute to pathogenesis of asthma and to develop the optimal treatment approach to control asthma exacerbations.

Keywords

Human rhinovirus; cellular receptor; ICAM-1; LDLR; CDHR3; asthma; allergy

Introduction

Human rhinoviruses (RVs) are non-enveloped positive-strand RNA viruses in the family *Picornaviridae*, genus *Enterovirus* classified into three species (RV-A, B and C) according to phylogenetic sequence criteria and distinct genomic features. Clinical isolates of RV-A and RV-B identified by 1987 [1] were classified into 100 serotypes based on their antigenic cross-reactivity in serum neutralization tests, while more recently isolated A and B (geno)types ($n = 15$) were assigned solely on sequence identity criteria [2]. The third species

[#]Correspondence: Yury A Bochkov, K4/945 CSC #9988, 600 Highland Ave, Madison, WI 53792-9988, Fax: (608) 265-2207, Phone: (608) 263-8553, yabochkov@wisc.edu.

Conflict of interest: YAB declares that he has no conflict of interest. JEG has served as a consultant to PREP Biopharm Inc, Janssen and Regeneron and has received a lecture honorarium from Boehringer Ingelheim.

(RV-C) were identified beginning in 2006 [3, 4] with the development of highly-sensitive molecular detection techniques since RV-C clinical isolates did not propagate in standard cell culture (such as HeLa or embryonic lung fibroblasts) [5–8]. Current genetically-based classification assigns RV-C isolates into 65 types (including 10 provisionally assigned types) using sequence diversity thresholds in two capsid-coding genes (13% nucleotide divergence in VP1 and/or >10% divergence in VP4/VP2 when VP1 sequences are lacking) [2, 9].

RVs is the most frequent cause of the common cold, but can also induce more severe lower respiratory tract illnesses such as bronchitis and pneumonia and provoke exacerbations of asthma, cystic fibrosis and chronic obstructive pulmonary disease [10–13]. It is now recognized that wheezing illnesses in infancy caused by RV are strongly associated with a high risk of developing asthma in genetically predisposed children, however, the pathogenic mechanisms underlying both asthma inception and exacerbation are not yet clearly understood [14–16]. RV-A and RV-C isolates are more virulent in infants, and are more likely to cause exacerbations of childhood asthma compared to RV-B [17–25].

RV-A and RV-B serotypes were classified into two groups, major and minor, on the basis of cellular receptor specificity, utilizing either intercellular adhesion molecule 1 (ICAM-1) or low density lipoprotein receptor (LDLR) family members for cell entry [26], whereas RV-C receptor remained unknown until recently [27]. Failure of the conventional cell culture systems to support RV-C growth along with the unique amino acid composition profiles of the available RV-C capsid sequences in the putative ICAM-1 and LDLR receptor footprint sites, inconsistent with both major and minor group receptor interactions, suggested unique receptor specificity. After development of a first reverse genetics system for RV-C, we demonstrated that the full-length viral RNA transcripts synthesized *in vitro* were infectious when transfected into cell lines resistant to RV-C infection [8]. We and others also developed the first culture systems for RV-C (sinus mucosal organ culture and air-liquid interface (ALI) culture of differentiated airway epithelial cells) [8, 28–31], and recently discovered that cadherin-related family member 3 (CDHR3), a transmembrane protein with yet unknown biological function, mediates virus binding and replication [27].

Allergic diseases are caused by a hypersensitivity to normally harmless non-infectious antigens and mediated by allergen specific immunoglobulin E (IgE) antibody response and T helper type 2 (Th2) cells. Chronic allergic inflammation induced by prolonged or repetitive exposure to allergens is characterized by the presence of large numbers of eosinophils, mast cells and some other immune cells, as well as physiological changes in structural cells and extracellular matrix in the affected tissues. A number of cross-regulatory mechanisms between the antiviral and allergic immune responses that might play a role in the pathophysiology of allergic diseases have been revealed in both the *in vitro* and *in vivo* human studies [32–35]. RV may also directly induce specific IgE response in children with high total IgE levels, however, its role in promoting allergic response and inflammation is uncertain [36].

Rhinoviruses replicate their genome and produce progeny in epithelial cells of upper and lower respiratory tract. They have been recovered in specimens obtained from the nose, sinuses, larynx, nasopharynx, trachea, bronchi as well as conjunctiva and middle ear [37–

42]. Diseases of the respiratory tract, including rhinosinusitis, allergic rhinitis and bronchial asthma are one of the most common reasons for doctor visits in the United States and their prevalence and the impact on health care costs keep increasing [43]. About 80% percent of childhood asthma [44, 45] and more than 50% of adult asthma have been reported to be allergic [46], and respiratory viral infections are the most important triggers for exacerbations in asthmatic patients [10, 47].

The relationship between viral respiratory infections, allergic inflammation and asthma as well as possible molecular mechanisms of virus-allergen interactions in development and exacerbation of asthma have been extensively reviewed [32, 34, 35]. In this article, we will briefly discuss known cellular receptors utilized by RVs, molecular signaling induced by virus binding, entry and replication in host cells, and provide an update on CDHR3 protein recently implicated in RV-C entry.

Rhinovirus receptors and entry to host cells

Receptor-mediated endocytosis

Rhinoviruses can utilize several cellular receptors in order to cross the plasma membrane by endocytosis, release their genome from viral capsid via structural rearrangements, and deliver it to the site of polyprotein translation and replication in the cytoplasm. Endocytosis, a form of active transport of various molecules into the cell, describes the *de novo* production of internal membranes from the plasma membrane. It plays a key role in nutrient uptake, cell signaling, cell shape changes and often exploited by viruses for internalization into cells. There are several distinct endocytic pathways coexisting in mammalian cells that are best defined through their differential dependencies on certain lipids and proteins, including clathrin, caveolin, flotillin, kinases, small G proteins, actin, dynamin etc. [48]. Although some cargoes enter exclusively by one pathway, most cargoes can enter by several pathways. Endocytosis of transmembrane receptors upon binding to specific extracellular ligands removes them from the surface; this process generally occurs via clathrin-coated pits and vesicles.

Productive entry pathways of RV-A and RV-B have been extensively studied, mostly in established model cell lines such as HeLa [49, 50], whereas molecular mechanisms of RV-C entry and receptor-mediated signaling are unknown. Both the major and minor group RVs are internalized by a clathrin- and dynamin-dependent receptor-mediated endocytosis in HeLa cells [51, 52], however, minor group RV can also enter via clathrin- and dynamin-independent pathway [53]. The only other known receptor that can be alternatively exploited by some major group RV types (RV-A8, A54 and A89) in cultured ICAM-1-negative cells is heparan sulfate [54, 55], and virus entry in this case depends primarily on low endosomal pH and dynamin but not on clathrin, caveolin, or flotillin [56].

Identification of RV-A and RV-B receptors

The major group RV cellular receptor ICAM-1 was identified in 1989 by three independent research groups [57–59], and five years later followed by the discovery of LDLR family members as the receptors for minor group rhinoviruses, which includes only 12 known RV-

A types [60]. In both cases, the functional receptors were identified by screening monoclonal antibodies that inhibit RV infection and recognize cellular membrane proteins with binding activity to RVs *in vitro*, and validated by up- or downregualtion of the target protein expression in cultured cells. These receptors belong to two different families of transmembrane glycoproteins with well-characterized properties.

ICAM-1 is a member of the immunoglobulin (Ig) superfamily of cell adhesion molecules expressed by several cell types including leukocytes, epithelial and endothelial cells. ICAM-1 is composed of five immunoglobulin (Ig) domains (extracellular part), a transmembrane region, and a short cytoplasmic domain [61]. It plays a major role in leukocyte migration from blood to the tissues in inflammatory sites via binding to two membrane-bound integrin receptors, leukocyte function-associated antigen (LFA-1) [62], and macrophage-1 antigen (Mac-1) [63].

