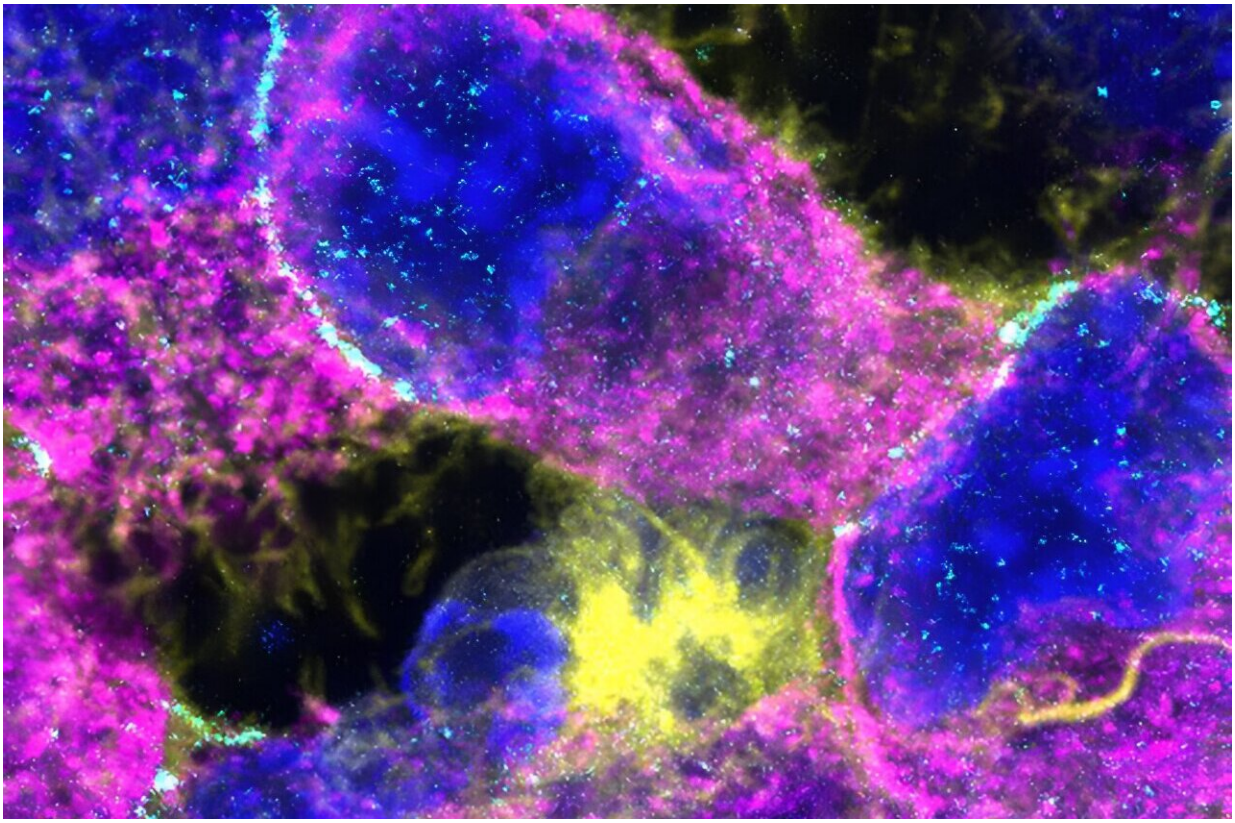
Study reveals 'cell death cascade' in airway cells infected with SARS-CoV-2

July 22 2024, by Kendall Daniels



A human airway epithelial cell (A549 cell line) undergoes necroptosis upon infection with the SARS-CoV-2 omicron variant (B.1.1.529). Active necroptosis is shown in cyan, SARS-CoV-2 nucleocapsid protein is shown in pink, the borders of the airway epithelial cells are shown in yellow, and the cell nucleus is shown in blue. Credit: Katherine Barnett

Researchers Jenny Ting, Ph.D., the William Kenan Distinguished Professor of Genetics and professor microbiology and immunology at the UNC School of Medicine, and Kaixin Liang, Ph.D., a postdoctoral researcher in the Ting lab, have identified how the COVID-19 virus causes death in the cells lining the human airways.

Their findings, which were published in *Science Immunology*, showed that infected cells and uninfected bystander cells undergo different versions of cell death. Researchers also concluded that the higher levels of viral replication directly influence disease severity and higher levels of cell death in different SARS-CoV-2 variants of concern.

Programmed cell death is an important part of cell development, the immune system, and viral infection. There are three well-studied forms. Apoptosis is a highly regulated process that allows cells to die without causing harm to the surrounding tissue, whereas necroptosis causes inflammation and tissue damage. Pyroptosis is a form of cell death that causes widespread inflammation as cells break down.

"Since we found that necroptosis is directly caused by SARS-CoV-2 infection, while apoptosis and pyroptosis are secondary to this, necroptosis makes an ideal therapeutic target because it is the initiator of this cell death cascade," said Katherine Barnett, Ph.D., postdoctoral fellow in the Ting lab and co-first author on the paper. "It will be interesting to follow up our basic research with more translational studies."

Under the microscope, researchers found that infected cells in the airway experienced necroptosis, a form of cell death associated with tissue damage. When they zoomed in on uninfected cells surrounding the infected ones, researchers made a surprising finding. Ting and Liang observed that these cells undergo apoptosis, a 'silent' form of cell death, followed by pyroptosis, a more aggressive, inflammatory type of cell

death.

"It is hard to distinguish the cell death events from cell to cell, but I am glad we got it to work and showed the different kinds of cell death in infected and uninfected cells," said Kaixin Liang, Ph.D., BDS, postdoctoral fellow in the Ting lab and co-first author on the paper. "Even though it is still a long way to unmask the complexity of the interplay between cell death events, we made one step forward to the ultimate goal."

This is the first time that death events have been described to differ between infected and uninfected cells in the airway epithelium during SARS-CoV-2 infection. These findings suggest that cell death may directly influence disease progression in patients.

Using cell lines, primary human airway epithelial cells, murine models, and other disease models, researchers compared and contrasted cell death in the two variants of concern to determine if there is a relationship between cell death and disease severity. They verified that mouse models infected with the delta variant of SARS-CoV-2 experienced higher rates of viral replication and cell death than did mouse models infected with the omicron variant.

More information: Kaixin Liang et al, Initiator cell death event induced by SARS-CoV-2 in the human airway epithelium, *Science Immunology* (2024). DOI: 10.1126/sciimmunol.adn0178

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