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Review Article

Rhinovirus – From bench to bedside

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Rhinovirus has been neglected in the past because it was generally perceived as a respiratory virus only capable of causing mild common cold. Contemporary epidemiological studies using molecular assays have shown that rhinovirus is frequently detected in adult and pediatric patients with upper or lower respiratory tract infections. Severe pulmonary and extrapulmonary complications are increasingly recognized. Contrary to popular belief, some rhinoviruses can actually replicate well at 37 °C and infect the lower airway in humans. The increasing availability of multiplex PCR panels allows rapid detection of rhinovirus and provides the opportunity for timely treatment and early recognition of outbreaks. Recent advances in the understanding of host factors for viral attachment and replication, and the host immunological response in both asthmatic and non-asthmatic individuals, have provided important insights into rhinovirus infection which are crucial in the development of antiviral treatment. The identification of novel drugs has been accelerated by repurposing clinically-approved drugs. As humoral antibodies induced by past exposure and vaccine antigen of a particular serotype cannot provide full coverage for all rhinovirus serotypes, novel vaccination strategies are required for inducing protective response against all rhinoviruses.

Introduction

Rhinovirus, which is often referred to as the "common cold virus", has been neglected as a cause of severe illness.[1] However, human volunteer studies with experimental infection have proven that rhinovirus can cause exacerbation of underlying lung disease. Rhinovirus can be detected frequently in critically ill patients with pneumonia with or

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without co-pathogens.[2] Although most clinicians are aware of rhinovirus, only few have access to diagnostic tests which can provide rapid virological confirmation. The increasing availability and affordability of commercially-available molecular diagnostic tests has allowed rapid diagnosis of rhinovirus infection in every day clinical practice. Recent advance in basic science research has improved our understanding on the virology, pathogenesis and immunological response of rhinovirus infection, which aids the development of antiviral treatment and vaccines. This review describes the advances in the understanding of rhinovirus from basic and clinical research studies that are relevant to clinical practice.

Virology

Taxonomy

Rhinovirus belongs to the *Picornaviridae* family. Before the molecular era, rhinovirus is differentiated from enterovirus phenotypically using acid stability test and serotyping with specific antisera. Rhinovirus is inactivated by acid, while enterovirus is acid stable. Different rhinoviruses can be classified into major and minor group depending on cellular receptor specificity, and into rhinovirus A and rhinovirus B by differential susceptibility to capsid-binding compounds.[3] The availability of molecular assay has further clarified the genetic relatedness between rhinovirus and enterovirus, and between different rhinovirus species. For example, rhinovirus 87 and enterovirus D68 are closely related genetically, and both are acid sensitive. Rhinovirus 87 is now reclassified as enterovirus D68.[4]

According to the latest ICTV release (http://ictvonline.org/virusTaxonomy.asp. 2015 release), there are 3 rhinovirus species (Rhinovirus A, Rhinovirus B, Rhinovirus C) under the genus *Enterovirus*, which also includes Enterovirus A—H and Enterovirus J. Current taxonomy and classification of rhinovirus and enterovirus are based on capsid region, particularly VP4/VP2 and VP1 (Fig. 1A).[5] Sequencing of the 5′ untranslated region (5′UTR) can differentiate rhinovirus from enterovirus, but cannot unequivocally determine genetic type of rhinovirus strains because 5′UTR is one of the hotspots of recombination.[6] In particular, 5′UTR cannot discriminate between rhinovirus A and C (Fig. 1B).

Viral genome and proteins

Rhinovirus is a non-enveloped, spherical virus with a diameter of about 30 nm. The icosahedral capsid encloses a 7.2-kb positive-sense single-stranded RNA viral genome.[7] The viral capsid is composed of the 4 capsid proteins. VP1, VP2, VP3 are present on the cell surface, while VP4 is found beneath the capsid. There are also several non-structural proteins, which include 2A, 2B, 2C, 3A, 3B, 3C and 3D. 2A and 3C are proteases, which cleaves viral