The LDLR family comprises at least three members that can bind and internalize RV including the LDLR, the very low density lipoprotein receptor (VLDLR), and the LDLR related protein (LRP). Receptors in this family are recognized by the presence of several structural modules in their extracellular regions and overall similar domain arrangements that include ligand-binding repeats, epidermal growth factor precursor repeats, YMTD spacer domains (β-propeller modules), a single transmembrane domain, and a relatively short cytoplasmic tail [64, 65]. LDLR is responsible for uptake of its natural ligand, cholesterol-carrying lipoprotein particles, into cells by endocytosis via clathrin-coated pits, and their release upon delivery to the low pH milieu of the endosome [66]. The cytoplasmic tail of the LDLR family members contains motifs for interaction with a number of cytoplasmic adaptor and scaffold proteins, and mediates signal transduction [64].

ICAM-1 vs LDLR binding and entry in HeLa cells

There are some differences in the subcellular localization between major and minor group receptors. ICAM-1 is located at the plasma membrane and also in the cytoplasm on the apicolateral portions of the airway epithelial cells [67, 68], whereas LDLR family members are endocytic recycling receptors found mainly in recycling endosomes and, to a lesser extent, at the plasma membrane [69, 70]. Although the structural changes in the viral capsid of both major and minor group RVs similarly result in a stepwise transition from native virus to subviral particles and release of the RNA, some key virus binding properties are receptor specific [50, 71].

Members of the both receptor groups require low endosomal pH for structural changes, however, in case of ICAM-1, the changes are catalyzed by the receptor and occur before and during the endocytosis [72–74]; whereas LDLR family members do not provide sufficient uncoating signals upon binding [75, 76]. The receptor binding sites were mapped around the 5-fold axis of symmetry in viral capsid but they have also shown to be different between the major and minor group RVs. The first domain of ICAM-1 binds the virus inside the canyon (a 2.5-nm depression) surrounding the dome at the vertex [77], whereas the LDLR ligand binding domain, that composed of multiple ligand-binding repeats, attaches to the top of the star-like surface exposed structure at the vertex [78]. In contrast to LDLR proteins containing the NPxY internalization motif (x, any amino acid residue), ICAM-1 short

cytoplasmic tail lacks any known endocytosis signal and is not required for RV internalization [79].

RV entry in primary airway epithelial cells

The entry mechanism of major group RVs is thought to be cell-type specific because in contrast to HeLa cells, RV-B14 endocytosis in rhabdomyosarcoma cells is independent of clathrin, caveolin, flotillin, and lipid rafts [50, 56]. Since most of the work on RV receptors and cell entry was done in HeLa and some other established cell lines, the mechanisms of viral entry in airway epithelial cells, natural RV host cells, have not been fully elucidated. ICAM-1 and LDLR expression was confirmed in both ciliated and non-ciliated cells of airway epithelium [50, 67, 68]. Studies on major group RVs in primary airway epithelial cells revealed some contradicting results on virus entry pathways.

Lau and colleagues proposed that internalization of RV occurs via clathrin-mediated endocytosis (in agreement with data from HeLa cells) and is regulated by the non-receptor tyrosine kinase Syk, which is widely expressed in both leukocytes and airway epithelial cells and fibroblasts. Briefly, RV-A16 binding to ICAM-1 leads to the recruitment of Syk to the plasma membrane and formation of an ICAM-1/ezrin/Syk complex resulting in phosphorylation and activation of Syk and subsequent downstream signaling to the phosphoinositide-3 (PI3) kinase pathway, that ultimately regulates RV internalization [80, 81].

In contrast, studies from Gulbins group revealed that both major and minor group RV infection of nasal mucosa (as well as lung fibroblasts and HeLa cells) occur via ceramide-enriched and ganglioside type 1 (GM-1) positive membrane platforms, and is independent of clathrin and dynamin [82, 83]. This apparent discrepancy might indicate that several pathways can be used for RV uptake in both primary airway epithelial cells and cell lines. Further studies in fully-differentiated airway epithelial cells are needed to understand RV binding and entry mechanisms in vivo.

CDHR3 mediates RV-C binding and entry

We have recently discovered that human cadherin-related family member 3 (CDHR3) protein mediates virus binding and replication in normally unsusceptible cultured cells [27]. Since both our group and others have demonstrated that only fully differentiated cultures of human airway epithelial cells support RV-C replication while undifferentiated monolayers (as well as many continuous cell lines) do not [28–30], we compared genome-wide gene expression profiles in these cells by microarrays and identified a total of 12 target genes encoding transmembrane proteins for functional validation. Transfection-induced expression of CDHR3 was sufficient to enable virus binding and subsequent replication in HeLa and 293T cell lines normally unsusceptible to RV-C infection. In the absence of human CDHR3 crystal structure, we modeled the ectodomains 1–6 relative to other known cadherin family protein structures and identified a putative docking site for CDHR3 domains 1 and 2 binding RV-C15 across the adjacent protomers, in a 5-fold to 2-fold axis orientation in a region with multiple residues conserved among all RV-C types [27].

CDHR3 is a member of cadherin superfamily of transmembrane glycoproteins with yet unknown biological function. Other members of this family such as classical cadherins and desmosomal cadherins are responsible for communication between identical cells through calcium-dependent interactions, and protocadherins are implicated in neuronal plasticity and tissue development [84, 85]. The functional role of many related members of the family remains largely unknown. Cadherins are the principal components of adherens junctions and desmosomes and also have functions beyond adhesion, including roles in signaling, mechanical transduction and brain morphogenesis [86].

A study of Danish children provided the first hints about possible functions of CDHR3. In a genome-wide association study, CDHR3 was reported as a novel gene associated with an increased risk of developing severe childhood asthma [87]. The CDHR3 genotype (rs6967330) that converts residue cysteine to tyrosine at position 529 (Cys529→Tyr), significantly increased the risk of asthma hospitalizations and severe exacerbations in young children (2–6 years old) compared with the control group. Transfection experiments *in vitro* have also shown that this mutation in ectodomain 5 near a calcium binding site leads to a marked increase in cell surface expression of the CDHR3 protein, presumably, by altering the protein conformation. We then confirmed that this mutation also mediates enhanced RV-C binding and replication *in vitro* and developed a HeLa cell line (HeLa-E8) stably expressing the CDHR3-Y_{529} variant that supports efficient propagation of RV-C by infection [27].

Although CDHR3 is the only cellular factor known so far that enables RV-C propagation in normally unsusceptible host cells, the loss-of-function and direct biochemical receptor-virus interactions have not yet been confirmed. Nevertheless, in agreement with its proposed RV-C receptor function, CDHR3 is highly expressed in differentiated human airway epithelial cells *in vitro* [27, 88] and in human lung tissue and bronchial epithelium *in vivo* [87, 89]. CDHR3 subcellular localization has not been mapped yet; however, high level of its expression was found in ciliated cells in differentiated airway epithelium [Griggs *et al.*, manuscript in preparation]. Recent RNA-seq analysis of RV-A16 infected ALI cultures found that CDHR3 mRNA expression at baseline was slightly lower in asthmatic epithelial cells compared to non-asthmatic cells ($p = 0.02$), however, the CDHR3 genotype was not provided for these donors [90]. Interestingly, in contrast to ICAM-1 and LDLR, CDHR3 expression was further decreased upon viral infection and its reduction was highly correlated with viral infection (Pearson correlation p-value = 1.6×10^{-4}) indicating different regulatory mechanisms. Rhinovirus-induced disruption of the barrier function of airway epithelial cells cultured at ALI along with downregulation of some tight and adherens junction mRNAs and proteins have been also documented [90–92].

