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Pathogenesis of Rhinovirus Infection

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Summary

Since its discovery in 1956, rhinovirus (RV) has been recognized as the most important virus producing the common cold syndrome. Despite its ubiquity, little is known concerning the pathogenesis of RV infections, and some of the research in this area has led to contradictions regarding the molecular and cellular mechanisms of RV-induced illness. In this article, we discuss the pathogenesis of this virus as it relates to RV-induced illness in the upper and lower airway, an issue of considerable interest in view of the minimal cytopathology associated with RV infection. We endeavor to explain why many infected individuals exhibit minimal symptoms or remain asymptomatic, while others, especially those with asthma, may have severe, even life-threatening, complications (sequelae). Finally, we discuss the immune responses to RV in the normal and asthmatic host focusing on RV infection and epithelial barrier integrity and maintenance as well as the impact of the innate and adaptive immune responses to RV on epithelial function.

Keywords

Rhinovirus; asthma; pathogenesis; viral-induced asthma exacerbations

Introduction

Rhinovirus (RV) was first isolated in 1956 by Dr. Winston Price at Johns Hopkins University and was quickly determined to be the most common cause of cold symptoms in adults [1, 2]. It is a positive sense, single-stranded non-enveloped RNA virus of the picornavirus family with well over 100 serotypes discovered to date [3]. The RNA genome serves as an mRNA, which encodes both structural (capsid) proteins and non-structural proteins that are involved in viral genome replication and virion assembly. Upon entry into a cell the viral genome is translated into a polyprotein, which in turn undergoes proteolytic cleavage to produce the structural and non-structural gene products. The RNA genome is packaged within a protein coat consisting of 4 viral capsid proteins 1, 2, 3, and 4 (VP1, VP2, VP3, and VP4) [3, 4](figure). Amino acid differences in one or more of these capsid

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proteins confer the antigenic differences among individual RV strains or serotypes. The serotypes can be classified as HRV-A, -B, or -C viruses based upon genetic homology [1, 3, 5].

Over 90% of the known RV serotypes of the HRV-A and -B families utilize ICAM-1 as their cell entry receptor, while the minor group receptor, low-density lipoprotein (LDL), is used by 10 serotypes [4, 6]. HRV binds ICAM-1 near the site of LFA-1 attachment and, as a consequence of binding, the virus loses its protein capsid. Though somewhat controversial, this uncoating process is thought to occur via intermediate particles characterized by the loss of VP4 and the externalization of the hydrophobic N-termini of VP1, and ultimately this leads to transmigration of viral RNA through the host cell membrane [4].

HRV-C has more recently emerged as a virus of interest, particularly in RV-induced exacerbations of asthma[7]. The genomes of several strains of HRV-C have been recently sequenced, but, to date, the structural information has not as yet shed light on a potential cellular receptor and the receptor it employs to infect epithelial cells remains unclear. Based upon structural modeling studies, this is unlikely to be either ICAM-1 or the LDL receptor. Gern, J. et al. were the first to grow HRV-C *in vitro*, utilizing sinus mucosal tissue as the cellular substrate for *in vitro* HRV-C replication [3]. At present, HRV-C infection has been studied to only a limited extent and little is known regarding pathogenic mechanisms unique to this RV subtype. Consequently, the remainder of this review will focus on findings involving infection with HRV-A and -B.

Upper and Lower Respiratory Tract Disease Pathogenesis

In non-asthmatic individuals, symptoms of RV infection are generally limited to the upper respiratory tract. Rhinorrhea and nasal obstruction, the most prominent symptoms, are associated with a neutrophilic inflammatory response that is associated with increased vascular permeability and stimulation of mucus hypersecretion. Cough is a less common but bothersome manifestation of rhinovirus URI. The pathogenesis of cough may involve irritation from posterior pharyngeal drainage or direct infection of the large airways. Gwaltney, J. et al. [8] demonstrated sinus involvement in many individuals with typical common cold symptoms. The sinus disease resolved without intervention suggesting that these upper respiratory illnesses should be more accurately characterized as a viral rhinosinusitis. However, the inflammation associated with obstruction of sinus openings and secondary Eustachian tube dysfunction can predispose to acute bacterial sinusitis and otitis media, respectively.

