Journal of Clinical Virology 53 (2012) 97–105

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Review

Ten years of human metapneumovirus research

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ARTICLE INFO

Article history:
Received 29 July 2011
Received in revised form 5 October 2011
Accepted 10 October 2011

Keywords:
hMPV
hRSV
Paramyxoviridae
Fusion glycoprotein
Therapeutic
Vaccine

ABSTRACT

Described for the first time in 2001, human metapneumovirus (hMPV) has become one of the main viral pathogens responsible for acute respiratory tract infections in children but also in the elderly and immuno-compromised patients. The pathogen most closely related to hMPV is human respiratory syncytial virus (hRSV), the most common cause of bronchiolitis and pneumonia in young children. hMPV has been classified into two main viral groups A and B and has a seasonal distribution in temperate countries with most cases occurring in winter and spring. Given the difficulties encountered in culturing hMPV *in vitro*, diagnosis is generally achieved using real-time polymerase chain reaction.

Like other *Paramyxoviridae*, hMPV has a negative-sense single-stranded RNA genome that includes 8 genes coding for 9 different proteins. The genomic organization and functions of surface attachment and fusion glycoproteins are relatively similar to those of hRSV. Although many groups have studied the viral life cycle of hMPV, many questions remain unanswered concerning the exact roles of the viral proteins in the attachment, fusion and replication of hMPV.

To date, there remains no approved modality to combat hMPV infections. The majority of treatments that have been tested on hMPV have already demonstrated activity against hRSV infections. Some innovative approaches based on RNA interference and on fusion inhibitors have shown efficacy *in vitro* and in animal studies and could be beneficial in treating human hMPV disease. Difficulties faced inducing a durable immune response represent the biggest challenge in the development of an effective hMPV vaccine. Several strategies, such as the use of live-attenuated viruses generated by reverse genetics or recombinant proteins, have been tested in animals with encouraging results.

Contents

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doi:10.1016/j.jcv.2011.10.002

1. Classification

The virus was first characterized by the team of Pr Osterhaus in 2001[1] although retrospective serological studies have revealed the existence of human metapneumovirus (hMPV) antibodies among the human population from as early as the 1950s. hMPV belongs to the *Pneumovirinae* subfamily of the family *Paramyxoviridae*.[2] This subfamily is made up of the genus *Pneumovirus* which includes human respiratory syncytial virus (hRSV) and the genus *Metapneumovirus* which includes the two viral species hMPV and avian pneumovirus (APV) (Fig. 1).

Genetic analysis of hMPV isolates has revealed two major groups (A and B) and four "minor" sub-groups (A1, A2, B1 and B2), mainly based on the sequence variability of the attachment (G) and fusion (F) surface glycoproteins.[2] The existence of two further subgroups, A2a and A2b, has also been suggested.[3]

The existence of multiple serotypes of hMPV remains however the subject of much debate. According to some authors, the highly conserved F protein constitutes an antigenic determinant that mediates cross-lineage neutralization and protection,[4] while other studies have reported a difference in reactivity between the two genotypes.[5]

2. Epidemiology and clinical features

Global epidemiological studies indicate that most children below the age of 5 years will already have been infected by hMPV.[6] Of all respiratory viral infections requiring hospitalization, 10% will be due to hMPV, 40% to hRSV and 5% to adenoviruses.[6] In adults, hMPV is the cause of between 4% and 5% of severe acute respiratory diseases.[6] hMPV shares epidemiologic features with hRSV in that it: (i) is present in all continents; (ii) has a seasonal distribution with main occurrence in winter and spring; (iii) is also likely transmitted via airborne respiratory droplets.[7] hMPV has also been found to infect chimpanzees (61% seroprevalence in captive animals in one study) with potential human-to-gorilla transmission cases.[4,8]