The molecular mechanisms involved in RV-C binding to CDHR3 as well as subsequent entry and signaling pathways are not yet defined. Studies on epithelial (E)-cadherin (CDH1), which is the prototype and well-characterized member of cadherin family widely expressed in epithelial cells, and on other classical cadherins, revealed that they can use many pathways for internalization from the cell surface, including clathrin-, dynamin- and caveolin-dependent and clathrin-independent pathways [93, 94]. These pathways can ultimately lead to recycling it back to the cell surface, sequestration inside the cells or target

it for degradation in lysosomes. The cytoplasmic domain of E-cadherin binds to β-catenin and p120 bridging it to the cytoskeleton through additional binding interactions with α-catenin and actin. Tyrosine kinase (such as Src and receptor tyrosine kinase family) signaling regulates trafficking of E-cadherin, e.g. tyrosine phosphorylation of the E-cadherin-catenin complex results in endocytosis and disruption of cell-cell adhesion [95] but other mechanisms of regulating cadherin endocytosis could exist including actin polymerization. If CDHR3 can function similarly to E-cadherin, then by analogy with other known RV receptors, RV-C can presumably hijack one of these endocytic pathways to enable cell entry.

Assuming that CDHR3 can play a role in maintaining epithelial barrier function, it could be inaccessible to virus approaching from the apical surface if localized to adherens junctions in polarized airway epithelium. Other viruses, including some enteroviruses, bind to various cell-adhesion molecules located in intercellular junctions to gain entry to the host cell [96]. For example, coxsackievirus B, which utilizes coxsackievirus and adenovirus receptor (CAR) in tight junctions for internalization, also interacts with additional decay-accelerating factor (DAF) on the apical cell surface to activate actin rearrangements that permit subsequent virus movement to the tight junctions [97]. Some human cadherins (e.g. E-cadherin) are utilized by a number of fungal, bacterial and viral pathogens (e.g. Candida albicans, Listeria monocytogenes, Leptospira interrogans and adenovirus) as entry cellular receptors [98–100]. In a recent study it has been found that desmoglein-2 (DSG-2), a member of the cadherin protein superfamily and constituent of desmosomes, is the attachment receptor for human species B adenoviruses (Ad3, Ad7, Ad11 and Ad14), which cause respiratory and urinary tract infections [101]. Adenovirus interaction with DSG-2 in epithelial cells results in the opening of intercellular junctions, thus increasing access to other receptors (e.g. CD46) that are generally not accessible.

There is evidence that dysregulated epithelial barrier function may promote airway inflammation and allergic sensitization [102]. Tight junctions serve to reduce exposure of dendritic cells and other leukocytes to allergens and pathogens, and compromised barrier function can thereby reduce tolerance to allergens. Asthma is also associated with reduced barrier function, and this could be a primary defect or a result of airway inflammation [103]. Th2 inflammatory cytokines such as interleukin (IL) 4 and IL-13 can reduce the expression of tight junction constituent proteins, leading to barrier disruption. It is likely that CDHR3 is preferentially localized on the cell surface within intercellular junctions, where it may be protected from exposure to the airway lumen and contact with RV-C. This suggests the possibility that reduced airway barrier function in asthma exposes CDHR3 to the environment and increases susceptibility to RV-C infections in addition to the effects of “asthma risk” genotype (rs6967330) (Fig. 1). Studies to test this theory are now in progress.

Rhinovirus-induced signaling with regard to allergic disease

RV infection and asthma

RV infections and allergy in early life synergize to increase the risk of developing asthma [35]. Several theories have been proposed to explain this interaction, including (i) causal role of viruses in asthma due to direct damage of developing airways and modulation of immune

responses, (ii) secondary role only as an early indicator of abnormal airway physiology and/or diminished antiviral responses, and (iii) a “two-hit hypothesis” in which genetic predisposition to atopy is combined with early respiratory viral infection in promoting asthma [13]. In agreement with the causal role, it has been shown that acute RV infections both *in vivo* and *in vitro* can induce a number of cellular factors regulating airway growth, development, fibrosis, repair and associated with bronchial remodeling (IL-6, TGF-b, VEGF, MMP-9, MUC5AC, FGF2, HBEGF etc.) and increase secretion of prostaglandins and cyclooxygenase-2 [104–107]. However, RVs usually cause very mild (if any) visible cytopathic effect in intact fully differentiated epithelium [29, 108], likely because they replicate only in a small subset of cells [40, 109]. In agreement with these findings, ICAM-1 is expressed in small proportion of the ciliated cells in airway epithelium in the absence of inflammation; therefore, plasma membrane concentration of receptors appears to determine at least in part susceptibility to RV infection [110, 111]. Notably, both ICAM-1 and LDLR expression is induced by RV infection regardless of receptor type, which may promote additional viral binding and infection spread [68, 112–114].

RV infection initiates signaling events leading to the production of multiple cytokines, chemokines, interferons and growth factors in airway epithelial cells, and these responses can promote cellular inflammation. Several clinical studies reported that RV-A and RV-C are more virulent than RV-B, suggesting differences in the biology of RV species that are independent of their receptor specificity [21, 24]. In agreement with these findings, experiments in cultures of differentiated airway epithelial cells indicate that RV-B types have lower and slower replication, lower cellular cytotoxicity and cytokine and chemokine production compared with RV-A or RV-C [108]. Although no striking differences in epithelial cell responses between major and minor RVs were noted [115], differential signaling and cytokine responses were recently between the major- and minor-group RV treatments of macrophages [116].

Animal models of paramyxovirus-induced respiratory inflammation confirmed that Th1-type mediators can recruit the high affinity IgE surface receptor (FcεRI)-expressing plasmacytoid dendritic cells (pDC), eosinophils and T cells to the lower airways resulting in IgE mediated Th2-type response and mucous cell metaplasia [117, 118]. Increased expression and cross-linking of FcεRI before RV stimulation inhibits type I and type III interferon (IFN) secretion from peripheral blood mononuclear cells [119]. These findings demonstrate that respiratory viral infections can block antiviral responses and promote viral replication by inducing Th2-type allergic inflammation. Surprisingly and in contrast to previously published findings [120], the structural changes in cultured primary airway epithelial cells associated with Th2-type cytokine-induced goblet cell metaplasia decreased their susceptibility to RV-A16 infection [107]. The absence of interferon-producing immune cells and a lower number of target epithelial cells suitable for viral replication could be responsible for these effects *in vitro*.

Virus recognition in host cell

The initial responses and signaling to major group RVs, mediated upon binding to ICAM-1 receptor in a replication-independent manner, result in the expression of chemokines such as

IL-8 [80] and C–X–C motif chemokine ligand 10 (CXCL10) [121] in epithelial cells and monocytes. Syk is an early signaling molecule, rapidly recruited to activated ICAM-1 at plasma membrane. It becomes phosphorylated and mediates signaling via p38 mitogen activation protein (MAP) kinase and PI3 kinase, leading to downstream activation of Akt1 kinase and transcription factor NF-κB, IL-8 expression and, ultimately, to tissue neutrophilia [80, 81].

Innate immune responses to viral and bacterial pathogens are mediated by pattern recognition receptors (PRR), which recognize a number of highly conserved pathogen associated molecular patterns. PRR signaling during viral infections results in activation of the two major classes of transcription factors, interferon regulatory factors (e.g. IRF-3, IRF-7) and NF-κB family members, which induce the expression of type I IFNs and pro-inflammatory genes [122, 123]. Three major types of PRRs, toll-like receptors (TLR), NOD-like receptors (NLR) and retinoic acid-inducible gene-I-like receptors (RLR), contribute to the sensing of RV infections.

