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Middle East respiratory syndrome and severe acute respiratory syndrome

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The recent emergence of the Middle East respiratory syndrome (MERS)-CoV, a close relative of the Severe Acute respiratory syndrome (SARS)-CoV, both of which caused a lethal respiratory infection in humans, reinforces the need for further understanding of coronavirus pathogenesis and the host immune response. These viruses have evolved diverse strategies to evade and block host immune responses, facilitating infection and transmission. Pathogenesis following infection with these viruses is characterized by a marked delay in the induction of Type I interferon (IFN I) and, subsequently, by a poor adaptive immune response. Therapies that expedite IFN I induction as well as interventions that antagonize immunoevasive virus proteins are thus promising candidates for immune modulation.

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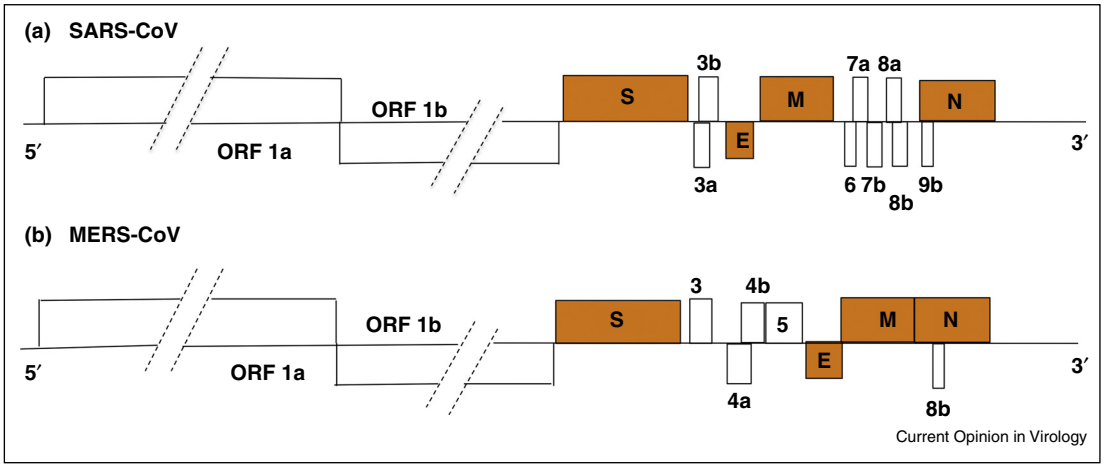
Introduction

While most CoVs cause the common cold in humans, infection with two recently emerged CoVs, SARS-CoV and MERS-CoV, resulted in more severe pulmonary disease with alarmingly high case fatality rates [1]. SARS-CoV first emerged in Guangdong province of China in the winter of 2002 [2]. With a high rate of nosocomial transmission to healthcare professionals combined with a lack of precedence for a CoV outbreak, SARS-CoV spread across 29 countries infecting more than 8000 humans and resulting in a staggering 774 deaths (~10%) [3]. MERS-CoV was first reported in Saudi Arabia a decade later in June 2012 [4••]. Cases were also detected in other parts of the Middle East including Jordan, Qatar, Oman and the United Arab Emirates. Virus was spread by travelers from the Arabian peninsula to Europe, Africa and other regions of Asia including, most recently, the Republic of Korea, infecting a total of 1626 people, with a case fatality rate of 36.0%, as of January 11, 2015 [5,6••,7••,8]. Both of these outbreaks were notably characterized by an age-dependent increase in morbidity and mortality. Thus, during the SARS epidemic no patients under the age of 24 years died, while mortality was more than 50% in those over 65 years of age [9]. Similarly, MERS also has a similar age-dependent pattern with elderly patients showing signs of more severe disease. MERS tends to be most severe in patients with co-morbidities such as diabetes, chronic pulmonary disease and renal disease [10]. While no more SARS cases were reported since 2004, new MERS cases continue to appear. The respiratory route of transmission of MERS-CoV combined with the geographical location of its persistence makes MERS a serious public health threat that if not curtailed, has the potential to develop as a major epidemic in the years to come. Although no MERS cases have been associated with the Hajj and Umrah pilgrimages, such large gatherings make this a potentially major problem [1]. In spite of the efforts by researchers across the globe, no effective drug treatments or vaccines have been formulated to control SARS or MERS. In this review we summarize the similarities and differences between SARS and MERS-CoV with an emphasis on the key features of the host immune response and tactics used by the viruses to evade the immune response.