hMPV preferentially targets ciliated epithelial cells of the human respiratory tract. The incubation period of the virus is between 4 and 6 days and its excretion spreads across a period of 5 days to 2 weeks.[9] Clinical signs often resemble bronchiolitis in children and HMPV generally accounts for 5–15% of hospitalizations for lower respiratory tract infections in that population.[10] Infected young adults generally only present with flu-like symptoms: however, the infection can turn out to be more severe in older or immunocompromised patients. Large outbreaks of hMPV infections with case fatality rates approaching 10% have been reported in long term care facilities.[11] Of note, clinical severity has also been found to be far higher in aged mice.[12] While hMPV is more often diagnosed in children, the elderly suffer more frequent recurrences. This would suggest that the re-infection of adults by hMPV may be due to incompletely protective immune responses and/or to the infection by different viral genotypes. Alternatively, the weak immune response has also been suggested to be the consequence of high levels of glycosylation of the G protein.[13]

3. Diagnosis

hMPV was first isolated and cultivated on a rhesus monkey cell line (LLC-MK2),[1] and since then also on the African green monkey kidney cell line (Vero).[6,14] Other cells (Hep2 and HepG2) can support the replication of some hMPV strains.[15,16] Its growth in cell culture is difficult and long and cytopathic effects (CPEs) are variable. The hMPV-induced CPE is characterized by a rounding of infected cells, subsequent detachment from cell culture matrix and occasionally the presence of small syncytia which do not usually appear before the second week of culture in LLC-MK2 cells.[1,17] The frequent need for initial blind passages before such virological features can be observed,[6] partly explains the relatively late discovery of hMPV. More rapid diagnostic techniques, such as direct immunofluorescence (DFA) or ELISA-based antigen detection can also be used.[6,18,19] Commercial anti-hMPV antibodies for direct antigen tests and shell vial cultures are available from Diagnostic Hybrids Inc. and Millipore Corporation.

Molecular diagnosis of hMPV infection is now commonly performed by real-time polymerase chain reaction (RT-PCR) from respiratory tract samples. The N gene is generally targeted in order to detect the 4 sub-groups of hMPV since it is highly conserved among the different strains of hMPV.[20] An FDA-approved hMPV real-time RT-PCR assay is available from Prodesse Inc. Also, multiplex respiratory viral panels including hMPV (xTAG RVP FAST from Abbott Molecular Diagnostics and FilmArray RP from Idaho Technology) are also FDA-approved.

In a study of 750 nasopharyngeal swabs, Gharabaghi et al. reported a detection rate for hMPV of 69% by DFA, 43% by shell vial culture (R-Mix, Diagnostic Hybrids Inc.) and 92% by multiplex RT-PCR (xTAG RVP FAST, Abbott Molecular Diagnostics).[21] Others have found better sensitivity of DFA and the shell vial assay (roughly 80%) compared to different multiplex RT-PCR assays.[19] Thus, single and multiplex RT-PCR assays constitute the most sensitive methods of detecting hMPV but careful evaluation of different assays is still needed.

4. Virological features

4.1. Virus structure and genomic organization

The morphology of the virion observed by electron microscopy (Fig. 2A) resembles that of other viruses in the *Paramyxoviridae* family. The metapneumoviruses are pleomorphic and measure between 150 and 600 nm in diameter.[1] Their lipid envelope, covered at its interior by the matrix protein M, contains three surface glycoproteins (F, SH and G) that form spikes of 13–17 nm (Fig. 2A). The viral RNA, of negative polarity (13 kDa), is associated to the nucleoprotein N, the phosphoprotein P, the polymerase L and likely also to factors M2-1 and M2-2 to form a nucleocapsid of helicoidal symmetry (17 nm in diameter and between 200 and 650 nm in length).[1] The order of genes is identical to that of avian pneumovirus (APV) (Fig. 2B) and partly determines their sequential expression (see following paragraph). While hMPV and hRSV genomes do closely resemble each other, that of hMPV presents certain differences in terms of its organization, notably concerning