According to the current model, RV penetrates into the cytoplasm via endosomal membrane destabilization and rupture (major group) or through an ion-conducting pore in the endosomal membrane (minor group) [50]. The mechanism of how viral RNA is released during this process and enters the cytosol together with empty capsids is still poorly understood. Free viral RNA was first seen as soon as 10–12 min post infection (p.i.) in the perinuclear area of the cell, which is indicative of RNA release from late endosomes, and remained in the cytoplasm, whereas the protein signal almost completely disappeared in 2 h p.i.; the newly synthesized protein and RNA were first detected at 3.5 h p.i. [124].

Studies in cultured monolayers of airway epithelial cells *in vitro* revealed that the innate responses to RV are mediated by the endosomal transmembrane TLR3, followed by additional signals from the cytoplasmic RLR melanoma differentiation associated protein 5 (MDA5) that both recognize viral double-stranded (ds)RNA generated during replication [125, 126]. However, the mechanism by which dsRNA reaches the endosome and associated early signaling pathways remain incompletely understood. Notably, impaired TLR3 and MDA5 signaling, potentially leading to an inability to activate type I and type III IFN responses to RV infection was found in bronchial epithelial cells from asthmatic subjects [127]. The involvement of TLR7 and 8, sensing single-stranded RNA, and TLR2 recognizing viral capsid was also confirmed [128, 129]; however, the role of retinoic acid inducible gene-1 (RIG-I) that binds to the 5' triphosphate motif (which is not exposed but covalently linked to the viral protein g (VPg) in all picornaviruses) is more controversial [130, 131]. RV-induced proinflammatory cytokine response in macrophages was mainly TLR2 dependent in a mouse model and did not require viral endocytosis or replication [132].

Animal models utilizing MDA5-, TLR3- and TLR7-deficient mice have been used to explore RV recognition and innate immune signaling mechanisms leading to RV-induced airway inflammation and hyperresponsiveness *in vivo*. Interestingly, MDA5 null mice showed a delayed type I IFN and attenuated type III IFN response to RV-A1b infection and increased viral titer, whereas TLR3 null mice showed normal IFN responses and unchanged

viral titers. Both MDA5- and TLR3-deficient mice also showed reduced lung inflammatory and contractile responses suggesting that TLR3 and MDA5 initiate pro-inflammatory signaling pathways which can lead to airway inflammation and hyperresponsiveness [133]. More intriguingly and in contrast to findings in TLR3-null mice, allergic TLR7-deficient mice displayed impaired type I and type III IFN release upon RV infection, increased virus replication and exaggerated eosinophilic inflammation and airway hyperreactivity [134]. TLR7 expression in the lungs was suppressed by Th2-type allergic inflammation and by IL-5-induced eosinophilia in the absence of allergy. These data demonstrate that a lack of TLR7 signaling under conditions that model a viral asthma exacerbation or its inhibition by IL-5-induced lung eosinophilia impairs IFN production and exaggerates Th2-driven inflammatory responses. Collectively, these data suggest that suppression of TLR3 and MDA5 and induction of TLR7 and their downstream signaling pathway may be novel therapeutic targets for the prevention and treatment of RV-induced asthma exacerbations.

Less is known regarding the role of NLRs in the sensing of RV infections. It has been recently shown that the newly discovered dsRNA receptor Nod-like receptor X-1 (NLRX-1) interacts with RV RNA and disrupts the barrier function of the airway epithelium by increasing reactive oxygen species (ROS) in the mitochondria. Thus, these findings suggest that ROS, if not neutralized efficiently, may not only enhance susceptibility to secondary infections but also alter innate immune responses to subsequently inhaled pathogens and allergens [135].

Conclusions

RV-A, B and C utilize three major types of cellular membrane glycoproteins to gain entry into the host cell: ICAM-1, LDLR and CDHR3. Despite some substantial differences in their structure, subcellular localization, virus binding sites, mechanisms of endocytosis and downstream signaling, they all support efficient virus entry and replication resulting in induction of antiviral and inflammatory response. In contrast to the first two known RV receptors studied in more detail, there is relatively little information about molecular mechanisms of RV-C interaction with CDHR3. Notably, a coding SNP (rs6967330) in CDHR3 could promote RV-C wheezing illnesses in infancy, which could in turn adversely affect the developing lung to increase the risk of asthma. Airway inflammation can increase expression of ICAM-1 and suppress TLR7 signaling in the airway, which could provide a link between diseases of chronic airway inflammation and increased severity of illnesses caused by rhinoviruses using this receptor. Further studies are needed to determine whether reduced epithelial barrier function, which also contributes to pathogenesis of asthma, leads to increased accessibility of CDHR3, and in turn promotes more severe RV-C illnesses. These concepts suggest that the optimal treatment approach to control asthma exacerbation may need to target both virus infection and allergic inflammation.

Acknowledgments

This work was supported by the following NIH grants: UM1 AI114271, U19 AI104317 and P01 HL070831.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Hamparian VV, Colonno RJ, Cooney MK, et al. A collaborative report: rhinoviruses--extension of the numbering system from 89 to 100. Virology. 1987; 159:191–2. [PubMed: 3037780]
2. McIntyre CL, Knowles NJ, Simmonds P. Proposals for the classification of human rhinovirus species A, B and C into genotypically assigned types. J Gen Virol. 2013; 94:1791–806. [PubMed: 23677786]
3. Lamson D, Renwick N, Kapoor V, et al. MassTag polymerase-chain-reaction detection of respiratory pathogens, including a new rhinovirus genotype, that caused influenza-like illness in New York State during 2004–2005. J Infect Dis. 2006; 194:1398–402. [PubMed: 17054069]
4. Arden KE, McErlean P, Nissen MD, et al. Frequent detection of human rhinoviruses, paramyxoviruses, coronaviruses, and bocavirus during acute respiratory tract infections. J Med Virol. 2006; 78:1232–40. [PubMed: 16847968]
5. Lau SK, Yip CC, Tsoi HW, et al. Clinical features and complete genome characterization of a distinct human rhinovirus (HRV) genetic cluster, probably representing a previously undetected HRV species, HRV-C, associated with acute respiratory illness in children. J Clin Microbiol. 2007; 45:3655–64. [PubMed: 17804649]
6. Arden KE, Mackay IM. Newly identified human rhinoviruses: molecular methods heat up the cold viruses. Rev Med Virol. 2010; 20:156–76. [PubMed: 20127751]
7. Arden KE, Faux CE, O'Neill NT, et al. Molecular characterization and distinguishing features of a novel human rhinovirus (HRV) C, HRVC-QCE, detected in children with fever, cough and wheeze during 2003. J Clin Virol. 2010; 47:219–23. [PubMed: 20106717]
8. Bochkov YA, Palmenberg AC, Lee WM, et al. Molecular modeling, organ culture and reverse genetics for a newly identified human rhinovirus C. Nat Med. 2011; 17:627–32. [PubMed: 21483405]
9. Simmonds P, McIntyre C, Savolainen-Kopra C, et al. Proposals for the classification of human rhinovirus species C into genotypically assigned types. J Gen Virol. 2010; 91:2409–19. [PubMed: 20610666]
10. Gern JE, Busse WW. Association of rhinovirus infections with asthma. Clin Microbiol Rev. 1999; 12:9–18. [PubMed: 9880472]
11. Hayden FG. Rhinovirus and the lower respiratory tract. Rev Med Virol. 2004; 14:17–31. [PubMed: 14716689]
12. McManus TE, Marley AM, Baxter N, et al. Respiratory viral infection in exacerbations of COPD. Respir Med. 2008; 102:1575–80. [PubMed: 18672353]
13. Gern JE. The ABCs of rhinoviruses, wheezing, and asthma. J Virol. 2010; 84:7418–26. [PubMed: 20375160]
14. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med. 2008; 178:667–72. [PubMed: 18565953]
15. Jackson DJ, Lemanske RF Jr. The role of respiratory virus infections in childhood asthma inception. Immunol Allergy Clin North Am. 2010; 30:513–22. vi. [PubMed: 21029935]
16. van der Gugten AC, van der Zalm MM, Uiterwaal CS, et al. Human rhinovirus and wheezing: short and long-term associations in children. Pediatr Infect Dis J. 2013; 32:827–33. [PubMed: 23584579]
17. Piralla A, Rovida F, Campanini G, et al. Clinical severity and molecular typing of human rhinovirus C strains during a fall outbreak affecting hospitalized patients. J Clin Virol. 2009; 45:311–7. [PubMed: 19473873]