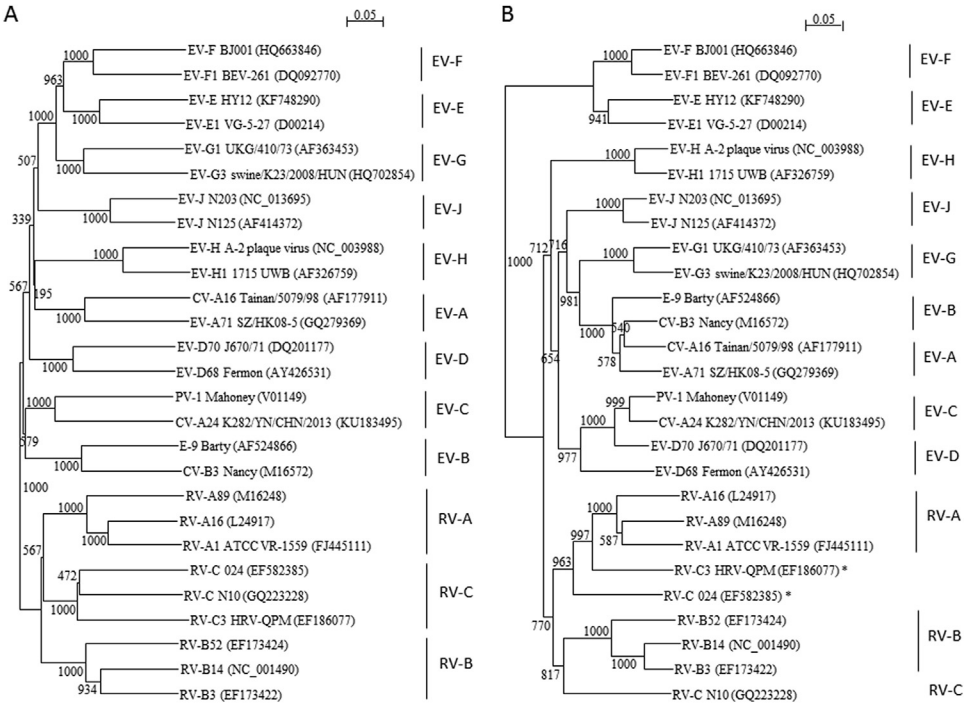

Fig. 1 Phylogenetic trees of VP4/VP2 (A) and 5′UTR (B) of rhinovirus and enterovirus strains of 12 species within the genus *Enterovirus*. Sequences for 1007 nucleotide positions in each VP4/VP2 and 718 nucleotide positions in each 5′UTR region were included in the analysis. The trees were constructed by neighbor-joining method, with bootstrap values calculated from 1000 trees. The scale bars indicate the estimated number of substitutions per 20 bases in VP4/VP2 and 5′UTR. The accession numbers (in parentheses) are presented as cited in the GenBank database. Asterisks indicate rhinovirus C variants with species A-like 5′UTR sequences.

polyprotein.[8] In addition to proteolytic cleavage of viral polyproteins, 3C is also important for antagonizing antiviral immunity. Rhinovirus 3C has been shown to cleave the host complement C3 which prevents complement signaling,[9] and may also cleave the pathogen recognition receptor (PRR) retinoic acid inducible gene I (RIG-I).[10] 3D is an RNA-dependent RNA polymerase. Protein 2C, 2B and 3A are important for anchoring replication complexes to membranous structure of the host cell. Protein 2B is important for the release of virus particles from cells by increasing the cell membrane permeability and calcium efflux from the endoplasmic reticulum. The viral capsid and proteases are currently the major targets of antivirals. The viral capsid is also the target site of neutralizing antibodies.

From 5′ end, the viral genome consists of a 5′VPg, a 5′UTR, a long open reading frame encoding a polyprotein, a 3′UTR and then a 3′ poly-A tail.[7] The viral genome is first translated into a single polyprotein. This polyprotein is then cleaved into P1, P2 and P3. P1 is further cleaved into VP0, VP3 and VP1; P2 is further cleaved into 2A and 2BC, and P3 is further cleaved into 3AB and 3CD. VP0 is then cleaved into VP4 and VP2; 2BC is cleaved into 2B and 2C; 3AB is cleaved into 3A and 3B; and 3CD is cleaved into 3C and 3D.

Virus replication

Rhinovirus first attaches to cell surface by the binding between viral VP1 and the host cell surface receptor. Depending on species, the host receptors can be intracellular adhesion molecule 1 (ICAM-1), low-density lipoprotein receptor (LDLR), heparan sulfate or cadherin-related family member 3 (CDHR3).[11] After attachment, viral entry occurred via receptor-mediated endocytosis by clarithrin-dependent or independent endocytosis, or via macropinocytosis. Uncoating then occurs in low pH endosomes. Inside the cytosol, viral RNA is translated into a polyprotein. This polyprotein is cleaved by viral proteases into smaller proteins. Viral RNA is also replicated to produce negative-sense RNA and then positive-sense RNA in the cytoplasm. Replication of rhinovirus requires the building up of a replication complex, which involves lipids, proteins and viral RNA. The new viral proteins and RNA are then packaged. Viral export occurs via cell lysis.

