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One of the critical determinants of viral host range is the interaction between the coronavirus spike protein and the host cell receptor.

Angiotensin-converting enzyme 2 (ACE2) has been identified as a receptor for the attachment to and uptake of SARS-CoV in host cells.[1] The distribution of ACE2 in human tissues corresponds mainly to the cell types in which SARS-CoV replication has been observed. Besides type II pneumocytes and bronchial epithelial cells, ACE2 expression has been found in type I pneumocytes, endothelial cells, and smooth muscle cells of blood vessels, but not alveolar macrophages.

Ferrets are susceptible to SARS-CoV infection[2] and can also transmit the virus at low levels by direct contact.[3-5] In different studies, they have shown diverse clinical signs but did not show significant mortality.[2,6] Ferrets can develop a fever in response to infection, which is characteristic of SARS-CoV-infected human patients.[7]

For MERS-CoV, the host cell receptor is dipeptidyl peptidase IV (DPPIV),[8] a ubiquitously expressed cell surface protein that functions in immune homeostasis. Interestingly, whereas MERS-CoV can utilize bat DPP4 (bDPP4), camel DPP4 (cDPP4), and human DPP4 (hDPP4) molecules for entry, it cannot infect cells using the DPP4 molecules from traditional small-animal models, including mice, ferrets, guinea pigs, and hamsters. The inability of MERS-CoV to infect these species in vivo and in vitro is primarily due to spike-receptor incompatibilities and not due to other species-specific host cell factors.

Ferrets are not susceptible to experimental MERS-CoV infection because their homologous DPP4 molecules do not function as receptors for MERS-CoV entry.[9] Even after administering a high dose of MERS-CoV, no viral replication can be detected.[10]

A newly published study[11] looked at the spike protein of the COVID-19 virus, and the ACE2 receptor that SARS uses as its binding site to invade cells. Their analysis “confidently predicts” that the COVID-19 virus also uses ACE2 as its receptor. The authors predict that a single genetic mutation at one location in the virus's genome could significantly enhance its ability to bind, and that surveillance for this mutation should be performed. The study also predicts that the COVID-19 virus can bind to ACE2 in ferrets (and pigs, cats and some non-human primates) with similar efficiency as it does in people.

An in-press article in *Cell Host & Microbe* (with an impact factor of 12.76 placing it in the top

1.5% of biological journals) entitled 'Infection and Rapid Transmission of SARS-CoV-2 in Ferrets'[12] found

- COVID-19-infected ferrets exhibit elevated body temperature and virus replication
- COVID-19 is shed in nasal washes, saliva, urine and feces
- COVID-19 is effectively transmitted to naive ferrets by direct contact
- COVID-19 infection leads acute bronchiolitis in infected ferrets

All ferrets were infected with a high virus dose (TCID50 of 10^5.5) that would not occur naturally, of a laboratory strain of COVID-19.

Another (unpublished) report on April 7, from the Friedrich-Loeffler-Institute (the German Federal Research Institute for Animal Health) experimentally infected fruit bats, ferrets, pigs and chicken with COVID-19. The animals were intranasally inoculated with 10^5 TCID50 and monitored for virus shedding by samples taken from the upper respiratory tract, and fecal samples. In addition, animals were euthanized for necropsy at different time points. In all experiments, contact animals were also investigated.

Pigs (n=9) and chickens (n=17) were not susceptible to intranasal infection by COVID-19. All swab samples, organ samples and contact animals remained negative for COVID-19-RNA. The most efficient virus replication was observed in ferrets, with high yields of viral RNA in nasal washing fluids from 8 of 9 animals from 2 days post infection (dpi) to 8 dpi. Interestingly, all 3 non-inoculated contact ferrets became infected and viral RNA was present in nasal washing fluids starting at 12 dpi. Screening of organ samples revealed prominent viral RNA loads only in the upper respiratory tract as confirmed by positive immunohistochemistry and in situ-hybridization in the nasal cavity. COVID-19 reactive antibodies were detected from day 8 in the inoculated ferrets and in one contact ferret on day 21 dpi. The virus replication in ferrets resembles a mild human infection.

In both reports all the infected ferrets recovered. This research means ferrets can be used as an infection and transmission animal model of COVID-19 that may facilitate the development of therapeutics and vaccines. **However, there is no evidence anywhere, other than the initial spillover where COVID-19 arose, that any animal has infected any person anywhere.**

The US Department of Agriculture (USDA), the World Organization for Animal Health and the American Veterinary Medical Association (AVMA) all say on their websites that there is so far no evidence that domestic animals can pass on an infection to people. But they all advise that people who are sick should take the same precautions about contact with their pets that they would with humans.

The primary scientific importance of understanding how the virus acts in animals is to learn more about it for human prevention and treatment. But the knowledge can also have an impact on the animals themselves. Animal welfare groups worry about a backlash against pets if people are worried that their animals might become infected. The World Organization for Animal Health urges people not to turn against their pets, saying, “There is no justification in taking measures against companion animals which may compromise their welfare.”

Uncategorized References

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