Mouse model mimics SARS-CoV-2 infection in humans

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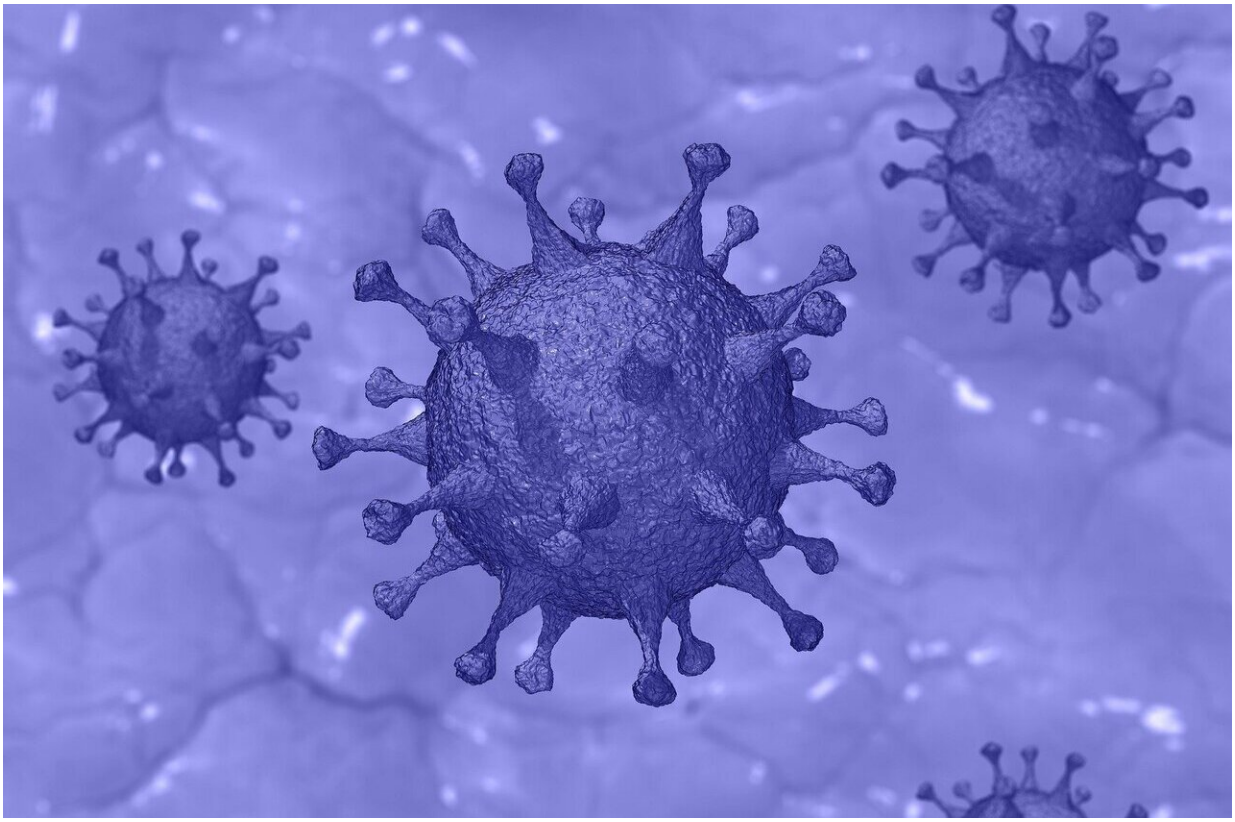

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A mouse model of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reproduces features observed in human patients, researchers report May 26 in the journal *Cell Host & Microbe*.

Using CRISPR/Cas9 gene editing technology, the researchers generated mice that produce human angiotensin-converting enzyme II (hACE2)—the receptor that SARS-CoV-2 binds to and uses to enter human cells.

"A small animal model that reproduces the clinical course and pathology observed in COVID-19 patients is highly needed," says co-senior study author You-Chun Wang of the National Institutes for Food and Drug Control (NIFDC) in Beijing, China. "The animal model described here provides a useful tool for studying SARS-CoV-2 infection and transmission."

Wang and his collaborators used CRIPSR/Cas9 to generate a mouse model that could express hACE2. According to the authors, their mouse model has several advantages compared with other genetically engineered mice that express hACE2 for modeling SARS-CoV-2 infection. Instead of being randomly inserted, hACE2 is inserted precisely into a specific site on the X chromosome, and it completely replaces the mouse version of the protein. In addition, this is a genetically stable model, with few differences among individuals. Moreover, the viral RNA loads in the lung are much higher, and the resulting distribution of hACE2 in various tissues better matches that observed in humans.

After being infected with SARS-CoV-2 through the nose, the genetically engineered mice showed evidence of robust viral RNA replication in the lung, trachea, and brain. "The presence of viral RNAs in brain was somewhat unexpected, as only a few COVID-19 patients have developed neurological symptoms," says co-senior study author Cheng-Feng Qin of the Academy of Military Medical Sciences (AMMS) in Beijing, China.

SARS-CoV-2 S protein, which binds to hACE2 to enter host cells, was also present in the lung tissue and brain cells. Moreover, the researchers

identified the major airway cells targeted by SARS-CoV-2 as Clara cells that produce the protein CC10. "Our result provides the first line of evidence showing the major target cells of SARS-CoV-2 in the lung," says co-senior study author Yu-Sen Zhou of AMMS.

In addition, the mice developed interstitial pneumonia, which affects the tissue and space around the air sacs of the lungs, causing the infiltration of inflammatory cells, the thickening of the structure that separates air sacs, and blood vessel damage. Compared with young mice, older mice showed more severe lung damage and increased production of signaling molecules called cytokines. Taken together, these features recapitulate those observed in COVID-19 patients.

When the researchers administered SARS-CoV-2 into the stomach, two of the three mice showed high levels of viral RNA in the trachea and lung. The S protein was also present in lung tissue, which showed signs of inflammation. According to the authors, these findings are consistent with the observation that patients with COVID-19 sometimes experience gastrointestinal symptoms such as diarrhea, abdominal pain, and vomiting. But 10 times the dose of SARS-CoV-2 was required to establish infection through the stomach than through the nose.

Future studies using this mouse model may shed light on how SARS-CoV-2 invades the brain and how the virus survives the gastrointestinal environment and invades the respiratory tract. "The hACE2 mice described in our manuscript provide a small animal model for understanding unexpected clinical manifestations of SARS-CoV-2 infection in humans," says co-senior study author Chang-Fa Fan of NIFDC. "This model will also be valuable for testing vaccines and therapeutics to combat SARS-CoV-2."

More information: Shi-Hui Sun et al, A mouse model of SARS-CoV-2 infection and pathogenesis, *Cell Host & Microbe* (2020). DOI:

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