Key nose cells identified as likely COVID-19 virus entry points

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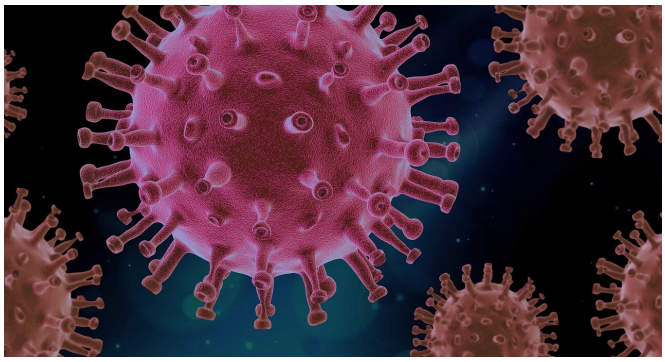

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Two specific cell types in the nose have been identified as likely initial infection points for COVID-19 coronavirus. Scientists discovered that goblet and ciliated cells in the nose have high levels of the entry proteins that the COVID-19 virus uses to get into our cells. The identification of these cells by researchers from the Wellcome Sanger Institute, University Medical Centre Groningen, University Cote d'Azur and CNRS, Nice and their collaborators, as part of the Human Cell Atlas Lung Biological Network, could help explain the high transmission rate of COVID-19.

Reported today (23rd April) in *Nature Medicine*, this first publication with the Lung Biological Network is part of an ongoing international effort to use Human Cell Atlas data to understand infection and disease. It further shows that cells in the eye and some other organs also contain the viral-entry proteins. The study also predicts how a key entry protein is regulated with other immune system genes and reveals potential targets for the development of treatments to reduce transmission.

Novel coronavirus disease—COVID-19—affects the lungs and airways. Patient's symptoms can be flu-like, including fever, coughing and sore throat, while some people may not experience symptoms but still have transmissible virus. In the worst cases, the virus causes pneumonia that can ultimately lead to death. The virus is thought to be spread through respiratory droplets produced when an infected person coughs or sneezes, and appears to be easily transmitted within affected areas. So far the virus has spread to more than 184 countries and claimed more than 180,000 lives.

Scientists around the world are trying to understand exactly how the virus spreads, to help prevent transmission and develop a vaccine. While it is known that the virus that causes COVID-19 disease, known as SARS-CoV-2, uses a similar mechanism to infect our cells as a related coronavirus that caused the 2003 SARS epidemic, the exact cell types involved in the nose had not previously been pinpointed.

To discover which cells could be involved in COVID-19 transmission, researchers analysed multiple Human Cell Atlas§ (HCA) consortium datasets of single cell RNA sequencing, from more than 20 different tissues of non-infected people. These included cells from the lung, nasal cavity, eye, gut, heart, kidney and liver. The researchers looked for which individual cells expressed both of two key entry proteins that are used by the COVID-19 virus to infect our cells.

Dr. Waradon Sungnak, the first author on the paper from Wellcome Sanger Institute, said: "We found that the receptor protein—ACE2—and the TMPRSS2 protease that can activate SARS-CoV-2 entry are expressed in cells in different organs, including the cells on the inner lining of the nose. We then revealed that mucus-producing goblet cells and ciliated cells in the nose had the highest levels of both these COVID-19 virus proteins, of all cells in the airways. This makes these cells the most likely initial infection route for the virus."

Dr. Martijn Nawijn, from the University Medical

Center Groningen in the Netherlands, said, on behalf of the HCA Lung Biological Network: "This is the first time these particular cells in the nose have been associated with COVID-19. While there are many factors that contribute to virus transmissibility, our findings are consistent with the rapid infection rates of the virus seen so far. 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."

The two key entry proteins ACE2 and TMPRSS2 were also found in cells in the cornea of the eye and in the lining of the intestine. This suggests another possible route of infection via the eye and tear ducts, and also revealed a potential for fecal-oral transmission.

When cells are damaged or fighting an infection, various immune genes are activated. The study showed that ACE2 receptor production in the nose cells is probably switched on at the same time as these other immune genes.

The work was carried out as part of the global Human Cell Atlas consortium which aims to create reference maps of all human cells to understand health and disease. More than 1,600 people across 70 countries are involved in the HCA community, and the data is openly available to scientists worldwide.

Dr. Sarah Teichmann, a senior author from the Wellcome Sanger Institute and co-chair of the HCA Organising Committee, said: "As we're building the Human Cell Atlas it is already being used to understand COVID-19 and identify which of our cells are critical for initial infection and transmission. This information can be used to better understand how coronavirus spreads. Knowing which exact cell types are important for virus transmission also provides a basis for developing potential treatments to reduce the spread of the virus."

The global HCA Lung Biological Network continues to analyse the data in order to provide further insights into the cells and targets likely to be involved in COVID-19, and to relate them to patient characteristics.

Professor Sir Jeremy Farrar, Director of Wellcome, said: "By pinpointing the exact characteristics of every single cell type, the Human Cell Atlas is helping scientists to diagnose, monitor and treat diseases including COVID-19 in a completely new way. Researchers around the world are working at an unprecedented pace to deepen our understanding of COVID-19, and this new research is testament to this. Collaborating across borders and openly sharing research is crucial to developing effective diagnostics, treatments and vaccines quickly, ensuring no country is left behind."

More information: et al, SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes, *Nature Medicine* (2020). DOI: 10.1038/s41591-020-0868-6

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