



Searching for animal models and potential target species for emerging pathogens: Experience gained from Middle East respiratory syndrome (MERS) coronavirus



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ARTICLE INFO

Article history:

Received 15 December 2016

Received in revised form 10 February 2017

Accepted 2 March 2017

Available online 3 March 2017

Keywords:

Animal model

Coronavirus (CoV)

Emerging pathogen

Middle East respiratory syndrome (MERS)

Reservoir

ABSTRACT

Emerging and re-emerging pathogens represent a substantial threat to public health, as demonstrated with numerous outbreaks over the past years, including the 2013–2016 outbreak of Ebola virus in western Africa. Coronaviruses are also a threat for humans, as evidenced in 2002/2003 with infection by the severe acute respiratory syndrome coronavirus (SARS-CoV), which caused more than 8000 human infections with 10% fatality rate in 37 countries. Ten years later, a novel human coronavirus (Middle East respiratory syndrome coronavirus, MERS-CoV), associated with severe pneumonia, arose in the Kingdom of Saudi Arabia. Until December 2016, MERS has accounted for more than 1800 cases and 35% fatality rate. Finding an animal model of disease is key to develop vaccines or antivirals against such emerging pathogens and to understand its pathogenesis. Knowledge of the potential role of domestic livestock and other animal species in the transmission of pathogens is of importance to understand the epidemiology of the disease. Little is known about MERS-CoV animal host range. In this paper, experimental data on potential hosts for MERS-CoV is reviewed. Advantages and limitations of different animal models are evaluated in relation to viral pathogenesis and transmission studies. Finally, the relevance of potential new target species is discussed.

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Abbreviations: BSL, biosafety level; DPP4, dipeptidyl peptidase-4; FDA, Food and Drug Administration; HCoV, human coronaviruses; hDPP4, human dipeptidyl peptidase-4; MERS-CoV, Middle East respiratory syndrome coronavirus; NHP, Nonhuman primates; PI, post-inoculation; RDB, receptor binding domain; SARS-CoV, severe acute respiratory syndrome coronavirus; URT, upper respiratory tract; WHO, World Health Organization.

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1. Introduction

Over the past years, outbreaks of zoonotic diseases and growing resistance against antibiotics have emphasized the need for interdisciplinary collaboration between human health, veterinary medicine and environmental sciences, a concept commonly known as “One health” [1]. Most of emerging diseases are zoonotic [2]. For instance, the human flu pandemics have originated in domestic animals and wildlife, and have been driven by ecological, behavioral, or socioeconomic changes [3]. In these cases, the reaction time between detection of a new outbreak and application of medical countermeasures are critical in terms of epidemic control. To understand the potential role that animal sources could play in virus dissemination and the epidemiology of the disease, surveillance studies, as well as experimental infections in potential target species, are required. Furthermore, after having identified the novel or re-emerged virus responsible of the outbreak, it is important to rapidly provide an accurate diagnosis as a basis for quarantine measures. It is also imperative to focus on the search for new vaccines and treatments for highly pathogenic viruses, especially for those that represent a threat to human and animal health, particularly livestock.

Until the beginning of the last decade, human coronaviruses (HCoV) infections were considered to be restricted to the upper respiratory tract (URT), with low mortality rate, and recognized as the second ranked cause of the common cold after rhinoviruses [4]. However, in the late-2002, the severe acute respiratory syndrome coronavirus (SARS-CoV) emerged in China. It rapidly spread worldwide with more than 8000 casualties and a lethality rate of 10% [5]. Ten years later, a novel HCoV associated with severe pneumonia emerged in the Kingdom of Saudi Arabia [6]. The new CoV was named Middle East respiratory syndrome coronavirus (MERS-CoV), and by March 2014, a total of 207 cases and 45% fatalities were recorded. One month later, only in April 2014, an increase in human cases was registered with at least 217 more infected people and 38 fatalities. More recently, as of December 2016, 1842 cases of MERS-CoV have been reported to the World Health Organization (WHO), including at least 652 deaths [7].

