Coronavirus likely infects upper airway cells first; blood pressure drugs unlikely to increase risk

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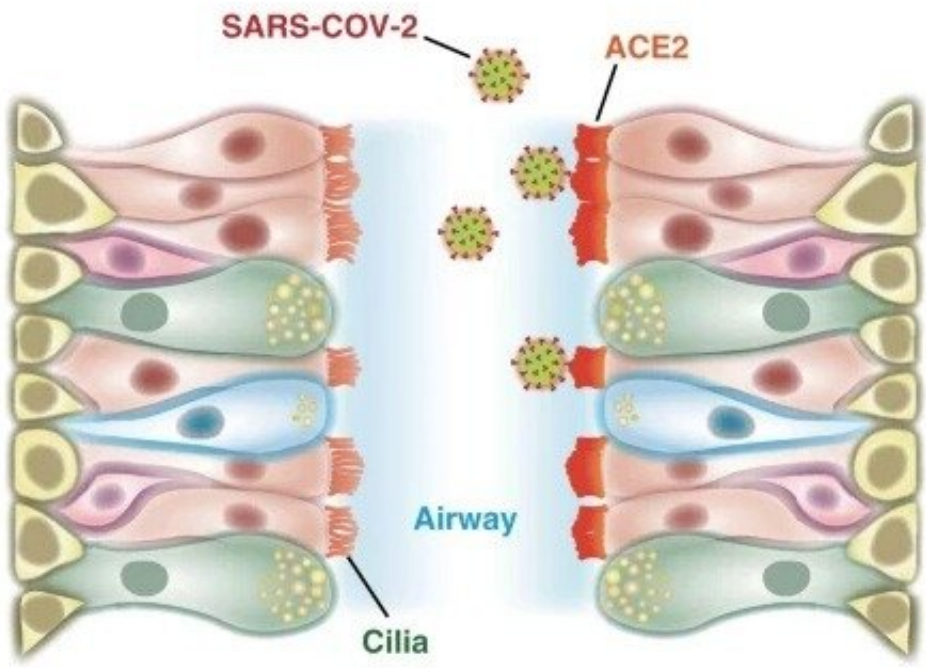

The coronavirus that causes COVID-19 binds to a protein on cells called ACE2, and researchers found high levels of ACE2 in airway cilia. Credit: Tsuguhisa Nakayama

Cells in the nasal passages and upper airways are likely the coronavirus' major point of entry into the body, according to a study by Stanford

Medicine researchers.

The finding further supports the use of masks to prevent viral spread and suggests that nasal sprays or rinses might be effective in blocking infection by the coronavirus.

The study also found that common blood pressure medications are unlikely to increase the risk of contracting COVID-19, countering concerns that hypertension drugs could make it easier for the coronavirus to enter human cells.

"Early in the pandemic, there were concerns that two classes of blood pressure medications may increase the risk for COVID-19," said Ivan Lee, MD, Ph.D., an instructor of allergy and immunology. "Our results suggest that this is not the case. Furthermore, face masks should be carefully worn to cover the nose, as the virus binds readily to cells in the nasal passage."

Lee, research scientist Tsuguhisa Nakayama, MD, Ph.D.; senior scientist Yury Goltsev, Ph.D.; and postdoctoral scholars Chien-Ting Wu, Ph.D., and Sizun Jiang, Ph.D., are co-lead authors of the study, which was published Oct. 28 in *Nature Communications*. The senior authors are Garry Nolan, Ph.D., the Rachford and Carlota A. Harris Professor and professor of microbiology and immunology; Jayakar Nayak, MD, Ph.D., associate professor of otolaryngology; and Peter Jackson, Ph.D., professor of microbiology and immunology.

Hijacking a defense mechanism

The coronavirus that causes COVID-19 enters human cells by binding to a protein on the cell surface called ACE2. Lee and his colleagues compared levels of ACE2 in the lungs, kidneys, testes and intestines with ACE2 levels in cells lining the upper and lower airways.

They found high levels of ACE2 in airway cilia—tiny, flexible projections on the respiratory cell surfaces that sweep the airway clean of foreign particles like dust and invading pathogens.

"The virus hijacks this protective feature by binding to ACE2 on cilia and infecting these cells," Lee said. "Because most people breathe primarily through their nose, this is mostly likely the site of initial viral contact and infection."

Because hypertension is a risk factor for severe COVID-19, Lee and his colleagues also assessed the levels of ACE2 in sinus tissue samples obtained from hundreds of people with chronic sinusitis. Some of these people were taking common blood pressure medications known as ACE inhibitors or angiotensin receptor blockers; others were not.

"Past studies have found that the use of ACE inhibitors for hypertension increases the expression of ACE2 in the kidney and heart," Lee said. "But the effect of these medications in the upper airways is more relevant when considering coronavirus infection."

However, Lee and his colleagues found that ACE2 levels in the upper airways did not vary significantly between those people taking blood pressure medications and those who were not.

"This is the first mechanistic-based evidence that the use of ACE inhibitors and angiotension receptor blockers don't increase levels of ACE2 in these upper airway cells," Lee said.

An opening for infection prevention?

The discovery of high levels of ACE2 protein in the airway cells might drive the development of new ways to prevent viral infection at the source, the researchers said.

"We are now examining how airway cilia detect and react to the virus," Jackson said. "There may be ways to promote rhythmic beating of cilia to increase the flow of mucus and help eliminate the virus."

"Currently, major efforts are devoted to medications that work systemically through either intravenous or oral delivery," Lee said. "But if the virus enters the body through the nasal lining, it also makes sense to explore nasally administered drugs and sprays to prevent infection. The nose is a very favorable location to deliver medications. Our findings also provide strong scientific justification to recommendations made by the health care community to use masks that cover the mouth and nose to prevent coronavirus infection."

More information: Ivan T. Lee et al. ACE2 localizes to the respiratory cilia and is not increased by ACE inhibitors or ARBs, *Nature Communications* (2020). DOI: 10.1038/s41467-020-19145-6

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