A respiratory model of COVID-19, made from patient-derived stem cells

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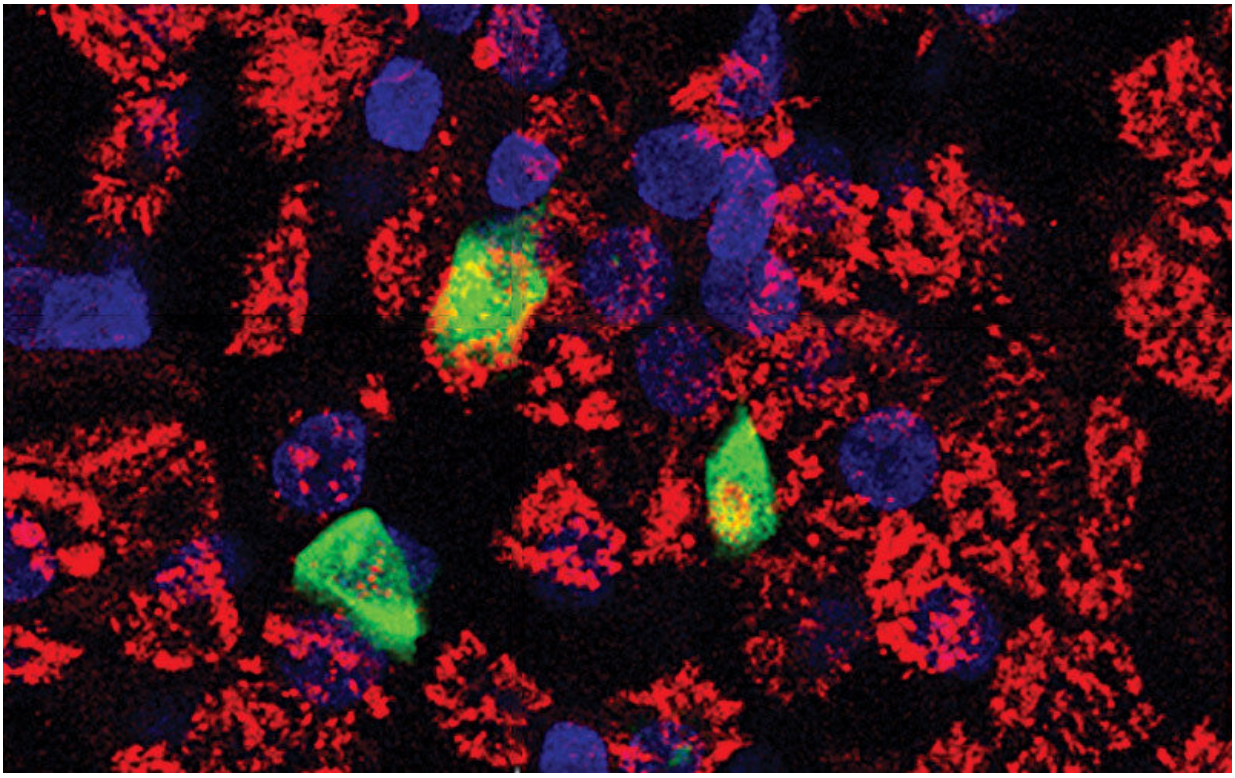

Derived from patients' cells, a new airway model containing ciliated respiratory endothelial cells recapitulates SARS-CoV-2 infection and can be used to test drugs. Three ciliated cells in this model are infected with the virus. Credit: Chantelle Simone Roach, Boston Children's, and Jake La Suer, Boston University.

What happens in our respiratory tract once we're exposed to COVID-19?

A three-dimensional airway model, made from patient-derived stem cells, could provide answers about the initial stages of infection. The model not only replicates the infection process, but can be used to test potential antiviral drugs.

Ruby Wang, MD, attending physician in Boston Children's Division of Pulmonary Medicine, led the research in collaboration with the Center for Regenerative Medicine of Boston University (BU) and Boston Medical Center and BU's National Emerging Infectious Disease Laboratories (NEIDL).

"Human primary bronchial cells are the gold standard for studying lower respiratory infections, but the value of our model is that it doesn't require getting tissue from patients' airways, an invasive procedure," says Wang. "Our platform provides an inexhaustible supply of cells for modeling purposes and produces the relevant airway cell types."

From blood cells to a model airway

To build the model, Wang and her BU colleagues Finn Hawkins, MB, BCh, and Darrell Kotton, MD, obtained blood cells from two individuals and genetically "reprogrammed" them back to a stem cell state, together with Thorsten Schlaeger, Ph.D., and George Daley, MD, Ph.D., from Boston Children's Stem Cell Program. They then added factors to get the stem cells to form all the major types of epithelial cells that line the trachea and bronchi, including multi-ciliated, secretory, and basal cells. The hallmark cell receptor ACE2 was present in the stem-cell-derived airways, as was TMPRSS2, a key enzyme that aids in viral entry.

Using live SARS-CoV-2 virus in BU's Biosafety Level 3 facility, Wang's group, working with NEIDL researchers Adam Hume, Ph.D., and Elke Muhlberger, Ph.D., successfully infected the model airway and showed that multi-ciliated airway cells are the initial point of viral entry.

"That's important, because ciliated cells have an important function in propelling airway mucus and entrapped pathogens up away from the lungs," says Wang. "If the ciliated cells are injured, the virus can be more easily propelled down to the lower lung."

Modeling SARS-CoV-2 infection, testing treatments

Once infected, the model airway mounted a robust antiviral response, producing type 1 and type 3 interferons. The team also observed a marked inflammatory response, with increased production of inflammatory signaling molecules and increased expression of interferon-stimulated genes and genes involved in activating immune cells.

Because the model airway genetically matches the patient from whom it's derived, it lends itself to testing how COVID-19 affects patients with specific underlying conditions that may affect their susceptibility.

"We can also use CRISPR gene editing to see the effects of different genetic mutations," says Wang. She, Stuart Rollins, MD, and other members of her lab are currently using stem cells from cystic fibrosis (CF) patients to study how a CF airway responds to SARS-CoV-2 and other pathogens.

Perhaps most importantly, the model can also be used to test potential treatments. The team tested the antiviral remdesivir and found a decrease in viral replication. They found the same when they tested camostat mesylate, which inhibits TMPRSS2, confirming that the virus requires TMPRSS2 to infect airway cells.

The team's findings are described in the journal *American Journal of Physiology—Lung Cellular and Molecular Physiology*. In the future, Wang plans to use the airway model to study Omicron, Delta, and other new variants and their response to treatments in both healthy patients

and those with airway diseases such as CF.

More information: Ruobing Wang et al, Human airway lineages derived from pluripotent stem cells reveal the epithelial responses to SARS-CoV-2 infection, *American Journal of Physiology-Lung Cellular and Molecular Physiology* (2022). DOI: 10.1152/ajplung.00397.2021

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