Human Coronavirus EMC Is Not the Same as Severe Acute Respiratory Syndrome Coronavirus

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ABSTRACT A newly identified betacoronavirus, human coronavirus EMC (HCoV-EMC), has been isolated from several patients with respiratory and renal disease in the Middle East. While only a few infected patients have been identified, the mortality of the infection is greater than 50%. Like its better-known cousin severe acute respiratory syndrome coronavirus (SARS-CoV), HCoV-EMC appears to have originated from bats. In a recent article in mBio, Müller et al. described several important differences between the two viruses [M. A. Müller et al., mBio 3(6):e00515-12, 2012, doi:10.1128/mBio.00515-12]. Unlike SARS-CoV, HCoV-EMC can directly infect bat cells. As important, HCoV-EMC does not enter cells using the SARS-CoV receptor, human angiotensin-converting receptor-2 (hACE2). These results provide a strong incentive for identifying the host cell receptor used by HCoV-EMC. Identification of the receptor will provide insight into the pathogenesis of pulmonary and renal disease and may also suggest novel therapeutic interventions.
and cleave N-terminal amino acids from small peptides. However, in neither instance is the enzymatic activity of the protein required for receptor function, suggesting that the structure of the ectodomain of each molecule is especially amenable to coronavirus binding. In addition to serving as the receptor for SARS-CoV, ACE2 has lung-protective properties. Downregulation of ACE2, as occurs during SARS-CoV infection, is believed to contribute to pathological changes in the lung (7). It will be of interest to determine if the receptor for HCoV-EMC has similar properties.

Identification of the receptor may also shed light on a potentially novel aspect of HCoV-EMC pathogenesis. Initial reports suggest that renal failure is part of the disease process (8), although at this point it is impossible to know whether this is a specific effect or a consequence of the multiorgan failure that often occurs in severely ill patients. If kidney involvement is documented in most patients, identification of the HCoV-EMC receptor may provide a basis for understanding why renal disease is common. The SARS-CoV receptor, ACE2, is present at high levels in the human kidney, and SARS-CoV was detected in the kidneys of some patients during the 2002-2003 epidemic, but renal disease did not occur commonly during the infection (5). Understanding the differential abilities of HCoV-EMC and SARS-CoV to cause renal disease will provide insight into a unique aspect of the HCoV-EMC infection. Of note, coronavirus infection of the respiratory tract and renal system has been described in chickens infected with another coronavirus, infectious bronchitis virus (IBV) (9). IBV is best known as an important causative agent for upper respiratory tract disease in young chickens, but strains that also infect the kidney have been identified. The cellular receptor for IBV has not been identified, so the relationship between receptor expression and disease for different IBV strains remains an area of active investigation.

Finally, Müller et al. demonstrated infection of bat-derived cultured cells, raising the possibility that HCoV-EMC jumped species directly from bats to humans. This also suggests that the host cell receptor, if a protein, is sufficiently similar between humans and bats to facilitate direct transmission. Bats are recognized as key reservoirs for viruses, including several coronaviruses and henipaviruses, such as Nipah virus and Hendra virus (5). In all cases, bats do not appear to develop clinical disease, but disease is severe when viruses cross over to infect human populations. This is analogous to the situation in humans and sooty mangabeys infected with human immunodeficiency virus (HIV) and the closely related simian immunodeficiency virus (SIV), respectively: sooty mangabeys infected with SIV do not develop significant disease, whereas HIV is fatal in humans (10). A critical question is why bats are “tolerant” of infections such as HCoV-EMC or SARS-CoV. How do they clear the virus without developing immunopathological disease? If coronavirus-infected bats are similar to SIV-infected sooty mangabeys, infection may not activate the host immune response to the same extent as it does in humans. Understanding how bats respond to the infection may provide insight into how specific aspects of the human immune response result in clinical disease. This, in turn, may result in novel therapeutic interventions to diminish immunopathological disease.

While identification of the receptor will be an important advance, the overarching question at present is whether HCoV-EMC is or will become an important human pathogen. At this point, fewer than 10 cases have been identified and the mortality rate has been greater than 50%. With so few cases, infection and analysis of laboratory animals will be required to fulfill Koch’s postulates and prove a causative role for HCoV-EMC in respiratory disease. If HCoV-EMC is associated with respiratory disease in animals, as seems likely, epidemiological studies to provide a denominator for the total number of cases will be essential. Is HCoV-EMC a common infection in the Middle East, with most patients remaining asymptomatic or developing mild disease, or is the infection rare, but when infection occurs, disease is severe? Development of tools to detect past and present infections is critical and will be facilitated by recent publications of the virus sequence and genomic analysis. Equally important will be the collection and analysis of samples from representative populations in the Middle East. Most patients infected with SARS-CoV developed clinical disease, with only a few infections remaining asymptomatic. If HCoV-EMC is a new pathogen, will it further adapt to human populations, as the SARS-CoV did during the 2002-2003 epidemic (4, 6)? If virus is detected only rarely in human populations and never spreads significantly from human to human, it may not be a major health issue, but the interesting question of how these unlucky individuals were infected remains to be addressed.

REFERENCES


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