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Cystic Fibrosis Research News

Title:

CF airway epithelia display exaggerated host defense responses and prolonged cilia loss during RSV infection

Lay title:

Viral infection causes an extreme immune response and loss of cilia function in airway cells of people with CF

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What was your research question?

Respiratory viral infections cause relatively more severe and longer lasting symptoms in people with CF, compared with Non-CF individuals. To better understand this, we wanted to know: What genes are turned on and off in CF airway cells in response to viral infection, and how are these responses different from Non-CF cells?

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Why is this important?

Recurrent viral infections have a significant impact on the daily life of a person with CF because they frequently trigger pulmonary exacerbations (flare-ups) and can sometimes lead to hospitalization. In addition, people with CF may acquire new bacteria after a viral illness, suggesting that viral infections help bacteria to gain a stronghold in the lungs. It is currently not well understood why people with CF have different responses to respiratory viruses, or how CF airways become more susceptible to bacterial colonization, compared to Non-CF individuals.

What did you do?

We cultured airway epithelial cells (which line the lungs) of 4 people with CF and 4 Non-CF individuals. We infected the airway epithelial cultures with respiratory syncytial virus (RSV) and collected samples from the infected cells at various timepoints out to 5 days after the initial infection. At each time point, we measured how much the virus was replicating, and used a technique called RNA-seq to learn what genes were activated or suppressed over time in response to the infection.

What did you find?

We found that the virus grew more in the CF cells than in the Non-CF cells at every timepoint, indicating that the CF cells had comparatively less effective defenses against the virus. Our RNA-seq analysis revealed two main findings. First - despite the relatively greater amount of viral replication in the CF cells - the CF cells actually showed a more pronounced increase in genes with defense and pro-inflammatory roles. Second, RSV infection caused a decrease in genes coding for proteins in cilia. Cilia are small hairlike structures that protrude from the surface of airway cells and protect the airways by sweeping away bacteria and other particles. This suppression of cilia genes was particularly pronounced in the CF cells.

What does this mean and reasons for caution?

Our study demonstrates that CF airway cells are primed to respond to viral infections by overproducing inflammatory molecules, which likely contributes to the more severe symptoms seen in people with CF during viral illness. It also suggests that there is a dramatic loss of cilia (hair-like structures) during viral infection in CF, which may reduce airway cells' ability to defend against bacterial infections following virus. More detailed studies will be needed to confirm and expand on our cilia observations. Many questions remain, including how long it takes for airway epithelia to regrow their cilia after a viral infection and whether prolonged loss of cilia in CF cells is also seen with other viruses besides RSV.

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What's next?
It will be important to test whether treating CF airway cells with CFTR modulator drugs can reverse or prevent these abnormal responses to viral infection.

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