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Middle East respiratory syndrome coronavirus vaccines: current status and novel approaches

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Middle East respiratory syndrome coronavirus (MERS-CoV) is a cause of severe respiratory infection in humans, specifically the elderly and people with comorbidities. The re-emergence of lethal coronaviruses calls for international collaboration to produce coronavirus vaccines, which are still lacking to date. Ongoing efforts to develop MERS-CoV vaccines should consider the different target populations (dromedary camels and humans) and the correlates of protection. Extending on our current knowledge of MERS, vaccination of dromedary camels to induce mucosal immunity could be a promising approach to diminish MERS-CoV transmission to humans. In addition, it is equally important to develop vaccines for humans that induce broader reactivity against various coronaviruses to be prepared for a potential next CoV outbreak.

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Introduction

Coronaviruses are the largest positive sense single stranded RNA viruses. There are six human coronaviruses (HCoV) to date; HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome (SARS)-CoV, and Middle East respiratory syndrome (MERS)-CoV. Prior to the SARS-CoV epidemic in 2002–2003, CoVs were known to cause mild respiratory infections in humans. SARS-CoV, on the other hand, infected around 8000 cases causing severe respiratory disease with a 10% fatality rate [1]. Ten years later, MERS-CoV emerged in the human population also to cause severe respiratory infection [2]. In contrast to the SARS-CoV epidemic, which was contained within one year, MERS-CoV still continues to cause outbreaks with increasing geographical distribution, four years after its first identification. As of March 2nd 2017, 1905 cases in 27 countries have been reported to the WHO with 677 deaths accounting for a 35% case fatality rate (http://www.who.int/emergencies/mers-cov/en/). Like SARS-CoV, MERS-CoV emerged as a result of zoonotic introduction to the human population. Despite its close genome similarity with bat coronavirus HKU4 and HKU5 [2], accumulating serological and molecular evidence pointed to dromedary camels as the most probable reservoir for MERS-CoV [3–5]. This poses a continuous risk of virus spill-over to people in contact with camels, such as those working in slaughter houses and animal farms, evidenced by the presence of MERS-CoV antibodies in sera of those individuals [6,7]. Nosocomial transmission, however, accounts for the majority of MERS-CoV cases reported in outbreaks [8–10], although a substantial part of infections that occur result in unrecognized asymptomatic or mild illnesses [11]. Thus, in addition to camel contacts, other highly-at-risk groups are healthcare workers and patient household contacts [8,12,13]. Considering the ongoing MERS-CoV outbreaks, it is crucial to develop intervention measures among which vaccines play an important role. Despite the fact that the emergence of MERS-CoV and SARS-CoV has dramatically changed the way we view CoVs, there is no licensed CoV vaccine or therapeutic drug available to date [14,15].

Immune correlates of protection

A cornerstone for rational vaccine design is defining the determinants of immune protection. Accumulating data from studies done so far on MERS-CoV and other coronaviruses revealed that a combination of both virus-specific humoral and cellular immune responses is required for full protection against coronaviruses. Especially neutralizing antibodies are considered key players in the protective immunity against CoVs. Neutralizing monoclonal antibodies (Mabs) reduced viral loads in MERS-CoV receptor-transduced mice, rabbits and macaques [16–19]. Similarly, convalescent camel sera increased virus clearance and decreased lung pathological outcomes in mice with an efficacy directly proportional to anti-MERS-CoV-neutralizing antibody (Nab) titers [20]. Also polyclonal sera produced in transchromosomic bovines protected mice against MERS-CoV challenge [21].

Evidence for the protective role of antibodies also comes from recent studies analyzing immune responses in patients that survived or succumbed to MERS-CoV.

Although neutralizing antibodies were only weakly inversely correlated to viral loads, serum antibody responses were higher in survivors compared to fatal cases but viral RNA was not eliminated from the lungs [22,23]. Administration of convalescent sera, however, did not lead to significant reduction in viral loads [22,24]. The presence of mucosal IgA Abs, on the other hand, was found to influence infectious virus isolation [25].