18. Han TH, Chung JY, Hwang ES, Koo JW. Detection of human rhinovirus C in children with acute lower respiratory tract infections in South Korea. Arch Virol. 2009; 154:987–91. [PubMed: 19415451]
19. Arden KE, Chang AB, Lambert SB, et al. Newly identified respiratory viruses in children with asthma exacerbation not requiring admission to hospital. J Med Virol. 2010; 82:1458–61. [PubMed: 20572080]
20. Xiang Z, Gonzalez R, Wang Z, et al. Human rhinoviruses in Chinese adults with acute respiratory tract infection. J Infect. 2010; 61:289–98. [PubMed: 20638411]
21. Bizzintino J, Lee WM, Laing IA, et al. Association between human rhinovirus C and severity of acute asthma in children. Eur Respir J. 2011; 37:1037–42. [PubMed: 20693244]
22. Moreira LP, Kamikawa J, Watanabe AS, et al. Frequency of human rhinovirus species in outpatient children with acute respiratory infections at primary care level in Brazil. Pediatr Infect Dis J. 2011; 30:612–4. [PubMed: 21248656]
23. Piralla A, Baldanti F, Gerna G. Phylogenetic patterns of human respiratory picornavirus species, including the newly identified group C rhinoviruses, during a 1-year surveillance of a hospitalized patient population in Italy. J Clin Microbiol. 2011; 49:373–6. [PubMed: 21068279]
24. Lee WM, Lemanske RF Jr, Evans MD, et al. Human rhinovirus species and season of infection determine illness severity. Am J Respir Crit Care Med. 2012; 186:886–91. [PubMed: 22923659]
25. Fawkner-Corbett DW, Khoo SK, Duarte MC, et al. Rhinovirus-C detection in children presenting with acute respiratory infection to hospital in Brazil. J Med Virol. 2015
26. Uncapher CR, DeWitt CM, Colonno RJ. The major and minor group receptor families contain all but one human rhinovirus serotype. Virology. 1991; 180:814–7. [PubMed: 1846502]
27. Bochkov YA, Watters K, Ashraf S, et al. Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication. Proc Natl Acad Sci U S A. 2015; 112:5485–90. [PubMed: 25848009]
Identifies the first cellular factor, CDHR3, mediating RV-C entry into host cells, and reports the development of the first transduced HeLa-E8 cell line for RV-C propagation. Data suggest that rs6967330 single nucleotide polymorphism in CDHR3 could be a risk factor for RV-C wheezing illnesses.
28. Hao W, Bernard K, Patel N, et al. Infection and propagation of human rhinovirus C in human airway epithelial cells. J Virol. 2012; 86:13524–32. [PubMed: 23035218]
29. Ashraf S, Brockman-Schneider R, Bochkov YA, et al. Biological characteristics and propagation of human rhinovirus-C in differentiated sinus epithelial cells. Virology. 2013; 436:143–9. [PubMed: 23199420]
30. Tapparel C, Sobo K, Constant S, et al. Growth and characterization of different human rhinovirus C types in three-dimensional human airway epithelia reconstituted in vitro. Virology. 2013; 446:1–8. [PubMed: 24074561]
31. Ashraf S, Brockman-Schneider R, Gern JE. Propagation of rhinovirus-C strains in human airway epithelial cells differentiated at air-liquid interface. Methods Mol Biol. 2015; 1221:63–70. [PubMed: 25261307]
32. Gavala ML, Bertics PJ, Gern JE. Rhinoviruses, allergic inflammation, and asthma. Immunol Rev. 2011; 242:69–90. [PubMed: 21682739]
33. Cheung DS, Grayson MH. Role of viruses in the development of atopic disease in pediatric patients. Curr Allergy Asthma Rep. 2012; 12:613–20. [PubMed: 22911226]
34. Gavala ML, Bashir H, Gern JE. Virus/allergen interactions in asthma. Curr Allergy Asthma Rep. 2013; 13:298–307. [PubMed: 23475539]
35. Rowe RK, Gill MA. Asthma: the interplay between viral infections and allergic diseases. Immunol Allergy Clin North Am. 2015; 35:115–27. [PubMed: 25459580]
36. Tam JS, Jackson WT, Hunter D, et al. Rhinovirus specific IgE can be detected in human sera. J Allergy Clin Immunol. 2013; 132:1241–3. [PubMed: 23992751]
37. Pitkaranta A, Arruda E, Malmberg H, Hayden FG. Detection of rhinovirus in sinus brushings of patients with acute community-acquired sinusitis by reverse transcription-PCR. J Clin Microbiol. 1997; 35:1791–3. [PubMed: 9196195]