In contrast, lower respiratory symptoms associated with RV infection are most prominent in patients who have underlying asthma or other chronic lung disease. These symptoms include cough, shortness of breath, chest tightness, and wheezing [9–13]. The basis for these lower respiratory symptoms has been a source of controversy concerning mechanisms of RV pathogenesis. Specifically, the underlying debate centers on the extent to which RV can infect cells of the lower respiratory tract and, as such, whether bronchial infection forms the basis for respiratory symptoms, as opposed to reflecting indirect influences related to the immune response to the upper airway infection. There are a variety of potential barriers to infection of lungs by RV including the temperature sensitivity of replication of the virus. RV replicates optimally at 33° C, a temperature significantly lower than that of bronchial airway epithelium [14]. It is noteworthy that RV has been concomitantly isolated with bacterial pathogens in 24–54% of children and 10–18% of adults with pneumonia [15–17]. From these studies it is unclear if RV is ever the cause of the agent for the development of pneumonia. Thus, more important to respiratory tract infectious disease pathogenesis during RV infection, may be the capacity of RV to predispose to concomitant or subsequent

infection with other respiratory pathogens. For instance, human tracheal epithelial cells simultaneously infected with RV14 and *Strept. pneumoniae* show increased adherence of the *Strept*. [18]. Similarly, macrophages exposed to RV showed impaired responsiveness of pattern recognition receptors (PRRs) following exposure to bacterial toll-like receptors (TLR) agonists e.g. lipopolysaccharide and lipoteichoic acid [19]. Furthermore, studies implicating RV involvement in lower airway pathology based on the detection of RV antigens (or genomes) in lower respiratory tract airways are confounded by the inability to exclude upper airway-derived RV contamination of bronchial samples. This is certainly problematic with sputum analysis, but even bronchoscopically-obtained samples can be contaminated during the bronchoscope's passage through the upper airway. However, several studies support the presence of RV in the lower airway [20, 21] including work showing RV by *in situ* hybridization after experimental RV16 infection [13]. Work by this group also demonstrates that while RV serotypes replicate optimally at 33° i.e., the temperature of the upper respiratory tract, the higher temperature of the lower airways is not an absolute barrier to RV replication [22]. The preponderance of current opinion therefore supports the concept that RV likely can productively infect cells of the lower airways.

Clinical and Subclinical Infections

Early studies utilizing tissue culture isolation to detect RV in the nasal secretions of patients with cold symptoms undoubtedly under-reported the frequency of RV infections. Since the advent of nucleic acid-based detection, it is possible to more reliably discern the actual prevalence of RV infection. However, the application of sensitive PCR based detection techniques immediately led to a quandary regarding the issue of the prevalence of asymptomatic infection with RV. This confirmed earlier suspicions regarding the likely prevalence of asymptomatic infection, recognized from the challenge model. RV is detected by RT-PCR in ~12–22% of asymptomatic individuals. Many of these may be false positives. Alternatively, if these do reflect non-infectious colonization, a mechanism for long-term survival of the RV in the nares in the absence of infection is not obvious. Plausibly, less virulent strains of RV could produce an asymptomatic infection. However, a study of asymptomatic individuals with positive PCR tests for RV found that asymptomatic infection was usually associated with simultaneous symptomatic infection in family members [5]. Similarly, in our own experience from experimental infections with RV39, quantitative RV titers from asymptomatic or minimally symptomatic subjects were equivalent to those with the worst symptoms. Along with the striking observations regarding the absence of direct cytopathology produced by RV (discussed next), these observations suggest that it is the nature and extent of the immune response to the virus that determines the symptom profile and not the severity or direct pathology caused by the infection itself.