Besides humoral immunity, cellular immune responses are also considered to play a crucial role in protection against coronaviruses. While B-cell deficient mice were able to clear MERS-CoV, those lacking T-cells failed to eliminate the virus, pointing out the crucial role of T-cells in viral clearance [26]. This is supported by the observation that T-cells were able to protect aged mice against SARS-CoV infection [27••] and the fact that a reduced T-cell count was associated with enhanced disease severity in SARS patients [28]. Along with other studies, these data highlight the importance of T-cells for virus clearance and protection against MERS-CoV [26,27••] and SARS-CoV [29,30]. It is also noteworthy to mention that while neither antibodies nor memory B cells were detectable 6-years post-infection [31], SARS-CoV-specific memory T-cells, despite being low in frequency, persisted up to 11 years post-recovery [32]. Nonetheless, the protective capacity of such memory response is not known. Hence, taking into account the waning of virus-specific humoral responses, generating a long-lived memory T cell response through vaccination could be favorable, but as proper B- and T-cell immune responses are required for efficient protection, vaccination should target the induction of both. At the moment we lack information concerning the longevity of anamnestic immune responses following MERS-CoV infection, except for a recent study showing that antibody responses, albeit reduced, persisted up to 34 months post-infection [33]. The role of immune responses in protection is also in line with the observed increased fatality among the aged population following MERS-CoV infection. Retrospective studies on MERS-CoV patients from Saudia Arabia and South Korea have found a significant correlation between old age and mortality [8,13,34–36], a pattern that has been also reported for other respiratory viruses such as SARS-CoV [1] and influenza virus [37]. This is most likely caused by immunosenescence; a failure to produce protective immune response to new pathogens in elderly due to impaired antigen presentation, altered function of TLRs, and a reduced naïve B and T cell repertoire [38]. This age-related increase in mortality was also reported in SARS-CoV laboratory-infected animals, that is, mice and non-human primates (NHPs) [39,40], and was associated with low neutralizing antibodies and poor T-cell responses [41,42,43•]. Several factors that play a role in T-cell activation were also found to be dysregulated in an age-related manner. Age-related increase in phospholipase A_2 group IID (PLA_2G2D), and prostaglandinD_2 in the lungs contributed to a diminished T-cell response and severe lung damage through diminishing respiratory dendritic cell (DC) migration [44,45]. Likewise, adoptive transfer of T-cells to mice enhanced viral clearance and survival [29], highlighting the contribution of a reduced T-cell response in severe disease outcome. These observations also highlight the need for more effective preventive measures for the elderly. In this sense, induction of a potent airway T-cell response may be crucial to protect against CoVs [27••]. Thus, a promising approach to protect against MERS-CoV-induced fatality is to enhance virus-specific tissue (airway) resident memory T-cell responses through intranasal vaccination.

Current MERS-CoV vaccine candidates

Although the MERS-CoV genome encodes for 16 non-structural proteins (nsp1-16) and four structural proteins, the spike (S), envelope (E), membrane (M), and nucleocapsid (N) [46], the viral structural proteins, S and N, show the highest immunogenicity [47]. While both S and N proteins can induce T-cell responses, neutralizing antibodies are almost solely directed against the S protein, with the receptor binding domain (RBD) being the major immunodominant region [48]. Thus, current MERS-CoV vaccine candidates mainly employ the spike protein or (parts of) the gene coding for this glycoprotein.

These MERS-CoV vaccines candidates were developed using a wide variety of platforms, including whole virus vaccines, vectored-virus vaccines, DNA vaccines, (Table 1) and protein-based vaccines (Table 2). Although live attenuated vaccines produce the most robust immune responses, they pose a risk from reversion to virulence. Inactivated virus vaccines may cause harm due to incomplete attenuation or the capacity to induce lung immunopathology [49]. Viral-vector-based vaccines, on the other hand, provide a safer alternative and have been developed using modified vaccinia virus Ankara (MVA) [50,51,52••], adenovirus (AdV) [53,54], measles virus (MeV) [55], rabies virus (RABV) [56], and Venezuelan equine encephalitis replicons (VRP) [26,57], all expressing MERS-S/S1 proteins. Additionally, VRP expressing the N protein have also been developed [27••]. A major hurdle facing these viral-vector-based platforms is pre-existing immunity in the host which potentially can impair the vaccine efficacy. However, this can be prevented by using virus strains not circulating in the targeted population or immunization strategies involving heterologous prime-boost immunization, for example, MVA and AdV. Although plasmid DNA vaccines are considered to be of low immunogenicty in humans, current versions developed seem to induce potent immune responses. DNA-based vaccines directed at inducing anti S responses were also shown to exert protection in NHPs [58,59]. Noteworthy to mention is