Lipids play an important role in the viral replication. Phosphatidylinositol 4-kinase III β (PI4KIIIβ) is required for rhinovirus infection.[12] Inhibitors of PI4KIIIβ has been shown to inhibit rhinovirus C replication using a replicon construct consisting of rhinovirus C genome sequences.[13] However, unlike enteroviruses, the recruitment of PI4KIIIβ is independent of GBF1 and ACBD3.[14] Upon release, rhinovirus is enclosed in phosphatidylserine vesicles, which enables them to be transferred to another cell for a new round of infection.[15]

Rhinovirus A and B can replicate in immortalized cell lines, and rhinovirus C can replicate in *ex vivo* organ culture of nasal epithelial cells.[16] Rhinovirus C generated by reverse genetics have also been shown to replicate in fully differentiated human airway epithelial cells.[17]

Traditionally, it was thought that rhinovirus mainly causes upper respiratory tract infection because it grows better at 33 °C than at 37 °C. However, studies have shown that some rhinovirus strains grew equally well at both 33 °C and 37 °C.[18]

Pathogenesis

Rhinovirus is primarily a respiratory tract pathogen. Experimental infection in human volunteers showed that rhinovirus can be detected throughout the respiratory tract. In the upper respiratory tract, rhinovirus can be detected in the nasal mucosa and posterior nasopharynx, and mainly affects the ciliated epithelial cells and to a lesser extent, non-ciliated cells.[19] In the lower airway, rhinovirus antigens can be detected in bronchial biopsy of patients with experimental rhinovirus infection using in situ hybridization.[20,21] Rhinovirus is detected mainly in columnar epithelial cells, and to a lesser extent, the basal cell layer.[20] Rhinovirus has also been shown to replicate in type II pneumocytes derived from human fetal lung.[22] Similar to other respiratory viruses,[23,24] systemic dissemination of rhinovirus can occur. Rhinovirus viremia has been associated with more severe disease.[25] Live rhinovirus was detected in blood and feces.[26,27] Rhinovirus C RNA was detected in fecal samples of patients with gastroenteritis,[28] and in the cerebrospinal fluid of a fatal case of lower respiratory tract infection.[27] Rhinovirus can also enter immune cells, including monocytes, T cells and B cells. Rhinovirus can replicate in B cells.[29]

Unlike influenza virus and adenovirus, rhinovirus does not cause cytopathology in human nasal epithelial cell line.[30] However, rhinovirus can cause cytopathic changes in human bronchial epithelial cells.[20] Rhinovirus can also cause disruption in the epithelial barrier, leading to vascular leakage and mucus secretion.[31] The disruption in epithelial barrier has also been shown to facilitate the binding, translocation and persistence of bacteria.[31]

Rhinovirus is a common co-pathogen in patients with respiratory tract infection. In patients with chronic obstructive pulmonary disease (COPD), there is significant increase in bacterial load, especially *Haemophilus influenzae*.[32] Rhinovirus may also predispose to secondary bacterial infection by increasing the levels of neutrophil elastase and decreasing the levels of antimicrobial peptides.[33]

Experimental rhinovirus infection studies in patients with asthma and COPD have significantly contributed to the understanding of the pathogenesis regarding rhinovirus-induced exacerbation of these chronic lung diseases. Rhinovirus infection can trigger an inflammatory response in the lower airway. In patients with asthma, rhinovirus infection induces an increase in the levels of eosinophils in bronchoalveolar lavage,[34] and an increase in the levels of IL-4, IL-5, IL-13, IL-25 and IL-33 in the nasal fluid.[34,35] In mice, antibody against IL-25 receptor abolished the expression of T_H2-related cytokines during rhinovirus infection.[35] IL-17A, which inhibits rhinovirus replication in A549 cells, has been shown to reduce the expression in peripheral blood mononuclear cells of asthmatic children with rhinovirus infection.[36] Experimental rhinovirus infection in COPD patients led to an increase in the level of IL-6 in the BAL, while no such increase occurs in non-COPD patients.[37]

