**MERS-CoV: current research progress and prospect**

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**ABSTRACT**

Coronaviruses (CoVs) are enveloped viruses, and belong to the family *Coronaviridae*, the order *Nidovirales*. CoVs distribute widely among animals and primarily cause the respiratory and gastrointestinal diseases. Since 2012, an outbreak of new human coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia has spread to 26 different countries and become a global threat. Here this article reviewed recent studies about the emergence, reservoir of MERS-CoV, and the animal models and treatments for MERS-CoV.

**Emergence of MERS-CoV**

Only two human coronaviruses (HCoVs), HCoV-229E and HCoV-OC43 were discovered before the 21st century. They were identified as the causative agents of common cold that caused the upper respiratory tract infection [1, 2]. HCoVs have not been the subjects of much interest until the outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) during 2002-2003 in China [3, 4]. The emergence of highly pathogenic SARS-CoV caused a worldwide epidemic, resulting in 8273 cases of infection and...
775 deaths [5]. With the advancements in HCoVs research, two more HCoVs, HCoV-NL63 and HCoV-HKU1 were identified in the following years [6, 7].

In 2012, a new highly pathogenic coronavirus was isolated from a 60-year old man in Saudi Arabia, who died of progressive respiratory and renal failure [8]. This novel coronavirus later was termed as Middle East respiratory syndrome coronavirus (MERS-CoV) according to the Coronavirus Study Group of the International Committee on Taxonomy of Viruses (ICTV) [9]. The genomic sequence analysis reveals that MERS-CoV is phylogenetically related to the BtCoV-HKU4 and BtCoV-HKU5, and thus belongs to lineage C of the genus betacoronavirus. MERS-CoV infection leads to fever, cough, shortness of breath and even severe pneumonia. Gastrointestinal symptoms, disseminated intravascular coagulation and kidney failure have also been reported [10]. The emergence of MERS-CoV renews the interest in HCoVs and highlights the HCoVs as an important highly pathogenic agent for human.

**MERS-CoV transmission**

As MERS-CoV shows high similarity to the bat coronaviuses, and the MERS-CoV-related viruses have been detected in bats, MERS-CoV is considered as a zoonosis that originates from bats [11]. However, it still remains doubt that bats are the direct reservoirs for MERS-CoV transmission, since human are unlikely to contact with them directly. Alagaili et al. undertook a nationwide survey and found that the neutralizing antibodies to MERS-CoV were detected in dromedary camels in Saudi Arabia, indicating that dromedary camels were the intermediate reservoirs for MERS-CoV transmission to humans. Intriguingly, the MERS-CoV antibodies were detected in the serum samples obtained from dromedary camels since at least 1992, suggesting that MERS-CoV has been circulating in dromedary camels for at least 20 years and become infective in humans after mutations in recent years [12]. In addition, the MERS-CoV genomic sequences from a sick dromedary camel were identical to the sequences of virus from a patient who had close contact with the sick camel [13]. Collectively, these findings provide the evidence for camel-to-human transmission of MERS-CoV.

Epidemiological statistics reveals that MERS-CoV infection is generally zoonotic in nature. Unlike to SARS-CoV, MERS-CoV shows limited human-to-human transmission, which occurs only under close contact with infected persons. However, without the implementation of strong infection control measures, MERS-CoV, as of 20 June 2015, has spread to 26 countries, resulting in 1334 cases of infection and 471 deaths.
Animal models for MERS-CoV

The availability of animal models is essential for clarification of viral pathogenesis and for development of preventive and therapeutic agents against virus infection. As a specific functional receptor, DPP4 was used by MERS-CoV to initiate virus infection [14]. MERS-CoV could not infect the normal animal models, such as mice, hamsters and ferrets. In 2013, de Wit et al. firstly reported an animal model Rhesus macaque, which could be infected by MERS-CoV, leading to lower respiratory tract infection and interstitial pneumonia [15]. Additionally, the common marmosets were also available to be infected by MERS-CoV via combined intratracheal, intranasal, oral and ocular routes [16]. However, it is not proper to use these animal models since the primates are expensive with limited availability.

