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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

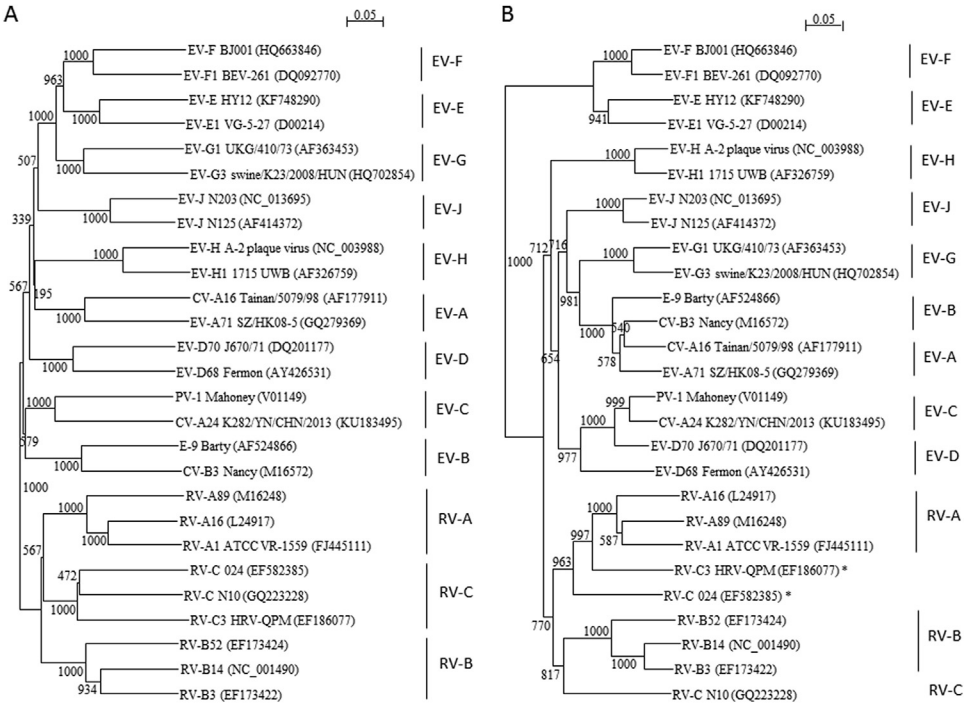

Fig. 1 Phylogenetic trees of VP4/VP2 (A) and 5′UTR (B) of rhinovirus and enterovirus strains of 12 species within the genus *Enterovirus*. Sequences for 1007 nucleotide positions in each VP4/VP2 and 718 nucleotide positions in each 5′UTR region were included in the analysis. The trees were constructed 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.