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Middle East respiratory syndrome vaccines

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SUMMARY

The Middle East respiratory syndrome coronavirus (MERS-CoV) has infected over 1600 individuals with nearly 600 deaths since it was first identified in human populations in 2012. No antiviral therapies or vaccines are available for its treatment or prophylaxis. Approaches to the development of MERS vaccines are discussed herein, including a summary of previous efforts to develop vaccines useful against human and non-human coronaviruses. A striking feature of MERS is the important role that camels have in transmission. Camel vaccination may be a novel approach to preventing human infection.

1. Introduction

Middle East respiratory syndrome (MERS), caused by a novel coronavirus (MERS-CoV), was first identified in 2012 in patients with severe respiratory disease in Jordan and Saudi Arabia.[1] Since its discovery, approximately 1600 cases have been reported, amounting to about 40 cases per month. While this number is low, the worrisome features of the disease are its propensity to cause severe disease in patients with underlying conditions, including diabetes, renal disease, lung disease, or an immunocompromised state, and its apparent ability to readily spread within hospital settings.[2] In addition, MERS-CoV has been identified in camel populations throughout the Arabian Peninsula and Africa,[3–5] and epidemiological evidence suggests that it is periodically introduced into human populations.[6] Further, coronaviruses have a well-described propensity to mutate and recombine.[7] Consistent with this propensity, the genomic sequence of MERS-CoV has changed since it first entered human populations in 2012, but these changes have not enhanced the ability to effect human-to-human transmission.[8] This lack of increased transmissibility is encouraging, but, on the other hand, the continued introduction into human populations from infected camels coupled with coronavirus mutability means that measures to prevent infection are important to develop anticipatorily.

Following the demonstration of the key role of hospitals in secondary spread,[9,10] efforts were made to introduce careful infection control measures into affected hospitals. These appear to have been effective in reducing virus transmission and greatly decreasing the number of MERS cases. However, these measures do not affect the acquisition of primary cases of MERS, which likely occur either directly or indirectly from camels. These primary cases are the source for subsequent hospital outbreaks, so preventing transmission from camels or within the community might be the best way to provide subsequent secondary cases and hospital spread.

'In addition to the appropriate infection control measures, virus transmission would be most effectively prevented by a combination of rapid and efficient diagnosis, treatment with antiviral therapy to decrease virus loads, and prophylactic treatment with an intervention that prevents infection or at least disease manifestations. Most often, the latter approach involves passive or active immunization, which will be discussed in this review. Efforts to prevent MERS by immunization are based in part on the extensive information gained from studies of coronavirus vaccines used to prevent infections in domesticated and companion animals. Additionally, a key piece of information required for the rational design of vaccines is knowledge of a protective immune response. Immune responses to some non-human coronaviruses have been characterized and these responses are also described below.

2. Protective immune response in animals experimentally infected, or patients naturally or experimentally infected with coronaviruses

In general, protective immune responses to coronaviruses involve a combination of virus-specific antibody and T-cell responses.[11] The neutralizing antibody response is primarily

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directed against the surface (S) protein, responsible for binding to the host cell receptor. The N terminal S1 fragment of the S protein binds to the host cell receptor, elicits neutralizing antibody, and perhaps not surprisingly, is also the part of the virus that is most variable between isolates.[12] This variability explains why neutralizing antibodies are generally virus strain-specific and do not provide cross-reactive protection against even closely related coronaviruses.[13] On the other hand, coronavirus-specific CD8 and CD4 T-cells recognize epitopes from across the genome, some of which are in conserved proteins, which do not readily undergo mutation.

Prior to the onset of severe acute respiratory syndrome (SARS) and MERS, many studies on protective immune responses used mice infected with the murine coronavirus, mouse hepatitis virus (MHV). These studies showed that virus clearance from infected mice required the development of an effective T-cell response. Both CD4 and CD8 T-cells were required for optimal kinetics of clearance.[14] The studies also showed that the T-cell response could be immunopathological.[14–16] Thus when irradiated mice or mice lacking T- and B-cells were infected with a strain of MHV that causes demyelination, the mice developed minimal clinical disease and showed no evidence of demyelination. However, within a few days of receiving virus-specific T-cells, severe myelin destruction occurred, along with hind limb paralysis. Neutralizing antibodies were also important in immune protection, serving at least two roles. First, in the absence of neutralizing antibody, MHV was cleared to very low levels by T-cells, but later recrudesced, resulting in lethal disease.[17] Second, virus-specific antibodies were most important for protecting mice against further challenge. Of note, immune protection was long-lived in immunocompetent mice that survived experimental infection with MHV, possibly because the infection was systemic, involving the central nervous system, or in some cases, the liver.