In addition to exacerbation of asthma and COPD, rhinovirus has been implicated in the development of asthma. It has been postulated that recurrent rhinovirus

infections can lead to airway remodeling that is seen in patients with asthma. Airway remodeling is characterized by changes in reticular basement membrane, smooth muscle mass, angiogenesis and barrier function. There is also goblet cell hyperplasia and metaplasia which can lead to increased mucus production.[38]

Immune response

Innate immune response

Rhinovirus can be recognized by host cell via PRRs, including toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs).[39] The activation of these PRRs will trigger downstream signals, which are important for limiting viral replication in immune regulation. For example, TLR7 deficient-mice were found to have increased in viral replication and exaggerated eosinophilic inflammation.[40] The binding of NLRs can activate caspase 1, which regulates the processing and release of IL-18. Blunted IL-18 response in the respiratory tract was associated with more symptoms in study participants with experimental infection.[41] Antimicrobial peptides may also be important. LL-37 has been shown to inhibit rhinovirus replication.[42]

Compared with RSV and influenza virus infection, rhinovirus shows a distinctive RNA expression profile in the peripheral blood. SOCS1 was uniquely found for rhinovirus.[43] SOCS1 is a member of the STAT-induced STAT inhibitor, which are negative regulators of cytokine signaling. SOCS proteins negatively regulate the JAK-STAT pathway, and Pim1 kinase can stabilize SOCS proteins. Inhibition of Pim1 kinase, which increases the degradation of SOCS proteins and augments the JAK-STAT pathway, has been shown to reduce viral replication.[44]

The study of immune response of viral infections can also be inferred by host genetic polymorphisms.[45] In a study with experimental rhinovirus infection, participants with a polymorphism in the interleukin 6 (IL-6) promoter at position −174 had more severe symptoms.[46] In preterm infants and term infants, genetic variants in vitamin D receptor and IL-10 were associated with the development of lower respiratory tract infection.[47,48]

Adaptive immunity

Rhinovirus infection can induce neutralizing antibody response for the same serotype, but not across different serotypes. Since there are >100 serotypes, frequent rhinovirus infections due to different serotypes occur. In human volunteers with experimental rhinovirus infection, serotype-specific antibodies were generated after rhinovirus infection, and that the IgG1 antibodies against the N-terminal of VP1 fragment correlated with the severity of upper and lower respiratory tract symptoms.[49] The VP1 of rhinovirus C has deletions where neutralizing antibody binds for other rhinoviruses.[50] However, it remains to be determined whether VP1 protein of rhinovirus C can be the binding site of neutralizing antibodies.

T cells also play a role in rhinovirus infection. Human intranasal challenge showed that there is rapid expansion of epitope specific memory T cells after rhinovirus infection.[51] T cell epitopes have been found on VP1 and VP2 capsid proteins.[51,52] The exact role of T cell immunity in limiting rhinovirus infection is not clear, but it has been suggested that T cell recruitment may facilitate viral clearance.[7] For asthma patients, T_H2 cells likely contribute to asthmatic exacerbation by secreting IL-5 and IL-13.

Epidemiology

Rhinovirus is circulating worldwide. Most infected patients are asymptomatic or only suffer from mild symptoms.[53] Rhinovirus is one of the most common respiratory viruses detected among patients with otitis media,[54] croup,[55] bronchiolitis,[56] pneumonia[57,58] and exacerbation of underlying lung diseases. Patients with severe rhinovirus infections are more likely to be immunocompromised than patients with influenza virus infection.[59] Patients with asthma also had more severe symptoms than healthy patients.[60] Mortality rate can be high among critically ill patients. In an outbreak among infants in Vietnam, 12 critically ill infants with acute respiratory distress syndrome were admitted to the intensive care unit, and 7 patients died.[61] Several studies have found that wheezing episodes or lower respiratory tract infections were more common among patients with rhinovirus C than rhinovirus A or rhinovirus B.[50,62,63] However, other studies did not find any relationship between rhinovirus species and clinical severity.[64–66]

In areas with temperate climates, the peak incidence of rhinovirus infection occurs in early fall and in the spring. In the subtropical areas such as Hong Kong, the seasonality is similar.[62,67] However, the severity of illness may depend on the season. In a study conducted in Wisconsin USA, rhinovirus is more likely to cause severe disease in the winter months.[68] In our recent study conducted in Hong Kong, rhinovirus infection in critically ill patients occurred most commonly during the summer and winter months, with relatively few cases in the fall and spring.[2] One possibility of more severe rhinovirus infection during the winter may be because at lower temperature, the induction of type I and III interferons are much lower than that at higher temperature.[69]