38. Pitkaranta A, Starck M, Savolainen S, et al. Rhinovirus RNA in the maxillary sinus epithelium of adult patients with acute sinusitis. Clin Infect Dis. 2001; 33:909–11. [PubMed: 11512099]
39. Pitkaranta A, Puhakka T, Makela MJ, et al. Detection of rhinovirus RNA in middle turbinate of patients with common colds by in situ hybridization. J Med Virol. 2003; 70:319–23. [PubMed: 12696124]
40. Mosser AG, Vrtis R, Burchell L, et al. Quantitative and qualitative analysis of rhinovirus infection in bronchial tissues. Am J Respir Crit Care Med. 2005; 171:645–51. [PubMed: 15591468]
41. Chantzi FM, Papadopoulos NG, Bairamis T, et al. Human rhinoviruses in otitis media with effusion. Pediatr Allergy Immunol. 2006; 17:514–8. [PubMed: 17014626]
42. Malmstrom K, Pitkaranta A, Carpen O, et al. Human rhinovirus in bronchial epithelium of infants with recurrent respiratory symptoms. J Allergy Clin Immunol. 2006; 118:591–6. [PubMed: 16950276]
43. D'Amato G, Holgate ST, Pawankar R, et al. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. World Allergy Organ J. 2015; 8:25. [PubMed: 26207160]
44. Gelfand EW. Pediatric asthma: a different disease. Proc Am Thorac Soc. 2009; 6:278–82. [PubMed: 19387030]
45. Gaffin JM, Kanchongkittiphon W, Phipatanakul W. Perinatal and early childhood environmental factors influencing allergic asthma immunopathogenesis. Int Immunopharmacol. 2014; 22:21–30. [PubMed: 24952205]
46. Schatz M, Rosenwasser L. The allergic asthma phenotype. J Allergy Clin Immunol Pract. 2014; 2:645–8. [PubMed: 25439351]
47. Dougherty RH, Fahy JV. Acute exacerbations of asthma: epidemiology, biology and the exacerbation-prone phenotype. Clin Exp Allergy. 2009; 39:193–202. [PubMed: 19187331]
48. Doherty GJ, McMahon HT. Mechanisms of endocytosis. Annu Rev Biochem. 2009; 78:857–902. [PubMed: 19317650]
49. Fuchs R, Blaas D. Uncoating of human rhinoviruses. Rev Med Virol. 2010; 20:281–97. [PubMed: 20629045]
50. Fuchs R, Blaas D. Productive entry pathways of human rhinoviruses. Adv Virol. 2012; 2012:826301. [PubMed: 23227049]
A detailed review on the RV-A and RV-B receptors and mechanisms of viral entry into host cells.
51. Grunert HP, Wolf KU, Langner KD, et al. Internalization of human rhinovirus 14 into HeLa and ICAM-1-transfected BHK cells. Med Microbiol Immunol. 1997; 186:1–9. [PubMed: 9255760]
52. Snyers L, Zwickl H, Blaas D. Human rhinovirus type 2 is internalized by clathrin-mediated endocytosis. J Virol. 2003; 77:5360–9. [PubMed: 12692238]
53. Bayer N, Schober D, Huttinger M, et al. Inhibition of clathrin-dependent endocytosis has multiple effects on human rhinovirus serotype 2 cell entry. J Biol Chem. 2001; 276:3952–62. [PubMed: 11073943]
54. Vlasak M, Goesler I, Blaas D. Human rhinovirus type 89 variants use heparan sulfate proteoglycan for cell attachment. J Virol. 2005; 79:5963–70. [PubMed: 15857982]
55. Khan AG, Pichler J, Rosemann A, Blaas D. Human rhinovirus type 54 infection via heparan sulfate is less efficient and strictly dependent on low endosomal pH. J Virol. 2007; 81:4625–32. [PubMed: 17301156]
56. Khan AG, Pickl-Herk A, Gajdzik L, et al. Human rhinovirus 14 enters rhabdomyosarcoma cells expressing icam-1 by a clathrin-, caveolin-, and flotillin-independent pathway. J Virol. 2010; 84:3984–92. [PubMed: 20130060]
57. Greve JM, Davis G, Meyer AM, et al. The major human rhinovirus receptor is ICAM-1. Cell. 1989; 56:839–47. [PubMed: 2538243]
58. Staunton DE, Merluzzi VJ, Rothlein R, et al. A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses. Cell. 1989; 56:849–53. [PubMed: 2538244]
59. Tomassini JE, Graham D, DeWitt CM, et al. cDNA cloning reveals that the major group rhinovirus receptor on HeLa cells is intercellular adhesion molecule 1. Proc Natl Acad Sci U S A. 1989; 86:4907–11. [PubMed: 2544880]

60. Hofer F, Gruenberger M, Kowalski H, et al. Members of the low density lipoprotein receptor family mediate cell entry of a minor-group common cold virus. Proc Natl Acad Sci U S A. 1994; 91:1839–42. [PubMed: 8127891]
61. Hubbard AK, Rothlein R. Intercellular adhesion molecule-1 (ICAM-1) expression and cell signaling cascades. Free Radic Biol Med. 2000; 28:1379–86. [PubMed: 10924857]
62. Staunton DE, Marlin SD, Stratowa C, et al. Primary structure of ICAM-1 demonstrates interaction between members of the immunoglobulin and integrin supergene families. Cell. 1988; 52:925–33. [PubMed: 3349522]
63. Diamond MS, Staunton DE, de Fougerolles AR, et al. ICAM-1 (CD54): a counter-receptor for Mac-1 (CD11b/CD18). J Cell Biol. 1990; 111:3129–39. [PubMed: 1980124]
64. Li Y, Cam J, Bu G. Low-density lipoprotein receptor family: endocytosis and signal transduction. Mol Neurobiol. 2001; 23:53–67. [PubMed: 11642543]
65. Jeon H, Blacklow SC. Structure and physiologic function of the low-density lipoprotein receptor. Annu Rev Biochem. 2005; 74:535–62. [PubMed: 15952897]
66. Beglova N, Blacklow SC. The LDL receptor: how acid pulls the trigger. Trends Biochem Sci. 2005; 30:309–17. [PubMed: 15950875]
67. Vignola AM, Chanez P, Campbell AM, et al. Quantification and localization of HLA-DR and intercellular adhesion molecule-1 (ICAM-1) molecules on bronchial epithelial cells of asthmatics using confocal microscopy. Clin Exp Immunol. 1994; 96:104–9. [PubMed: 7908615]
68. Winther B, Arruda E, Witek TJ, et al. 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. 2002; 128:131–6. [PubMed: 11843719]
69. Kang RS, Folsch H. ARH cooperates with AP-1B in the exocytosis of LDLR in polarized epithelial cells. J Cell Biol. 2011; 193:51–60. [PubMed: 21444685]
70. Pietiainen V, Vassilev B, Blom T, et al. NDRG1 functions in LDL receptor trafficking by regulating endosomal recycling and degradation. J Cell Sci. 2013; 126:3961–71. [PubMed: 23813961]
71. Suomalainen M, Greber UF. Uncoating of non-enveloped viruses. Curr Opin Virol. 2013; 3:27–33. [PubMed: 23332135]
72. Greve JM, Forte CP, Marlor CW, et al. Mechanisms of receptor-mediated rhinovirus neutralization defined by two soluble forms of ICAM-1. J Virol. 1991; 65:6015–23. [PubMed: 1681115]
73. Hoover-Litty H, Greve JM. Formation of rhinovirus-soluble ICAM-1 complexes and conformational changes in the virion. J Virol. 1993; 67:390–7. [PubMed: 8093221]
74. Nurani G, Lindqvist B, Casasnovas JM. Receptor priming of major group human rhinoviruses for uncoating and entry at mild low-pH environments. J Virol. 2003; 77:11985–91. [PubMed: 14581535]
75. Schober D, Kronenberger P, Prchla E, et al. Major and minor receptor group human rhinoviruses penetrate from endosomes by different mechanisms. J Virol. 1998; 72:1354–64. [PubMed: 9445036]
76. Brabec M, Baravalle G, Blaas D, Fuchs R. Conformational changes, plasma membrane penetration, and infection by human rhinovirus type 2: role of receptors and low pH. J Virol. 2003; 77:5370–7. [PubMed: 12692239]
77. Kolatkar PR, Bella J, Olson NH, et al. Structural studies of two rhinovirus serotypes complexed with fragments of their cellular receptor. EMBO J. 1999; 18:6249–59. [PubMed: 10562537]
78. Hewat EA, Neumann E, Conway JF, et al. The cellular receptor to human rhinovirus 2 binds around the 5-fold axis and not in the canyon: a structural view. EMBO J. 2000; 19:6317–25. [PubMed: 11101504]
79. Staunton DE, Gaur A, Chan PY, Springer TA. Internalization of a major group human rhinovirus does not require cytoplasmic or transmembrane domains of ICAM-1. J Immunol. 1992; 148:3271–4. [PubMed: 1349619]
80. Lau C, Wang X, Song L, et al. Syk associates with clathrin and mediates phosphatidylinositol 3-kinase activation during human rhinovirus internalization. J Immunol. 2008; 180:870–80. [PubMed: 18178826]
81. Sanderson MP, Lau CW, Schnapp A, Chow CW. Syk: a novel target for treatment of inflammation in lung disease. Inflamm Allergy Drug Targets. 2009; 8:87–95. [PubMed: 19530990]

82. Grassme H, Riehle A, Wilker B, Gulbins E. Rhinoviruses infect human epithelial cells via ceramide-enriched membrane platforms. J Biol Chem. 2005; 280:26256–62. [PubMed: 15888438]

83. Dreschers S, Franz P, Dumitru C, et al. Infections with human rhinovirus induce the formation of distinct functional membrane domains. Cell Physiol Biochem. 2007; 20:241–54. [PubMed: 17595532]

84. Halbleib JM, Nelson WJ. Cadherins in development: cell adhesion, sorting, and tissue morphogenesis. Genes Dev. 2006; 20:3199–214. [PubMed: 17158740]

85. Nelson WJ, Dickinson DJ, Weis WI. Roles of cadherins and catenins in cell-cell adhesion and epithelial cell polarity. Prog Mol Biol Transl Sci. 2013; 116:3–23. [PubMed: 23481188]

86. Sotomayor M, Gaudet R, Corey DP. Sorting out a promiscuous superfamily: towards cadherin connectomics. Trends Cell Biol. 2014; 24:524–36. [PubMed: 24794279]

87. Bonnelykke K, Sleiman P, Nielsen K, et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. Nat Genet. 2014; 46:51–5. [PubMed: 24241537]

Identifies a novel asthma susceptibility gene CDHR3 that is highly expressed in airway epithelium, and suggests that Y_{529} variant of CDHR3 is associated with a high risk of severe childhood asthma.

