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Vaccination approaches to combat human metapneumovirus lower respiratory tract infections

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Abstract

Human metapneumovirus (hMPV) was discovered in 2001 as a causative agent of respiratory disease in young children, immunocompromised individuals and the elderly. Clinical signs of hMPV infection range from mild respiratory illness to bronchiolitis and pneumonia. Two main genetic lineages of hMPV that circulate worldwide were found to be antigenically different, but antibodies against the F protein, the major determinant of protection, were shown to be cross-protective. Since the discovery of hMPV in 2001, several research groups have developed vaccine candidates that may be used to protect different risk groups against hMPV-induced respiratory disease. The studies in rodent and non-human primate models look promising, but none of the vaccine candidates has been tested yet in human volunteers. Here we give an overview of the immunogenicity and protective efficacy of a variety of live attenuated, virus vectored, inactivated virus and subunit vaccines that have been tested in animal models.

Keywords: Metapneumovirus; Immunization; Protective efficacy; Vaccine; Animals

The human metapneumovirus (hMPV) was first isolated from respiratory specimens obtained from children in The Netherlands hospitalized for acute respiratory tract illness (RTI) (van den Hoogen et al., 2001). Based on genomic organization, hMPV was classified as the first mammalian member of the Paramyxoviridae family, subfamily Pneumovirinae, genus Metapneumovirus. Clinical manifestations of hMPV infections are similar to those caused by respiratory syncytial virus (RSV), ranging from mild respiratory illness to bronchiolitis and pneumonia (van den Hoogen et al., 2003; Williams et al., 2006). Phylogenetic analysis of fusion (F) and attachment (G) genes of a large number of hMPV isolates revealed the existence of two main genetic virus lineages each divided into at least two sublineages. The two main lineages were found to be antigenically distinct in virus-neutralization assays with ferret sera (van den Hoogen et al., 2004). However, the F protein is highly conserved between the two major lineages, and antibodies induced against the F protein correlate with protection in animal models (Tang et al., 2005; Skiadopoulos et al., 2006). Since hMPV-associated RTI has been demonstrated in young children, individuals with underlying disease and the elderly, a variety of vaccination strategies may be required to prevent hMPV respiratory tract infections in the community. Live attenuated viruses may be useful to prevent infection in young naïve children, while inactivated viruses or subunit vaccines may be useful to boost existing immune responses in immunocompromised individuals and the elderly. A major drawback for using inactivated vaccines is the experience with a formalin-inactivated (FI-) RSV vaccine in the 1960s. Immunization of naïve children with this vaccine induced enhanced disease upon subsequent infection (Kim et al., 1969). The upper respiratory tract (URT) of cotton rats immunized with FI-hMPV was almost completely protected against infection, but an increase in lung pathology combined with a change in cytokine profiles was observed (Table 1) (Yim et al., 2007). Thus, alternative vaccine candidates for hMPV may be required. Here we give an overview of approaches explored to protect mammals against hMPV infections.

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1. Live attenuated vaccines

Live attenuated vaccines (LAVs) have the advantage of mimicking a natural infection and may provide protection against subsequent infections without inducing enhanced disease. The development of reverse genetics systems for hMPV provides a powerful tool to design LAV (Biacchesi et al., 2004a; Herfst et al., 2004). A number of strategies for attenuating RSV have been explored, which may be helpful for the development of LAV against hMPV.

1.1. Vectored vaccines

The first described LAV was a chimeric bovine parainfluenza virus type 3 (PIV3), harboring the F and hemagglutinin-neuraminidase (HN) genes of human PIV3 (Table 1). This b/hPIV3 virus was used as a vector to express the F protein of hMPV, from position 2 of the genome (b/hPIV3/hMPV F2) (Tang et al., 2003). Immunization of hamsters and African green monkeys (AGMs) with b/hPIV3/hMPV F2 induced both PIV3 and hMPV-specific neutralizing antibodies that protected against PIV3 and hMPV challenge infection (Tang et al., 2003, 2005). In AGMs, no hMPV replication was observed in the lower respiratory tract (LRT) after challenge infection and the virus titer in the URT was more than 100-fold reduced. Additional studies in rhesus monkeys demonstrated that the b/hPIV3/hMPV F2 virus replicated to the same extent as a recombinant bovine PIV3 (rbPIV3), that was previously found to be attenuated and safe in human infants (Karron et al., 1995; Tang et al., 2005).

1.2. Deletion mutants

Recombinant hMPVs lacking the small hydrophobic (ΔSH), attachment (ΔG) or second ORF of the M2 (ΔM2-2) proteins have been described to replicate efficiently in vitro, while being attenuated in vivo (Table 1) (Biacchesi et al., 2004b; Buchholz et al., 2005). After initial experiments in hamsters, replication kinetics, immunogenicity and protective efficacy of these viruses were studied in AGMs (Biacchesi et al., 2005). Replication of ΔG and ΔM2-2 viruses was reduced 6- and 160-fold in the URT and 3200- and 4000-fold in the LRT respectively, whereas viral titers for the ΔSH virus were only slightly lower as compared to wild type (wt) hMPV. Upon challenge infection, only trace amounts of virus were detected in the URT, and virus shedding in the LRT was virtually undetectable.

1.3. Chimeric viruses

Chimeric viruses have been generated by replacing the nucleoprotein (N) or phosphoprotein (P) proteins of hMPV by their counterparts of avian metapneumovirus type C (aMPV-C) (Table 1) (Pham et al., 2005). aMPV-C is the closest known relative of hMPV and causes respiratory illnesses in poultry. In hamsters, high levels of protective neutralizing antibodies were induced after intranasal infection with such chimeric metapneumoviruses, although virus titers in the lungs and nasal turbinates were approximately 100-fold reduced compared to wild type hMPV at 3 days post infection (dpi). At 5 dpi, there was only a small difference between viral titers of the chimeras and wt hMPV. In AGMs, the N-chimera replicated to ∼10-fold lower titers in the lower respiratory

Table 1

Vaccine	Animal model	Outcome	Refs.
FI-hMPV	Cotton rats	Almost complete protection in lungs, but dramatic increase in lung pathology	Yim et al. (2007)
B/hPIV3 expressing hMPVF	Hamsters, AGM	b/hPIV3/ hMPV F2 was sufficiently attenuated in rhesus monkeys. Immunization of AGMs resulted in complete protection of the LRT and virus titers in the URT were >100-fold reduced	Tang et al. (2003, 2005)
HMPV deletion mutants	Hamsters, AGM	ΔG and ΔM2-2 viruses were attenuated in AGMs. After challenge, virus shedding in the LRT was virtually undetectable	Biacchesi et al. (2004b, 2005); Buchholz et al. (2005)
Chimeric hMPV/aMPV-C	Hamsters, AGM	The P-chimera was attenuated 100- and 1000-fold in the URT and LRT of AGMs. Protective efficacy is comparable with wt hMPV.	Pham et al. (2005)
Soluble F protein	Hamsters, cotton rats	Immunization with adjuvanted soluble F protein induced complete protection of the LRT against heterologous challenge infection	Herfst et al. (2007)
Soluble F protein and F DNA vaccine	Cotton rats	Viral replication after challenge infection was 10-fold reduced in the LRT. No significant reduction was observed in the URT compared to non-immunized animals	Cseke et al., 2007

FI: formalin-inactivated, hMPV: human metapneumovirus, b/hPIV3: bovine/human parainfluenzavirus type 3, AGM: African green monkeys, F: fusion protein, LRT: lower respiratory tract, URT: upper respiratory tract, G: attachment protein, M2-2: second ORF of M2, P: phosphoprotein, wt: wild type.