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Review

Animal models of Middle East respiratory syndrome coronavirus infection

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ABSTRACT

The emergence of the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 marked the second time that a new, highly pathogenic coronavirus has emerged in the human population in the 21st century. In this review, we discuss the current state of knowledge of animal models of MERS-CoV infection. Commonly used laboratory animal species such as Syrian hamsters, mice and ferrets are not susceptible to MERS-CoV, due to differences in the MERS-CoV receptor dipeptidyl peptidase 4 (DPP4). The initially developed animal models comprise two nonhuman primate species, the rhesus macaque and the common marmoset. Rhesus macaques develop a mild to moderate respiratory disease upon inoculation, reminiscent of milder MERS cases, whereas marmosets develop a moderate to severe respiratory disease, recapitulating the severe disease observed in some patients. Dromedary camels, considered to be the reservoir for MERS-CoV, develop a mild upper respiratory tract infection with abundant viral shedding. Although normal mice are not susceptible to MERS-CoV, expression of the human DPP4 (hDPP4) overcomes the lack of susceptibility. Transgenic hDPP4 mice develop severe and lethal respiratory disease upon inoculation with MERS-CoV. These hDPP4 transgenic mice are potentially the ideal first line animal model for efficacy testing of therapeutic and prophylactic countermeasures. Further characterization of identified countermeasures would ideally be performed in the common marmoset model, due to the more severe disease outcome. This article forms part of a symposium in *Antiviral Research* on "From SARS to MERS: research on highly pathogenic human coronaviruses."

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1. Introduction

The Middle East respiratory syndrome coronavirus (MERS-CoV) was initially identified in a fatal case of severe respiratory illness in the Kingdom of Saudi Arabia (KSA) in September 2012, and earlier cases were retrospectively identified from an outbreak of severe respiratory illness in Jordan in 2012. Since then, MERS-CoV has caused 1366 laboratory confirmed cases with a case-fatality rate of 36% as of July 7, 2015 (Hilgenfeld and Peiris, 2013; WHO, 2015). The majority of cases has been detected in KSA and to a lesser extent the United Arab Emirates (UAE), Qatar and Jordan. In addition, travel-associated MERS cases have been reported from countries in Europe, Asia, Africa and North-America. Most recently, introduction of one travel-associated MERS case in South Korea resulted in a subsequent hospital-associated outbreak involving >180 cases (WHO, 2015).

MERS-CoV is a species in the lineage C of the β-coronavirus genus, which additionally only contains bat coronaviruses (de Groot et al., 2013). Severe acute respiratory syndrome coronavirus (SARS-CoV) is an example of another species of the β-coronavirus genus, which infected >8000 people in 2002–2003 (Bolles et al., 2011b). Although the close relationship to several bat coronaviruses suggests a bat-related origin, an overwhelming body of evidence points to the involvement of dromedary camels in the transmission of MERS-CoV to a human host. Index cases have reported exposure to dromedary camels and other livestock (Buchholz et al., 2013; Drosten et al., 2013); serological studies have revealed the presence of antibodies against MERS-CoV in dromedary camels, but not in other livestock (Alagaili et al., 2014; Haagmans et al., 2014; Reusken et al., 2013): virus was isolated from dromedary camels (Azhar et al., 2014; Raj et al., 2014a); and inoculation of dromedary camels with MERS-CoV results in a mild upper respiratory tract infection associated with large quantities of viral shedding (Adney et al., 2014). These results do not exclude an ancestral bat origin; MERS-CoV might have jumped from a bat species to dromedary camels decades ago. The earliest evidence of a MERS-CoV-like infection in dromedary camels from Eastern Africa is the detection of neutralizing antibodies in sera from 1983 (Muller et al., 2014).

1.1. MERS-CoV infection in humans

Infection with MERS-CoV in humans results in a range of different clinical manifestations, from mild to severe disease. Infection is frequently associated with respiratory disease, although in rare cases viral RNA has been found in blood, stool and urine suggesting a systemic infection (Drosten et al., 2013; Guery et al., 2013; Kapoor et al., 2014). Based on detection of a higher viral load in bronchoalveolar lavage (BAL) compared to oral swabs, viral replication is thought to predominantly take place in the lower respiratory tract (Bermingham et al., 2012; Drosten et al., 2013; Guery et al., 2013). This is supported by radiology as well as the development of severe acute respiratory syndrome in a portion of the patients. A broad range of different symptoms has been reported, including fever, cough, sore throat, shortness of breath, chest pain, myalgia, vomiting and diarrhea. In severe cases, patients present with acute hypoxic respiratory failure requiring mechanical ventilation. Underlying comorbidities such as obesity, hypertension, diabetes mellitus type II and cardiac disease have been associated with a fatal outcome of MERS-CoV infection (Al-Abdallat et al., 2014; Al-Tawfiq et al., 2013; Arabi et al., 2014; Assiri et al., 2013; Bermingham et al., 2012).

As of yet, no autopsy data of MERS-CoV-associated fatal cases is available and the description of MERS progression in humans is limited to clinical data such as radiographs, clinical biochemistry and hematology findings. Imaging of MERS-CoV patients has commonly revealed unilateral to bilateral consolidation and ground-glass opacities, airspace opacities, patchy infiltrates and interstitial changes. High numbers of neutrophils and macrophages in BAL have been documented. Both lymphopenia and lymphocytosis were reported, as well as thrombocytopenia, elevated lactate dehydrogenase, alanine aminotransferase, aspartate transferase and creatinine, suggesting liver, kidney and general tissue damage (Ajlan et al., 2014; Al-Abdallat et al., 2014; Assiri et al., 2013; Guery et al., 2013).

Human-to-human transmission of MERS-CoV seems relatively limited; based on data obtained from documented clusters, the R_0 (the expected number of secondary infectious cases generated by an average primary infectious case in an entirely susceptible population) of MERS-CoV was estimated to be between 0.60 and 0.69 (Breban et al., 2013; Kucharski and Althaus, 2015). This suggests that virus transmission in humans is currently self-limiting. Clusters of transmission are associated with a hospital setting often lacking appropriate infection control measures, or close contacts (Al-Abdallat et al., 2014; Assiri et al., 2013; Guery et al., 2013; Health Protection Agency, 2013). The relative contribution of nosocomial transmission is modeled to be four times higher than that of community-acquired infection (Chowell et al., 2014).

MERS-CoV is the second introduction of a highly pathogenic coronavirus into the human population in the 21st century. The recurrent outbreaks of MERS-CoV in humans in the Arabian peninsula and the identification of travel-related MERS cases in Africa, Europe, North America and Asia, highlights the need for medical countermeasures. Currently no vaccines or effective antiviral drugs exist against MERS-CoV, SARS-CoV or any other human coronavirus. For the preclinical development of MERS-CoV-specific medical countermeasures there is need for established animal models that recapitulate the severe disease observed in humans. In addition, animal models are needed for dissection of the underlying mechanisms of pathogenicity of MERS-CoV and the study of cross-species and human-to-human transmission. The continuous development of appropriate animal models to conduct medical countermeasure research is therefore of utmost importance.

1.2. Animal models for emerging viruses

Small animal models are regularly used as a first line of research on emerging viruses. Often a virus needs to be adapted to the small animal model of interest, such as was the case for SARS-CoV (Roberts et al., 2007) and Ebola virus (Bray et al., 1998), potentially altering the disease-causing mechanisms in comparison to wild-type virus in the human host. Ideally an animal model should reproduce the hallmarks of human disease as closely as possible in an immunocompetent animal following a realistic dose of