Research probes why COVID-19 seems to spare young children

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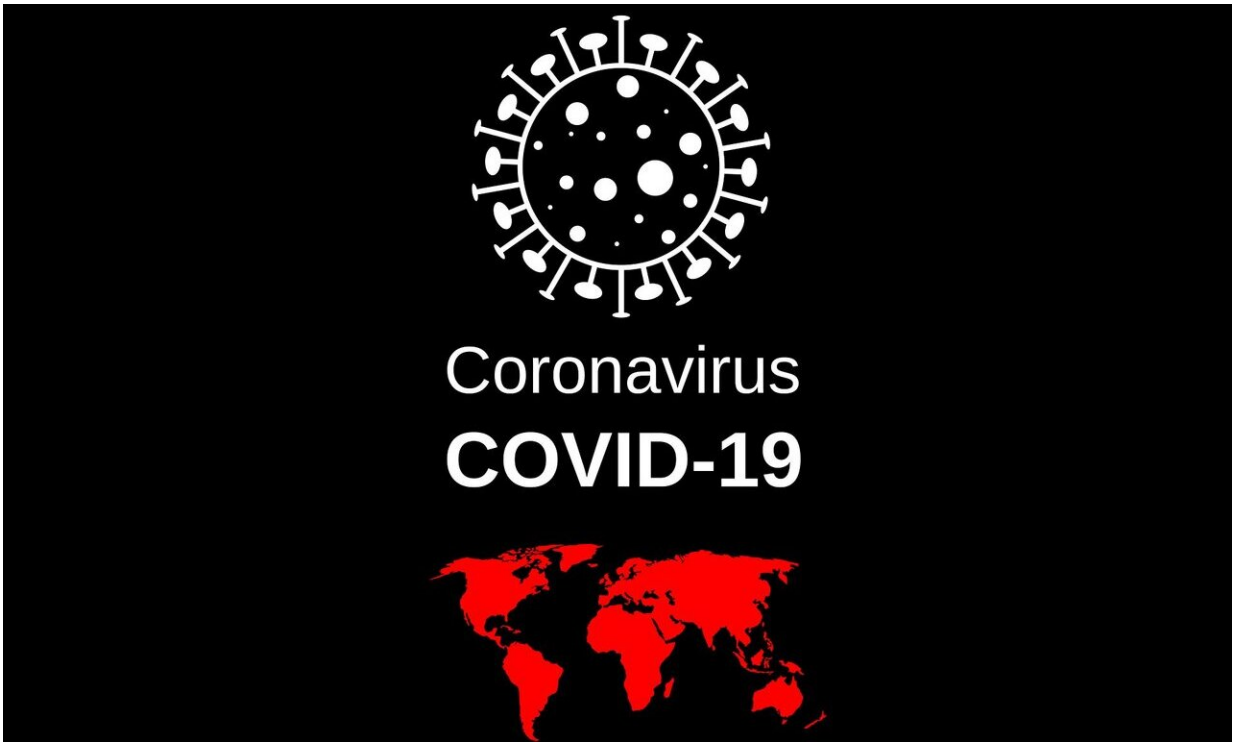

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Lung disease experts at Vanderbilt University Medical Center and their colleagues have determined a key factor as to why COVID-19 appears to infect and sicken adults and older people preferentially while seeming to spare younger children.

The researchers discovered that children have lower levels of an enzyme the virus needs to invade airway epithelial cells in the lung. Their preliminary findings, has been posted online by the preprint server bioRxiv, suggest that blocking this enzyme potentially could prevent COVID-19 infection in older people.

There is still much to learn about SARS-CoV-2, the one-stranded RNA virus that causes COVID-19, said Jonathan Kropski, MD, assistant professor of Medicine and Cell & Developmental Biology in the Vanderbilt University School of Medicine, who led the study with Jennifer Sucre, MD.

But this much we do know: After a viral particle is inhaled into the lungs, protein "spikes" that stick out of its surface like nail studs in a soccer ball attach to a receptor called ACE2 on the surfaces of certain types of lung cells.

A cellular enzyme called a protease chops up the spike protein, enabling the virus to fuse into the cell membrane and "break into" the cell. Once inside, the virus hijacks the cell's genetic machinery to make copies of its RNA.

Sucre and Kropski wondered whether levels of ACE2 and the protease, called TMPRSS2, change during lung development. If infants and children express less of these proteins, maybe that's why they seem to be less vulnerable than older people to severe illness if they are exposed to SARS-CoV-2.

The researchers were well suited to investigate that possibility. As members of the international Human Cell Atlas (HCA) Lung Biological Network, they and their colleagues had built a dataset on lung development in the mouse using a technique called single-cell RNA-sequencing.

The technique can detect the expression of genes in individual cells of tissues such as the lung. In this way the researchers were able to track the expression of genes known to be involved in the body's response to COVID-19 over time.

They found that while the gene for ACE2 was expressed at low levels in the mouse lung, "TMPRSS2 stood out as having a really striking trajectory of increased expression during development," said Sucre, assistant professor of Pediatrics and Medicine.

The researchers next applied another technique called RNA in situ hybridization, which uses fluorescent probes to visualize how expression of the TMPRSS2 gene increased over time in specific types of epithelial cells that line the lungs.

With the help of VUMC pathologists, the researchers obtained and analyzed human lung specimens collected from donors of different ages, and confirmed a similar trajectory in TMPRSS2 expression to what they'd found in mice.

Finally the researchers used fluorescent probes to analyze an autopsy specimen from a patient who had died from COVID-19. They found the virus in three types of cells that express TMPRSS2. In essence, Sucre said, they caught the virus "red-handed," at the scene of the "crime."

These findings, the researchers concluded, "underscore the opportunity to consider TMPRSS2 inhibition as a potential therapeutic target for SARS-CoV-2."

In a previous study of the first SARS virus, which caused a worldwide outbreak in 2002, researchers from Japan reported that a combination of protease inhibitors prevented the virus from entering human bronchial epithelial cells grown in the laboratory.

Kropski said much of the background work for this paper was built upon the collaborative efforts of the Human Cell Atlas (HCA) Lung Biological Network.

The Vanderbilt COVID-19 Consortium Cohort, a multi-disciplinary effort to understand more fully why some people are at greater risk of COVID-19 infection and illness, also aided in the acquisition and analysis of human tissues, he said.

More information: Bryce A. Schuler et al. Age-related expression of SARS-CoV-2 priming protease TMPRSS2 in the developing lung, (2020). DOI: 10.1101/2020.05.22.111187

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