Pathogenic Influences of RV on the Epithelium

While other respiratory viruses such as influenza and respiratory syncytial virus destroy the airway epithelial barrier, studies demonstrate that RV by itself does not cause cytopathology. For these studies, monolayers of adenoid tissue were infected with RV and, at the time of peak secreted viral titers, no detectable damage or other cytopathic effect was observed [23]. This is consistent with the failure to observe cytopathology in RV-infected nasal or bronchial biopsy tissue. Infection does, however, disrupt epithelial barrier function. The effects of RV to increase vascular leakage and mucus secretion reflect in part this ability of the RV to disrupt the epithelial barrier, specifically the disruption of tight junctions. Studies utilizing cultured human nasal epithelial cells showed decreased zona occluden-1, claudin-1, and E-cadherin mRNA and protein levels after infection with RV [24]. This is consistent with observations regarding the disruption of airway epithelial apical junctions by poly dI:dC [25]. In addition to increasing permeability, this disruption of the epithelial

barrier will facilitate translocation of pathogens (including non-RV pathogens) and their soluble products, and expose basolateral epithelial receptors, where TLR and other PRRs are prominently located.

Immune Response to Rhinovirus

In the absence of an ability to ascribe the presence and extent of symptoms to either virus titer or cytopathology, we propose that it is the characteristics of the host response to RV that are the primary determinant of symptoms. The host response to the virus includes those mediated by the innate, humoral, and cellular immune systems. To some extent these distinct responses represent a continuum with the progressive evolution of more severe (and more symptomatic) responses, although the specific sequence of this continuum may vary from patient to patient.

Innate Immunity

In the absence of pre-existing humoral immunity (discussed below) or presumably other mucosal surface-associated factors, RV will infect the epithelium and this will initially lead to the induction of an innate immune response. This occurs very rapidly as evinced by our studies showing appearance of type I interferon along with a drop in airway pH less than 24 hrs after experimental infection [26]. Early innate detection of RV depends on the host's ability to recognize RV-associated pattern recognition receptors including via TLR and other PRRs (e.g. retinoic acid inducible gene- I (RIG-I) and melanoma differentiation associated gene-5 (MDA-5)). RV capsid is recognized by TLR2 on the epithelial surface, whereas, after internalization and initiation of RV-directed RNA translation, RV-associated ssRNA and dsRNA are recognized by endosomal TLR3, TLR7, and TLR8. In addition, dsRNA is also recognized by MDA-5 and RIG-I [27, 28]. Engagement of these receptors induces cytokine expression including type I (IFN-α/-ß) and type III interferons (IL-28A, IL-28B, and IL-29), but also IL-6, IL-12, and IL-15. IFNs directly restrict virus replication but these and other cytokines including IL-12 and IL-15 play important roles in cytotoxic and natural killer cell differentiation, survival, and recruitment [29]. Elicited NK cells are an important early source of IFN-γ. IL-6 is involved in numerous facets of innate immunity that influence RV elimination [30] and an IL-6 single nucleotide polymorphism predicts worse illness [31]. Other important cytokines released by RV-infected epithelium include IL-1ß and IL-11.

Arguably the most important determinants of the clinical outcome of RV infection comprise growth factors, such as G-CSF and GM-CSF, and chemokines, such as CXCL8 (IL- 8), CXCL5 (ENA-78), CXCL10 (IP-10), and CCL5 (RANTES), that together drive granulocyte recruitment, survival and activation. These granulocytes are primarily neutrophils, reflecting especially the activities of CXCL8 and CXCL10. These mediators appear rapidly in nasal lavage fluid and serum of RV-infected patients and their concentrations parallel increases in peripheral blood neutrophils. The role – if any – of PMN in RV eradication is unclear but the ensuing neutrophil-laden nasal exudate is one of the more characteristic features of “colds” and the early expression of CXCL8 and CXCL10 links to the presence of *symptomatic* RV infections [32]. A neutrophilic exudate has also been associated with increases in kallikrein, which drives the production of kallidin and bradykinin [33]. These kinins are elevated in the nasal washes of subjects with symptomatic RV infections, particularly in those with allergies and asthma [34–37]. Eosinophils can also be robustly expressed [38]. The induction of eosinophilia may influence the ability of RV to produce nasal symptoms by enhancing bystander allergic reactions (discussed below). In contrast, eosinophils, in part through their ability to secrete numerous potent RNAses, appear to promote virus eradication [39].