Virology and transmission

Coronaviruses are enveloped RNA viruses that fall under the Nidovirus superfamily (Figures 1 and 2). With a positive-sense single-stranded RNA genome of 31 kb, coronaviruses contain the largest RNA genome identified to date [11]. Both SARS and MERS-CoVs are betacoronaviruses, belonging to lineages b and c respectively. They share similar genomic structures with multiple open reading frames (ORFs). While the genes required for viral RNA replication are located on the 5′-terminal two thirds of the genome, those that encode the structural proteins are located on the 3′ end [11]. Other genes, which encode accessory proteins not required for virus replication and viability, are distributed throughout the structural genes. MERS-CoV has five different accessory proteins while SARS-CoV has eight of them (Figure 1) [12••]. Some of these genes including some of the non-structural proteins encoded at the 5′ end of the genome are involved in induction and modulation of innate immune responses in the host (humans).

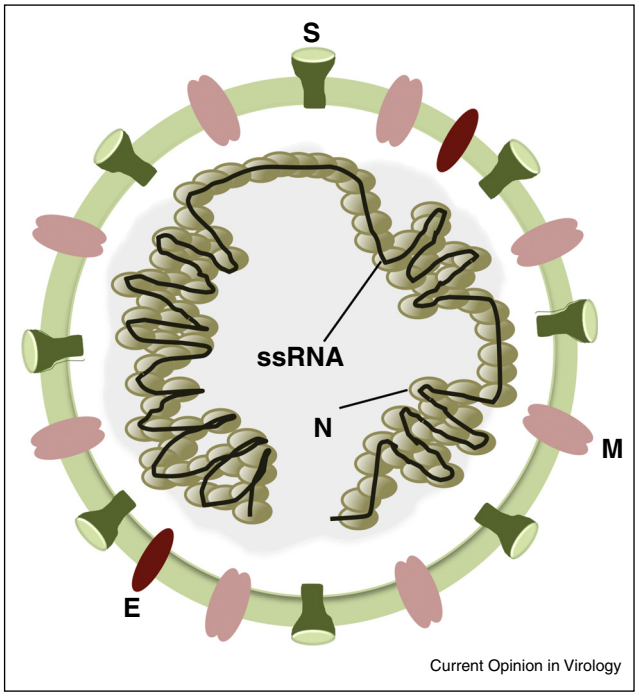
Figure 1



Genome organization of CoVs. Organization of genes and ORFs in the genome of SARS-CoV **(a)** and MERS-CoV **(b)** is illustrated. The 5′ 2/3 of the genome is comprised ORF1a and ORF1b, which code for various non-structural proteins, many of which are involved in virus replication [11]. The 3′ 1/3 of the genome encodes for structural proteins: spike (S), envelope (E), matrix (M) and nucleocapsid (N). Interspersed between these structural proteins are accessory proteins: SARS-CoV has 8 accessory proteins and MERS-CoV has 5. These include SARS-CoV ORF 6 and MERS-CoV ORF 4a and ORF 4b, with well-described roles in immune evasion. Not drawn to scale.

The initiation of infection by CoVs begins with entry into host cells. Being close relatives in the phylogenetic tree, it may not be surprising that both SARS-CoV and MERS-CoV utilize large ectopeptidases on the surface of the host cell to gain entry; SARS-CoV binds to angiotensin converting enzyme 2 (ACE-2) and MERS-CoV attaches to dipeptidyl peptidase 4 (DPP4) [13,14]. While it has been shown that the spike (S) glycoprotein of SARS-CoV underwent extensive mutation in the region that binds to ACE2 [15], facilitating species to species transmission, the glycoprotein of MERS-CoV has not undergone substantial change in the DPP4-binding region during passage in humans [16••,17]. The absence of any mutation in DPP4-binding region suggests that receptor binding is not the rate-limiting step in virus transmission and human adaptation. After binding to their respective receptors, proteolytic cleavage of the S protein results in virus-cell fusion and release of genomic RNA into the cytosol of the host cell. Following the release of RNA, the virus undergoes transcription and replication on rearranged host membranes, including double-membrane vesicles (DMVs) [18]. Newly synthesized RNA is encapsidated within the nucleocapsid protein and then buds into vesicles derived from the endoplasmic reticulum-golgi intermediate compartment (ERGIC) for further assembly into new virions. These vesicles are eventually transported to the cell surface to be released outside the cell.

Figure 2



Structure of CoV virion. Schematic representation of the structure of the CoV virion is shown, with structural proteins S, M, E and N marked.

Seroprevalence studies strongly support the notion that camels are one, if not the only, reservoir of MERS-CoV [17,19,20,21,22••,23]. Transmission from camels to humans is likely, although not all MERS patients have a history of direct camel exposure [24]. This could mean that other means of indirect transmission like consumption of camel milk or meat or transfer from an intermediate host to humans contribute to spread [20].