In marked contrast, coronaviruses that are primarily mucosal induce short-lived protection. This is most evident in studies of patients or human volunteers infected with respiratory coronaviruses such as HCoV-229E or HCoV-OC43.[18,19] These viruses generally cause mild upper respiratory tract disease and only rarely cause severe disease. In human volunteer studies, the presence of pre-existing anti-HCoV-OC43 or HCoV-229E antibodies did not provide protection against experimental challenge with the same virus, in terms of clinical disease or virus titers. Similarly, experimental challenge provided only partial protection against subsequent re-challenge and this protection waned over several months. In these studies, systemic antibodies were generally measured, so less is known about the levels of IgA, which are likely most important for protection against viruses that remain confined to the upper respiratory tract.

From these data, one might predict that infection with MERS-CoV or SARS-CoV would result in a long-lived protective response, since SARS-CoV and MERS-CoV cause severe respiratory illness based in the lungs, and SARS-CoV (and perhaps MERS-CoV) causes a systemic infection.[20] However, this may not be the case. While only a few SARS survivors have been followed longitudinally, anti-SARS-CoV antibody titers were not detectable after 6 years.[21] Longitudinal studies of T-cell responses in these patients are even fewer in number, but T-cell responses were detected at low levels in some survivors.[21–24] While these data suggest that coronavirus-specific T-cells are more likely to persist than B-cells, it is still possible that there are sufficient numbers of residual memory T- and B-cells to protect patients from infection or severe disease on rechallenge.

3. Previous studies of coronavirus-vaccinated domesticated and companion animals

Prior to the outbreak of SARS, coronaviruses were considered most important as causes of infections of domesticated and companion animals. Vaccines to prevent several of these diseases were developed over the years, but none were very successful in preventing disease. Infectious bronchitis virus (IBV) is an economically important infection of young chickens, causing bronchitis as well as renal disease (reviewed by Cavanagh[25]). Live attenuated vaccines were developed, which were efficacious in providing short-term protection to challenge with homologous but not heterologous IBV strains. Levels of circulating IBV did not diminish substantially because many strains of IBV co-circulate in chicken populations. Recombination between the vaccine and circulating strains resulted in the emergence of novel strains of IBV.

Live attenuated vaccines were also developed for a swine coronavirus, transmissible gastroenteritis virus (TGEV), which causes fatal diarrhea with associated high mortality in very young pigs.[26] These vaccines were administered to pregnant sows but did not protect piglets to a great extent; the use of virulent virus in sows was more successful in protecting baby animals from lethal disease. Remarkably, however, a deletion variant of TGEV, porcine respiratory coronavirus (PRC), appeared in swine populations in North America and Eurasia.[27] PRC caused only a mild respiratory disease, but induced an immune response that was cross-reactive and protective against TGEV, resulting in the disappearance of TGEV from most locales.

Finally, feline infectious peritonitis virus (FIPV) causes a lethal granulomatous disease in domestic cats and other felines, with wet (pyogranulomatous, effusive) and dry (classic granulomatous) forms.[28] FIP is uncommon and most often occurs in animals chronically infected with feline coronavirus (FCV), which mutates during the course of persistence. A vaccinia virus-based vaccine expressing the FIPV surface (S) glycoprotein was developed, and was shown to induce high levels of anti-FIPV neutralizing antibody.[29] However, this anti-S antibody was not protective against challenge with virulent FIPV. Rather, it induced an antibody-dependent accelerated and enhanced disease after challenge. Of note, antibody-dependent enhancement has never been observed in naturally infected felines, but the possibility that it might develop has been a concern as vaccines for SARS-CoV and MERS-CoV are developed.[30]

4. Development of anti-SARS-CoV and MERS-CoV vaccines

Vaccines useful for preventing SARS or MERS have been developed, based on information learned from the studies described above (Table 1). Because both SARS and MERS tend to spread extensively within hospital settings, initial efforts were directed at developed reagents that could be used for passive immunization; more recent efforts have focused on methods useful for active immunization. In this section, vaccines targeting SARS-CoV are described first, since many of the approaches used in developing MERS vaccines were initially investigated in the context of SARS.

4.1. Passive immunization

4.1.1. SARS

Monoclonal antibodies (mAb) with neutralizing activity against SARS-CoV have been isolated from non-immune human volunteers.[31,32] The advantage of this approach is that protective antibodies can be isolated, cloned, and propagated without the need to obtain patient specimens. Other approaches have included identifying and cloning memory B-cells obtained from SARS survivors and amplifying those that produce the most potently neutralizing antibodies.[33] In all of these vaccines, neutralizing antibodies have been directed against the S protein. Stockpiled anti-SARS-CoV antibodies would be especially useful in the