The small and economical models were also developed in different laboratories. Mice were susceptible to MERS-CoV after infection with a DPP4-expressing adenovirus, which was used to express the DPP4 receptor in the lung cells [17]. Recently, a stable model fully permissive to MERS-CoV infection was established in the DPP4 transgenic mice. MERS-CoV replicated in the lung and brain, and viral RNA could also be detected in the heart, spleen, and intestine [18]. With a clear background of genetics and immunology, the transgenic mouse model provides a useful tool for evaluating the efficacy of drugs and vaccines for MERS.

Therapies and vaccination strategies for MERS-CoV

The clinical trials suggest that interferon (IFN) combined with ribavirin may improve the outcome of SARS treatment. The efficacy of IFN-α2b and ribavirin to MERS was assessed in vitro and in vivo. MERS-CoV was sensitive to a combination of IFN-α2b and ribavirin at lower concentrations in Vero and LLC-MK2 cells [19]. This therapeutic intervention was also evaluated in rhesus macaques. With the treatment 8hr after infection, the infected rhesus macaques showed virus replication reduction and clinical outcome improvement [20]. However, the clinical experience from MERS patients showed that critically ill patients did not respond to this combination antiviral therapy [21]. New antiviral compounds targeting to MERS-CoV are still in early development. A small polypeptide, HR2P, designed based on the core structure of MERS-CoV S2 protein was found to inhibit virus infection by blocking the virus-cell membrane fusion process [22]. Recently, Lundin et al. isolated a small-molecular inhibitor K22, which showed most potent anti-coronavirus activity from a compounds library. K22 exerted nearly-complete inhibition of viral RNA synthesis, and could be a promising
antiviral drug against MERS.

Antibodies directed to the cellular receptor DPP4 and receptor binding domain (RBD) on S1 protein of MERS-CoV have been shown to inhibit virus infection in vitro [14, 23-25]. However, these non-human antibodies were used with a limitation since adverse effects were induced when applied to human. Therefore, high potency human neutralizing antibodies targeted to the viral proteins are more favored and urgent needed. Jiang et al. identified two potent human neutralizing monoclonal antibodies (MAbs), MERS-4 and MERS-27, which blocked the interaction between DPP4 and RBD, thus inhibiting MERS-CoV infection [26]. Ying et al. isolated three MAbs, m336, m337 and m338, targeting the RBD of MERS-CoV S1 protein with high affinity. Significantly, the m336 neutralized the MERS-CoV with exceptional potency, 50% neutralization at 0.07 μg/ml [27].

Development of effective vaccines against MERS-CoV is also in the early stages. Using a reverse genetics system, a mutant virus lacking the structural E protein of MERS-CoV was engineered. This mutant virus was replication-competent, propagation-defective in cell cultures, and thus could be a promising vaccine candidate [28]. Recently, Volz et al. engineered a recombinant Modified Vaccinia virus Ankara (MVA), a safety-tested vector platform for vaccines development, stably expressing the MERS-CoV S protein (MVA-MERS-S). The protective capacity of MVA-MERS-S vaccine against MERS-CoV infection was evaluated in mice. Interestingly, all vaccinated mice were protected against MERS-CoV infection, suggesting MVA-MERS-S could be a potential candidate vaccine for human [29].

Without specific therapy and vaccine for MERS, the mortality rate of MERS-CoV infection is approximately up to 35%. There is an urgent need for specific therapies and (or) vaccination strategies to control this emerging human pathogen.

Conclusions

Approximately 10 years after the SARS outbreak, a novel HCoV, MERS-CoV, emerged from Saudi Arabia and resulted in high mortality among infected patients. MERS-CoV is likely to be transmitted from bats to dromedary camels, which are responsible for transmission to humans. As MERS-CoV could be transmitted between humans through the air, especially the rapid spread in Republic of Korea, there is reason to be concerned that it may become a global pandemic when possible mutations occur during transmission. The emergence of highly pathogenic MERS-CoV once again demonstrates that the zoonotic viruses could be a serious threat to public health security. Therefore, viral surveillance in the live-animal markets is important to discover and understand the potential
zoonotic transmission.

References