Most of the rhinovirus infections are acquired in the community. However, several nosocomial or institutional outbreaks have been reported, which affected both patients/residents or staff members.[70,71] Being a non-enveloped virus, rhinovirus is relatively resistant to alcohol hand rub and disinfectants.[72] Rhinovirus can be detected on environmental surfaces for a prolonged period of time.[73]

Clinical features

Rhinovirus most commonly causes "common cold", an ill-defined term which usually describes a clinical syndrome with rhinorrhea, nasal congestion, sore throat, cough, headache, and malaise, and can be caused by many respiratory viruses and atypical bacteria. Other upper

respiratory tract infections include acute otitis media,[74] rhinosinusitis[75] and croup.[76]

Lower respiratory tract involvement is increasingly recognized. Rhinovirus is commonly detected in patients with bronchiolitis and community acquired pneumonia (CAP).[57,58,76] Rhinovirus can also predispose to secondary bacterial pneumonia. Since asymptomatic shedding is common, the pathogenic role of rhinovirus in lower respiratory tract infection has been questioned. In case—control studies, rhinovirus was detected less frequently among children with CAP than those who are apparently healthy.[77,78] In a prospective study comparing CAP patients and asymptomatic controls, rhinovirus was associated with CAP only in adults, but not in children.[53] However, several lines of evidence suggest that rhinovirus can cause lower respiratory tract infection. Firstly, experimental infections in human volunteers showed that rhinovirus can infect the bronchial tissue.[20,21] Secondly, rhinovirus can replicate in cells originated from the lower respiratory tract,[22] and able to replicate at 37 °C. Thirdly, experimental infection in human volunteers with asthma or COPD showed that rhinovirus infection can induce lower respiratory tract symptoms and decrease peak expiratory flow and forced expiratory volume.[34,37] Fourthly, the viral load is significantly higher in patients with symptoms than those who are asymptomatic.[74,79]

Rhinovirus has been associated with the exacerbation of chronic lung diseases, including asthma,[80] COPD,[81] bronchiectasis,[82] bronchiolitis obliterans organizing pneumonia[2] and cystic fibrosis.[83] Rhinovirus infection triggers more severe symptoms and greater reduction in airway obstruction in patients with asthma than non-asthmatic controls.[34,84] Experimental rhinovirus infection in humans also induced COPD exacerbation.[37]

Extrapulmonary complications are frequently seen in critically ill patients with rhinovirus infection. In our study on critically ill patients, seizure was identified in 23% of patients with rhinovirus infection.[2] Other extrapulmonary complications include pulmonary edema, diabetic ketoacidosis and hyperosmolar coma.

Diagnosis

Currently, reverse transcription-polymerase chain reaction (RT-PCR) is the most common method in the detection of rhinovirus from clinical specimens because it is much more sensitive than viral culture. A major problem in the molecular diagnosis of rhinovirus is the difficulty in differentiating rhinovirus from enterovirus. The 5′UTR is the most popular target for the detection of rhinovirus because of high sensitivity. However, RT-PCR targeting 5′UTR without sequencing cannot reliably differentiate between rhinovirus and enterovirus, because it is difficult to find primer target sites that are substantially different between rhinovirus and enterovirus but identical among all rhinovirus species. There is also some concern regarding the sensitivity in the detection of rhinovirus C. The sensitivity of detection seems to be lower for rhinovirus C than that for other rhinovirus species,[85] which may be related to the highly variable target region.