Humoral Immune Responses

The therapeutic importance of humoral immune responses to RV is increasingly recognized. In experimental RV inoculation, B cell responses in the form of mucosal RV serotype-specific IgA were detected by day 3 and IgG at days 7–8 [40]. A role for this humoral response is suggested by observations that the presence of serotype-specific neutralizing IgG antibodies precludes subsequent challenge infection following experimental inoculation with an RV of that serotype [41]. It should be emphasized that given the need for neutralizing antibody to be present at the nasal mucosa boundary, it is likely that secretory IgA would be the actual determinant of protective humoral immunity. Antibodies could contribute to viral clearance by acting as neutralizing antibodies, e.g., blocking cellular attachment ligands, opsonizing the virus for presentation to phagocytic cells, or by initiating NK cell-mediated antibody-dependent cellular cytotoxicity. In addition to direct virus neutralization, pre-existing antibodies may also serve to mediate antibody-facilitated antigen uptake and promote more rapid and effective cellular immune responses.

The concept that humoral immune responses have *primary* importance in preventing and eradicating infection is further derived from observations regarding the increased frequency and severity of infection in patients with humoral immune failure (e.g., common variable immune deficiency). In these conditions, RV was the most common virus producing respiratory infections [42]. This was not corrected with replacement immunoglobulin, further implicating the need for serotype-specific antibodies, which could be lacking in any given commercial immunoglobulin preparation.

Cellular Immune Responses

In the absence of neutralizing antibodies or an effective innate immune response, RV-specific T-cells become central in virus eradication. The rapidity with which viral titers begin to decline after an RV infection, usually at ~72 hours, precludes the possibility that this reflects the *de novo* activation of naïve RV serotype-specific T cells. This observed timeframe is only consistent with activation of pre-existing effector/memory T cells, which must therefore responding to shared epitope(s) displayed by the infecting RV. In unpublished work (Woodfolk, J. and Kwok, W., personal communication), an HLA-DR4-restricted CD4-specific epitope of RV39 VP1 was found to map to a region of the molecule that is conserved across RV groups A, B and C. These observations imply that $CD4^+$ T cells induced by one RV strain are capable of responding to other strains and could drive the observed rapid and potent T cell recall response.

Both CD4- [43] and CD8-specific T cell responses develop as consequences of RV infection. CD4 cells are largely Th1-like and their production of IFN-γ contributes to the anti-viral immune response, but these CD4 cells will also facilitate development of the humoral immune response. CD8 T cells are likely central to the adaptive immune response driving RV eradication, although their presence and role has not been extensively evaluated. In our unpublished studies, these cells can be identified after infection and are also characterized by robust IFN-γ production. An additional mechanism that may contribute to the degree of symptoms developing with RV infection could reflect – similar to other respiratory virus-targeting immune responses – the propensity of these cells to concomitantly express IL-10 and thereby mitigate bystander immune-mediated damage [44, 45].

Mechanism of Asthma Exacerbations in Association with RV Infections

Any discussion of RV-associated disease pathogenesis must appreciate the striking capacity of this virus to drive asthma exacerbations. Among children, 80 to 85% of asthma

exacerbations are associated with upper respiratory viral infections [46, 47] and RV consistently accounts for ~60–70% of these virus-associated exacerbations [48–55]. For example, in our studies, viral infections were identified in 61% of children aged 3–18 years hospitalized with an asthma exacerbation. RV accounted for 77% of all positive tests and was the only virus significantly associated with asthma [56]. It should be noted, however, that RV infections are common and most do not produce exacerbations ([57] and unpublished data) and, similarly, asthma exacerbations are not a frequent response to experimental RV challenges, including in our published studies [58, 59].