88. Ross AJ, Dailey LA, Brighton LE, Devlin RB. Transcriptional profiling of mucociliary differentiation in human airway epithelial cells. Am J Respir Cell Mol Biol. 2007; 37:169–85. [PubMed: 17413031]

89. Yanai I, Benjamin H, Shmoish M, et al. Genome-wide midrange transcription profiles reveal expression level relationships in human tissue specification. Bioinformatics. 2005; 21:650–9. [PubMed: 15388519]

90. Bai J, Smock SL, Jackson GR Jr, et al. Phenotypic responses of differentiated asthmatic human airway epithelial cultures to rhinovirus. PLoS One. 2015; 10:e0118286. [PubMed: 25706956]

91. Sajjan U, Wang Q, Zhao Y, et al. Rhinovirus disrupts the barrier function of polarized airway epithelial cells. Am J Respir Crit Care Med. 2008; 178:1271–81. [PubMed: 18787220]

92. Yeo NK, Jang YJ. Rhinovirus infection-induced alteration of tight junction and adherens junction components in human nasal epithelial cells. Laryngoscope. 2010; 120:346–52. [PubMed: 20013846]

93. Perez-Moreno M, Jamora C, Fuchs E. Sticky business: orchestrating cellular signals at adherens junctions. Cell. 2003; 112:535–48. [PubMed: 12600316]

94. Bryant DM, Stow JL. The ins and outs of E-cadherin trafficking. Trends Cell Biol. 2004; 14:427–34. [PubMed: 15308209]

95. Daniel JM, Reynolds AB. Tyrosine phosphorylation and cadherin/catenin function. Bioessays. 1997; 19:883–91. [PubMed: 9363682]

96. Bhella D. The role of cellular adhesion molecules in virus attachment and entry. Philos Trans R Soc Lond B Biol Sci. 2015; 370:20140035. [PubMed: 25533093]

97. Coyne CB, Bergelson JM. Virus-induced Abl and Fyn kinase signals permit coxsackievirus entry through epithelial tight junctions. Cell. 2006; 124:119–31. [PubMed: 16413486]

98. Mengaud J, Ohayon H, Gounon P, et al. E-cadherin is the receptor for internalin, a surface protein required for entry of L. monocytogenes into epithelial cells. Cell. 1996; 84:923–32. [PubMed: 8601315]

99. Phan QT, Fratti RA, Prasadarao NV, et al. N-cadherin mediates endocytosis of Candida albicans by endothelial cells. J Biol Chem. 2005; 280:10455–61. [PubMed: 15632157]

100. Evangelista K, Franco R, Schwab A, Coburn J. Leptospira interrogans binds to cadherins. PLoS Negl Trop Dis. 2014; 8:e2672. [PubMed: 24498454]

101. Wang H, Li ZY, Liu Y, et al. Desmoglein 2 is a receptor for adenovirus serotypes 3, 7, 11 and 14. Nat Med. 2011; 17:96–104. [PubMed: 21151137]

102. Lambrecht BN, Hammad H. Allergens and the airway epithelium response: gateway to allergic sensitization. J Allergy Clin Immunol. 2014; 134:499–507. [PubMed: 25171864]

103. Lambrecht BN, Hammad H. Asthma: the importance of dysregulated barrier immunity. Eur J Immunol. 2013; 43:3125–37. [PubMed: 24165907]

104. Proud D, Turner RB, Winther B, et al. Gene expression profiles during in vivo human rhinovirus infection: insights into the host response. Am J Respir Crit Care Med. 2008; 178:962–8. [PubMed: 18658112]

105. Leigh R, Oyelusi W, Wiehler S, et al. Human rhinovirus infection enhances airway epithelial cell production of growth factors involved in airway remodeling. J Allergy Clin Immunol. 2008; 121:1238–45. [PubMed: 18355907]

106. Bochkov YA, Hanson KM, Keles S, et al. Rhinovirus-induced modulation of gene expression in bronchial epithelial cells from subjects with asthma. Mucosal Immunol. 2010; 3:69–80. [PubMed: 19710636]

107. Jakiela B, Gielicz A, Plutecka H, et al. Th2-type cytokine-induced mucus metaplasia decreases susceptibility of human bronchial epithelium to rhinovirus infection. Am J Respir Cell Mol Biol. 2014; 51:229–41. [PubMed: 24588727]

108. Nakagome K, Bochkov YA, Ashraf S, et al. Effects of rhinovirus species on viral replication and cytokine production. J Allergy Clin Immunol. 2014; 134:332–41. [PubMed: 24636084]

Provides data showing that RV-B, which is typically associated with less severe illnesses in children, also have lower replication, cellular cytotoxicity and cytokine production in vitro compared with RV-A or RV-C

109. Mosser AG, Brockman-Schneider R, Amineva S, et al. Similar frequency of rhinovirus-infectible cells in upper and lower airway epithelium. J Infect Dis. 2002; 185:734–43. [PubMed: 11920291]

110. Winther B, Greve JM, Gwaltney JM Jr, et al. Surface expression of intercellular adhesion molecule 1 on epithelial cells in the human adenoid. J Infect Dis. 1997; 176:523–5. [PubMed: 9237723]

111. Jakiela B, Brockman-Schneider R, Amineva S, et al. Basal cells of differentiated bronchial epithelium are more susceptible to rhinovirus infection. Am J Respir Cell Mol Biol. 2008; 38:517–23. [PubMed: 18063839]

112. Papi A, Johnston SL. Rhinovirus infection induces expression of its own receptor intercellular adhesion molecule 1 (ICAM-1) via increased NF-kappaB-mediated transcription. J Biol Chem. 1999; 274:9707–20. [PubMed: 10092659]

113. Grunberg K, Sharon RF, Hiltermann TJ, et al. Experimental rhinovirus 16 infection increases intercellular adhesion molecule-1 expression in bronchial epithelium of asthmatics regardless of inhaled steroid treatment. Clin Exp Allergy. 2000; 30:1015–23. [PubMed: 10848925]

114. Suzuki T, Yamaya M, Kamanaka M, et al. Type 2 rhinovirus infection of cultured human tracheal epithelial cells: role of LDL receptor. Am J Physiol Lung Cell Mol Physiol. 2001; 280:L409–L420. [PubMed: 11159023]

115. Alves MP, Schogler A, Ebener S, et al. Comparison of innate immune responses towards rhinovirus infection of primary nasal and bronchial epithelial cells. Respirology. 2016; 21:304–12. [PubMed: 26611536]

A recent study showing that both major and minor group RVs induce overall similar responses in nasal and bronchial epithelial cells