Current commercially available multiplex PCR assays can detect rhinovirus. Since most multiplex PCR assays cannot reliably differentiate rhinovirus and enterovirus, the result is reported as rhinovirus/enterovirus.[86] Some commercially available multiplex diagnostic platforms report rhinovirus separately from enterovirus. Anyplex II RV16 has shown good differentiation between rhinovirus and enterovirus for a limited number of rhinovirus and enterovirus species tested, but this assay has lower sensitivity than xTAG respiratory pathogen panel.[87] Cross reactivity has been found for enterovirus 68 in the GenMark Diagnostics eSensor respiratory viral panel.[88]

Since prolonged viral shedding can occur, the detection of rhinovirus may be related to a past infection rather than the current infection. However, in children <1 year old, it was found that prolonged viral shedding beyond 30 days is uncommon (<5%).[89]

Treatment

There is currently no approved treatment for rhinovirus infections. Pleconaril, a capsid-binding drug which prevents the interaction between virus and host cell receptor, was the first antiviral against rhinovirus which has undergone clinical trial. In two parallel randomized, double-blind, placebo-controlled trials, the duration of symptoms was significantly shorter than the placebo group if the drug is taken within the first 24 h of symptoms.[90] However, the United States Food and Drug Administration advisory committee rejected the manufacturer's application. The safety concerns included menstrual disorders in women taking pleconaril and oral contraceptives, and two women became pregnant while taking pleconaril and oral contraceptives.[91] Several capsid-binding drugs have been developed recently.[7] WIN56921 can inhibit both rhinovirus-A16 and rhinovirus-C15, but not rhinovirus-B14.[16]

Other potential antiviral targets are the protease proteins. Ruprintrivir is an inhibitor of the rhinovirus 3C protease. In double-blind placebo-controlled clinical trials, intranasal ruprintrivir spray was effective in both the prevention and treatment of experimental rhinovirus infection in humans.[92] However, in subsequent natural infection studies, there was no significant reduction in viral load or disease severity.[93]

Repurposing of approved drug is a popular strategy to identify new drugs against respiratory virus infection. Using a chemical screening library, the antifungal drug itraconazole has been found to have antiviral activities against various viruses in the Picornaviridae family, including rhinovirus.[94] The antiviral action on rhinovirus was based on the inhibition of oxysterol-binding protein (OSBP). OSBP is involved in the shuttling of cholesterol and PIP4 between ER and Golgi, which is important for rhinovirus replication.[95] In a murine model, oral administration of itraconazole reduced the replication of rhinovirus in the lung of infected mice.[96] Nasal itraconazole prior to infection showed good protection in mice as well.[96] Another clinically-approved drug with antiviral activity against rhinovirus is niclosamide, an anti-helminth drug. Niclosamide inhibits viral entry by neutralizing the acidic endosome.[97]

Phase 3 trials have been completed for echinacea, vitamin C, zinc and anti-histamines. There is improvement in symptoms for vitamin C, zinc and anti-histamines.[7] However, there was no significant reduction in viral load.

Since rhinovirus is very common, pooled immunoglobulin should contain antibodies against different serotypes of rhinoviruses. Intravenous immunoglobulin has been used in patients with severe rhinovirus infection.[98]

Vaccine

Studies conducted over 50 years ago showed that immunization with live attenuated or inactivated rhinovirus can protect humans from challenge with homologous virus, but not from heterologous virus from different serotypes.[99] In recent years, there are two mains strategies to induce protective immunity against different rhinovirus serotypes. A polyvalent inactivated rhinovirus vaccine, which contains 50 rhinovirus serotypes, has been tested in rhesus macaques, and was shown to induce potent neutralizing antibody against a broad range of subtypes.[100] Another approach is to use a conserved region of the rhinovirus as the vaccine antigen, together with an adjuvant which enhances T cell response. In a mouse model, immunization with recombinant rhinovirus 16 VP0 protein and incomplete freund's and CpG adjuvant elicited neutralizing antibodies against both homologous and heterologous serotypes and an increase in lung memory T cells.[101] Mice immunized with this adjuvanted VP0 vaccine showed more rapid viral clearance when compared with non-immunized mice.

Conclusion

Besides being the most common cause of absence from work or school, rhinovirus is increasingly recognized as a cause of severe respiratory tract infection, which may be followed by pulmonary and extrapulmonary complications in patients with predisposing factors. The increasing availability of molecular test, which allows the early detection of rhinovirus, has now provided the window of opportunity for treatment studies during acute infection. Furthermore, early detection will allow prompt recognition of outbreaks, which frequently occur in hospitals and long term care facilities. Better understanding of the virus will allow the development of antivirals and therapeutic neutralizing antibody besides symptomatic treatment. An effective vaccine, which either contains multiple rhinovirus serotypes or a conserved region, will be needed to overcome the difficulty in inducing immunity against heterologous serotypes. It remains to be determined whether an effective vaccine can reduce pneumonia, development or exacerbation of chronic pulmonary diseases, and extrapulmonary complications.

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