Determining the underlying mechanisms for asthma exacerbations caused by RV has remained elusive. One theory entertains the notion that asthmatics have a deficient innate immune response to the virus. A study of bronchial epithelial cells observed decreased IFN-ß expression in asthmatics [60] and more recently, the same group has reported that asthmatics have deficient IL-15 [61]. These authors posit that this deficiency led to increased virus load and prolonged symptoms during experimental RV16 infections.

However, other studies including our unpublished work do not confirm that asthmatics exhibit more robust RV replication during an infection when compared to non-asthmatics [62]. Our studies show a strong correlation of the ability of RV to induce an asthma exacerbation to the presence of *relevant* aeroallergen sensitization [59]. The concept that RV may act to synergize with a bystander IgE-mediated allergic reaction to drive asthma exacerbations is supported by a multi-center trial showing the ability of anti-IgE therapy (omalizumab) to block the seasonally-observed pattern of asthma exacerbations, which included subjects infected with RV [63]. Although the mechanism by which RV could enhance an ongoing allergic reaction is not known, one possible contribution pertains to the observation previously discussed regarding the ability of RV to alter intracellular connections between epithelium, a process that would allow free access of allergens to mucosal tissue.

Summary

A debate remains as to whether it is the inherent pathogenicity of RV that leads to the associated symptoms, or whether it is the environment in which the virus replicates that determines the induction of symptoms. We argue that it is that various facets of the immune response to the virus that are important in restricting the infection but simultaneously drive the symptoms of RV infection, as the virus itself is not cytopathic. Whether features of physical barrier function, the innate immune system, or the adaptive immune response determine the pathogenesis of this virus, or different combinations acting in different subjects remains to be determined. Enhancing the understanding of these mechanisms will dictate future directives for treatment in patients, especially those whose asthma undergoes severe exacerbations by this virus.

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Highlights

- Rhinovirus is a ubiquitous virus and the usual cause of the common cold, yet little is known regarding its pathogenic mechanisms.
- The upper and lower airways are the primary targets of RV, but, surprisingly, this virus causes little cytopathology.
- Many patients will have positive tests to RV, yet remain subclinical.
- The host epithelial barriers and both innate and adaptive immune responses influence the reaction of the host.
- The various immune responses lead to the distinct outcomes from subclinical to severe and even life-threatening infections.

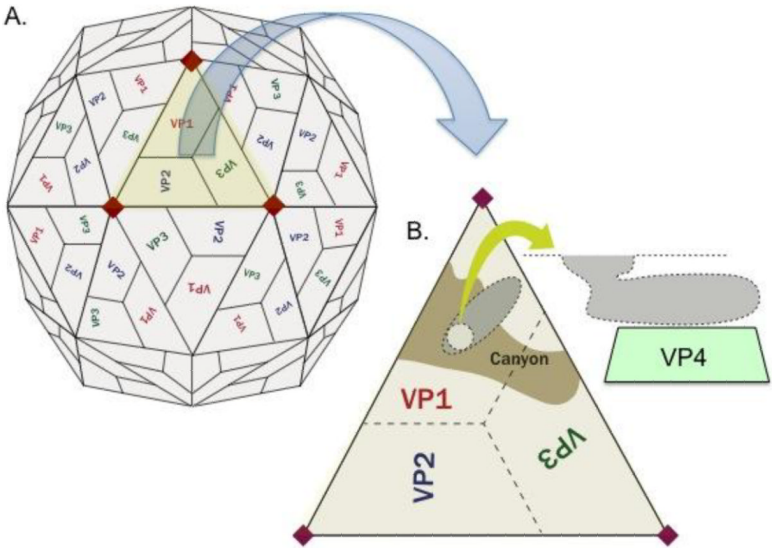

Figure 1.

(A) Rhinovirus is a non-enveloped, spherical virus composed of a protein shell surrounding the naked RNA genome. The protein capsid consists of 4 polypeptides, viral capsid protein 1 (VP1), VP2, VP3, and VP4, in an icosahedral formation. (B) A hydrophobic pocket or "canyon" exists within VP1, which is the likely point of contact for ICAM-1 [4, 64, 65]. VP4 is located on the internal surface of the virus and is important in assembly of the virus during replication and infection of new cells [66].