Besides coronaviruses, highly pathogenic viruses belonging to other families represent a threat to either human or animal health, or both. One of the most recent examples is the outbreak of Ebola virus (*Filoviridae*) in West Africa, which started in December of 2013 in Guinea and evolved as the largest Ebola outbreak recorded with more than 28,600 cases [8]. Furthermore, during recent years, outbreaks caused by other emerging viral pathogens from *Arenaviridae*, *Bunyaviridae*, and *Flaviviridae* families among others, disturbed public and private health, social networks and the economies of the affected countries [9, 10]. Prevention and control of emerging and reemerging viral diseases is efficient when several actions are combined: i.e. creating diagnostic networks and surveillance programs, training medical and veterinary staff, informing the population about sanitary measures, and also promoting research on prophylaxis, treatments and on the causative agent pathogenesis. Regarding the last point, animal models are crucial to study the viral and host factors contributing to the disease as well as transmission outcomes of virus infection and to allow pre-clinical testing of antiviral drugs and vaccines. Non-human primates (NHP) are the preferred models for pathogenesis studies, and potential vaccine and treatment testing, as they better translate to humans [11]. However, working with NHP is costly, with limited availability, and raises ethical problems. Therefore small-animal models are usually the first choice for drug screening. The United States Food and Drug Administration's (FDA) Animal Rule provides guidelines concerning the appropriateness of animal models for licensing purposes [12]. Additionally, by controlling the disease in animal reservoirs and/or in intermediate hosts, virus transmission to humans can be significantly reduced [13,14]. This is particularly true for domestic or feral animals for which efficient vaccines and vaccination strategies can be implemented [15]. Therefore, in cases of new pathogenic virus outbreaks, the search for natural hosts or potential target animals (as opposed to laboratory animals) seems to

be relevant not only to implement prophylactic solutions but also to improve the preparedness for an eventual global extension of diseases. Nowadays, this task is rendered possible by the availability of improved biosafety levels 3 and 4 (BSL3 and 4) animal facilities, which can accommodate large animal experimentation with such highly virulent pathogens [16].

In this article, the current situation of comprehension on potential hosts for MERS-CoV is reviewed. Based on the coronaviruses experience, benefits and limitations of these species as animal models and transmission studies are discussed.

2. Animal models for MERS research

Several review articles have described and discussed animal models for MERS-CoV infection [17–20]. In this section, the current status of animal models for MERS disease reproduction is briefly summarized.

After the identification of MERS-CoV in 2012 [6], the efforts were directed to develop an animal model to study pathogenesis and to test the efficacy of vaccines and/or treatments in vivo. Similar to SARS-CoV, rhesus macaques have demonstrated susceptibility to MERS-CoV [21–23]. A work led by Munster demonstrated that the common marmoset is also suitable as a MERS-CoV model [24]. They showed that this model recapitulates the disease observed in humans; therefore, findings in the evaluation of potential therapeutic strategies might be implemented in humans. However, small animals are required for controlled, large and comprehensive studies. While, at first, experiences with SARS-CoV turned out to be very helpful for the research on MERS-CoV, the development of a small animal model for MERS was a more difficult task [18,19]. Raj and collaborators rapidly identified dipeptidyl peptidase-4 (DPP4) as the functional receptor for MERS-CoV [25], and DPP4 is present in lung cells of many rodents. Thus, rodents were expected to be susceptible for MERS-CoV. However, and as predicted by the crystal structure analysis of the MERS-CoV receptor binding domain (RBD) with the human DPP4 (hDPP4) extracellular domain [26], so far, no rodent model is naturally permissive for MERS-CoV infection. In Syrian hamster, the DPP4 receptor was shown to be expressed on bronchiolar epithelium, but inoculation of MERS-CoV via aerosols or intratracheal routes with different doses did not lead to productive infection [27]. Wild type and immune-deficient mice were also tested for MERS-CoV infection without success [28]. Since then, several groups have been focused on new strategies to develop a small animal model susceptible to MERS-CoV infection. It was found that mouse cells could be made permissive for MERS-CoV when expressing hDPP4. Consequently, the hDPP4 was transduced into mouse lungs using an adenovirus vector, which resulted in animals susceptible to MERS-CoV infection. These mice exhibited pneumonia and extensive inflammatory-cell infiltration with the presence of virus in the lungs [29]. Recently, a transgenic mice model expressing hDPP4, highly susceptible to MERS-CoV infection and able to display systemic lesions, has been developed [30]. As demonstrated for several diseases, transgenic animal models have become an important tool to improve medical research [31]. On the other hand, glycosylation of the murine DPP4 is a major factor impacting the receptor function by blocking the binding to MERS-CoV [32]. Therefore, the modification of the mouse genome to match the sequence in the hDPP4 made this species susceptible to MERS-CoV infection [33]. Accordingly, these newly established mice models are useful to evaluate the efficacy of vaccines and therapeutic agents against MERS-CoV infection [30,34–36]. VelocImmune and VelociGene technologies have been used to develop a humanized mouse model for MERS-CoV infection [36]; these methodologies can be also applied for other pathogens in future emerging epidemics.

3. MERS-CoV animal reservoir and the role of domestic animals

Researchers worldwide have identified several animal species which could have a role in the transmission of MERS-CoV to humans (summarized in Fig. 1). Bats have been suggested to be the reservoir for MERS-

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