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# Researchers identify how coronavirus enters body

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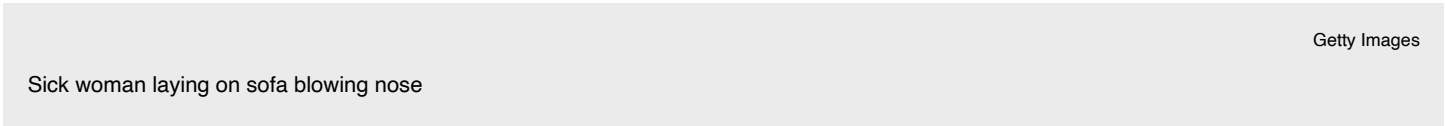

Getty Images

Sick woman laying on sofa blowing nose

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SARS-CoV-2, the virus that causes COVID-19, uses its spike protein to bind to cellular receptors in the human body. The virus relies on the ACE2 receptor protein and the TMPRSS2 protease to enter cells, but which cells are initially infected has been unclear.

An international team of researchers used single-cell RNA sequencing datasets put together by the Human Cell Atlas consortium to search for cell types that express both the ACE2 and TMPRSS2 genes. As they reported in Nature Medicine on Thursday, they found a number of cells in different organs express the genes encoding these proteins, but they homed in on cells of the respiratory system, especially goblet cells and ciliated cells in the nose.

"Mucus-producing goblet cells and ciliated cells in the nose had the highest levels of both these [genes], of all cells in the airways," first author Waradon Sungnak from the Wellcome Sanger Institute said in a statement. "This makes these cells the most likely initial infection route for the virus."

Using the Human Cell Atlas dataset, Sungnak and his colleagues analyzed ACE2 and TMPRSS2 expression in a range of tissues, including not only respiratory tissue — previous analyses using immunohistochemistry had detected both ACE2 and TMPRSS2

in the nasal and bronchial epithelium — but also tissue from the eyes, digestive tract, muscle, and more.

ACE2 gene expression was generally low across the datasets analyzed, while TMPRSS2 was more broadly expressed, the researchers found. This suggested that ACE2 expression might be the limiting factor for viral entry in initial infections.

However, ACE2 was expressed in a number of epithelial cell types of respiratory tissues, and its expression was particularly high among goblet cells and ciliated cells of the nose. The researchers confirmed this finding using data from two other scRNA-seq studies.

Other genes often co-expressed alongside ACE2 in the respiratory system included ones involved in carbohydrate metabolism — possibly due to their role in goblet cell mucin synthesis — and those involved in innate and antiviral immune functions.

The ACE2 and TMPRSS2 genes were also expressed outside of the respiratory system, including by cells of the cornea and the lining of the intestine, which the researchers noted is in line with some clinical reports suggesting fecal shedding of the virus.

Where these viral entry receptor genes are expressed in the respiratory system could influence how transmissible a virus is. The researchers compared the tissue expression patterns of these viral receptor genes to those of receptor genes used by other coronaviruses and influenza viruses. The receptors used by highly infectious viruses like influenza were expressed more in the upper airway, while receptors for less infectious viruses like MERSCoV were expressed in the lower airway. This indicated to the researchers that the spatial distribution of the viral receptors may influence how transmissible a virus is.

"This is the first time these particular cells in the nose have been associated with COVID-19," study co-author Martijn Nawijn from the University Medical Center Groningen and the HCA Lung Biological Network said in a statement. "The location of these cells on the surface of the inside of the nose make them highly accessible to the virus, and also may assist with transmission to other people."

Another study that appeared in Cell on Thursday also used single-cell RNA-sequencing datasets from humans, nonhuman primates, and mice to examine where cells expressing both the ACE2 and TMPRSS2 genes are located. Those researchers, led by the Broad Institute's Jose Ordovas-Montanes, found both genes were expressed among type II pneumocytes and ileal absorptive enterocytes as well as among nasal goblet secretory cells.

*This story first appeared in our sister publication, Genomeweb.*

Inline Play

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