116. Schuler BA, Schreiber MT, Li L, et al. Major and minor group rhinoviruses elicit differential signaling and cytokine responses as a function of receptor-mediated signal transduction. PLoS One. 2014; 9:e93897. [PubMed: 24736642]

117. Grayson MH, Cheung D, Rohlfing MM, et al. Induction of high-affinity IgE receptor on lung dendritic cells during viral infection leads to mucous cell metaplasia. J Exp Med. 2007; 204:2759–69. [PubMed: 17954569]

118. Cheung DS, Ehlenbach SJ, Kitchens T, et al. Development of atopy by severe paramyxoviral infection in a mouse model. Ann Allergy Asthma Immunol. 2010; 105:437–43. [PubMed: 21130381]

119. Durrani SR, Montville DJ, Pratt AS, et al. Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. J Allergy Clin Immunol. 2012; 130:489–95. [PubMed: 22766097]

120. Lachowicz-Scroggins ME, Boushey HA, Finkbeiner WE, Widdicombe JH. Interleukin-13-induced mucous metaplasia increases susceptibility of human airway epithelium to rhinovirus infection. Am J Respir Cell Mol Biol. 2010; 43:652–61. [PubMed: 20081054]

121. Korpi-Steiner NL, Bates ME, Lee WM, et al. Human rhinovirus induces robust IP-10 release by monocytic cells, which is independent of viral replication but linked to type I interferon receptor ligation and STAT1 activation. J Leukoc Biol. 2006; 80:1364–74. [PubMed: 17020930]

122. Harris KG, Coyne CB. Enter at your own risk: how enteroviruses navigate the dangerous world of pattern recognition receptor signaling. Cytokine. 2013; 63:230–6. [PubMed: 23764548]

123. Girkin J, Hatchwell L, Foster P, et al. CCL7 and IRF-7 Mediate Hallmark Inflammatory and IFN Responses following Rhinovirus 1B Infection. J Immunol. 2015; 194:4924–30. [PubMed: 25847975]

Data reveal an important role of CCL7 and IRF-7 in regulating RV-induced inflammation and interferon responses in a mouse model

124. Brabec-Zaruba M, Pfanzagl B, Blaas D, Fuchs R. Site of human rhinovirus RNA uncoating revealed by fluorescent in situ hybridization. J Virol. 2009; 83:3770–7. [PubMed: 19158243]

125. Hewson CA, Jardine A, Edwards MR, et al. Toll-like receptor 3 is induced by and mediates antiviral activity against rhinovirus infection of human bronchial epithelial cells. J Virol. 2005; 79:12273–9. [PubMed: 16160153]

126. Wang Q, Nagarkar DR, Bowman ER, et al. Role of double-stranded RNA pattern recognition receptors in rhinovirus-induced airway epithelial cell responses. J Immunol. 2009; 183:6989–97. [PubMed: 19890046]

127. Parsons KS, Hsu AC, Wark PA. TLR3 and MDA5 signalling, although not expression, is impaired in asthmatic epithelial cells in response to rhinovirus infection. Clin Exp Allergy. 2014; 44:91–101. [PubMed: 24131248]

128. Triantafilou K, Vakakis E, Richer EA, et al. 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. 2011; 2:22–9. [PubMed: 21224721]

129. Bosco A, Wiehler S, Proud D. Interferon regulatory factor 7 regulates airway epithelial cell responses to human rhinovirus infection. BMC Genomics. 2016; 17:76. [PubMed: 26810609]

Study showing that IRF-7 regulates the expression of RV induced genes involved in antiviral immunity, inflammation, and the response to oxidative stress in cultured human bronchial epithelial cells

130. Slater L, Bartlett NW, Haas JJ, et al. Co-ordinated role of TLR3, RIG-I and MDA5 in the innate response to rhinovirus in bronchial epithelium. PLoS Pathog. 2010; 6:e1001178. [PubMed: 21079690]

131. Calven J, Yudina Y, Uller L. Rhinovirus and dsRNA induce RIG-I-like receptors and expression of interferon beta and lambda1 in human bronchial smooth muscle cells. PLoS One. 2013; 8:e62718. [PubMed: 23658644]

132. Saba TG, Chung Y, Hong JY, et al. Rhinovirus-induced macrophage cytokine expression does not require endocytosis or replication. Am J Respir Cell Mol Biol. 2014; 50:974–84. [PubMed: 24783958]

133. Wang Q, Miller DJ, Bowman ER, et al. MDA5 and TLR3 initiate pro-inflammatory signaling pathways leading to rhinovirus-induced airways inflammation and hyperresponsiveness. PLoS Pathog. 2011; 7:e1002070. [PubMed: 21637773]

134. Hatchwell L, Collison A, Girkin J, et al. Toll-like receptor 7 governs interferon and inflammatory responses to rhinovirus and is suppressed by IL-5-induced lung eosinophilia. Thorax. 2015; 70:854–61. [PubMed: 26108570]

These data from a mouse model study determines that a lack of TLR7 signaling under conditions that mimic a virus-induced asthma exacerbation or its inhibition by IL-5-induced lung eosinophilia impairs IFN production and exaggerates Th2-driven inflammatory responses

135. Unger BL, Ganesan S, Comstock AT, et al. Nod-like receptor X-1 is required for rhinovirus-induced barrier dysfunction in airway epithelial cells. J Virol. 2014; 88:3705–18. [PubMed: 24429360]

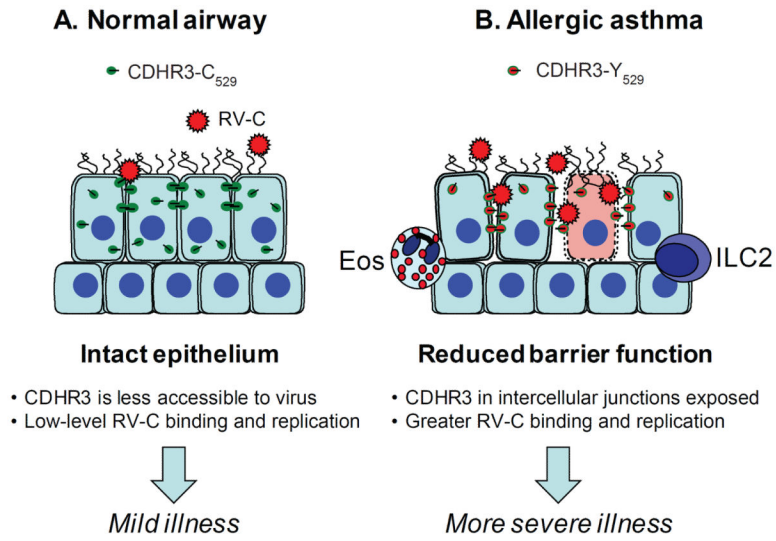

Fig.1.

Potential mechanisms of RV-C infection in normal and asthmatic airway epithelium. We speculate, based on function of other cadherins, that CDHR3 could be preferentially localized on the cell surface within intercellular junctions. The CDHR3 genotype (rs6967330) that converts amino acid residue cysteine to tyrosine at position 529 ($C_{529}\rightarrow Y$) leads to an increased cell surface expression of CDHR3. **a**. In a healthy intact epithelium with normal barrier function, CDHR3 is likely to be less accessible for RV-C binding resulting in a reduced infection and mild illness. **b**. Chronic allergic inflammation in asthmatic airways reduces epithelial barrier function, and this could secondarily increase accessibility of CDHR3 for RV-C binding in individuals with “asthma risk” genotype. As a result, RV-C could infect more cells, leading to more severe respiratory illness. Eos, eosinophils; ILC2, type 2 innate lymphoid cell.