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Functional Dipeptidyl Peptidase 4 (DPP4) in mink supports entry and replication of Middle Eastern respiratory syndrome coronavirus: American Mink (Neovision vision), a novel in vivo model of MERS-CoV infection

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Background: A novel coronavirus, named the Middle East Respiratory Syndrome coronavirus (MERS-CoV), was first identified in humans in 2012. MERS infections are characterized by acute respiratory distress with fatal cases often diagnosed with comorbidity factors including diabetes, cardiovascular disease, or obesity. Continued emergence of MERS-CoV, coupled with a lack of understanding of the natural history of MERS highlights the importance of identifying therapeutics for treatment of MERS-CoV infections in humans. Like other coronaviruses, the MERS-CoV virion utilizes a large surface spike (S) glycoprotein for interaction with and entry into the target cell. The host cell protein dipeptidyl peptidase 4 (DPP4, aka CD26) was identified as a cellular receptor for MERS-CoV and the specific interaction of the receptor-binding domain (RBD) of MERS-CoV spike protein and DPP4 was determined recently by crystallography.

Methods & Materials: Our laboratory has been working to develop rational *in vitro* and *in vivo* models of MERS-CoV infection to allow better understanding of the pathogenesis and transmission potential of virus, and also to evaluate potential therapeutic and vaccine approaches to treat or prevent MERS in humans. Here we present studies focused on characterization of the MERS-CoV receptor, DPP4 in cells from the American mink (*Neovision vision*) as well evaluation of mink as an animal model of MERS-CoV infection. Using multiple approaches we have shown a cell line derived from mink lung epithelium to be susceptible to infection by MERS-CoV.

Results: Western blot and PCR analysis of mink lung epithelium cells demonstrate the presence of DPP4, the receptor for MERS-CoV expressed in mink, suggesting a role for this receptor in viral entry in this species. Characterization of the expression of DPP4 in mink cells reveal multiple isoforms, which show varying patterns of expression in cells transfected with each DPP4 isoform using confocal microscopy.

Conclusion: In conclusion, evaluation of known DDP4 inhibitors for antiviral activity against MERS-CoV reveal potential therapeutic approaches to treatment of MERS with existing, licensed compounds. Studies underway using mink as an *in vivo* model of MERS-CoV infection and pathogenesis support it's use in discovery and development of therapeutic and vaccines for MERS-CoV in humans.

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Multiple introductions of MERS-CoV in a 2014 hospital outbreak in Riyadh, Saudi Arabia

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Background: In 2012, the Middle East respiratory syndrome (MERS), a zoonotic disease caused by the MERS Coronavirus (MERS-CoV) emerged in Saudi Arabia as a disease with global health implications. Though much of its transmission dynamics remain unclarified, most cases (over 1250) have occurred in Saudi Arabia with substantial contribution from hospital outbreaks. This molecular epidemiological study investigated a MERS outbreak at the King Fahad Medical City (KFMC), a 1,200-bed tertiary care hospital in Riyadh that occurred between March 29 and May 21, 2014.

Methods & Materials: Following MOH guidelines, respiratory specimens (nasopharyngeal swab, tracheal aspirate or bronchoalveolar lavage) from persons including health care workers (HCWs) suspected to have MERS-CoV infection were tested using a reverse transcription PCR targeting the Orf1a and upstream E-gene (upE). In parallel, these samples were tested for 15 other respiratory viruses using a Multiplex PCR platform. Epidemiologic data were extracted from electronic health records, sick leave records of HCWs and direct interviews. Stored remnants of PCR positive samples were retrieved and sent to The University of Hong Kong where overlapping PCR products generated from multiple sets of PCR on synthesized cDNA were used to sequenced the entire MERS-CoV genome with >3–5 times genome coverage. BEAST (version 1.8) was used for phylogenetic analysis.

Results: 45 MERS-CoV infected persons were documented during this period: 23 HCWs; 13 long stay in-patients; and 8 patients infected outside KFMC. The source of infection for 1 person was inconclusive. Comparison of retrieved full-length MERS-CoV sequences from 10 patients and a partial sequence from another with other publicly available MERS-CoV sequences revealed that this outbreak was part of a larger outbreak that involved several hospitals in Riyadh. The larger outbreak seemed to have originated from a zoonotic transmission event around December 2013 (95% highest posterior density interval November 8, 2013–February 10, 2014) thus indicative of probable sustained human-to-human spread over a 5-month period.

Conclusion: Using whole genome sequencing, we demonstrated multiple introductions of MERS-CoV in a hospital outbreak that was hitherto thought to be otherwise.

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