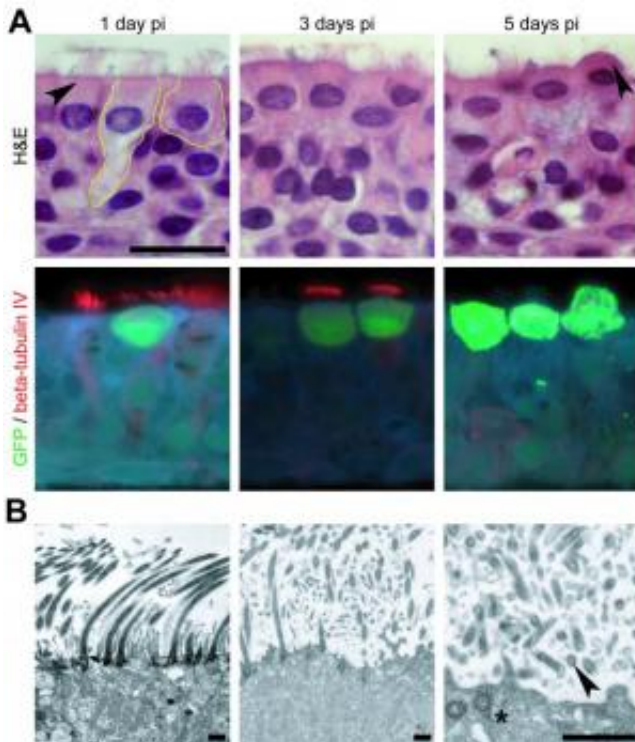


# Researchers find genetic trigger for RSV-induced infant hospitalizations

April 8 2014



Top series: Images show the elongated shape of cells transforming into a ball shape before they shed from the lining of the airway to cause obstruction, a key reason why RSV leads to bronchiolitis. Middle series: Cilia (red), the hair-like projections of epithelial cells, are eradicated in the RSV-infected cells. It is the cilia of healthy cells that move mucus out of the airway. Bottom series: Close up of cilia being ravaged during infection. Credit: Rachael Liesman, Ph.D., UNC School of Medicine

Researchers at UNC School of Medicine have pinpointed a viral protein that plays a major role in making respiratory syncytial virus (RSV) the most common cause of hospitalization in children under one year of age.

The discovery, published April 8 in the *Journal of Clinical Investigation*, is the first step toward identifying better diagnostics and potential treatments for an infection that strikes nearly all children before they reach the age of three and causing severe disease in 3 percent of infected children. RSV infection leads to the hospitalization of between 75,000 and 125,000 babies under one year of age in the United States every year; globally, RSV is the second-leading cause of infant mortality due to infectious disease behind only malaria.

"We've known for a long time that RSV has an increased propensity, compared to other respiratory viruses, for causing obstruction and inflammation in the narrowest airways of the infant lung, leading to severe bronchiolitis," said Raymond Pickles, PhD, associate professor of microbiology and immunology and senior author of the JCI paper. "But what we've now shown is that RSV has an increased ability to cause airway obstruction because, during an RSV infection, the virus expresses a specific RSV-encoded non-structural protein, or NS2, in [epithelial cells](#), causing the cells to shed from the airway lining and into the airway lumen. This leads to obstruction of airflow in the small airways and overwhelming inflammation."

According to this study, it's this NS2 protein and its effect on epithelial-cell shedding that makes RSV by far the most common cause of bronchiolitis in otherwise healthy young children. The finding was years in the making.

"It was a real struggle to put our finger on differences between RSV and other common respiratory viruses that might account for the increased

disease caused by RSV," Pickles said. "We compared the ability of RSV and parainfluenza virus (PIV3) – another common virus in children that causes much less severe airway disease – to infect and cause inflammatory responses in a cell culture model of human epithelial cells, which compose the lining of the lung airway. But comparing these consequences of infection did not provide hints as to why RSV and PIV3 produced such differences in disease severity. We did notice, though, that the epithelial cells infected by RSV looked very different during infection compared to those infected by PIV3."

While the PIV-infected epithelial cells retained their natural elongated, columnar shape, the same cells infected with RSV balled up and puffed out of the airway epithelium, causing the infected cells to accumulate in the lumen of the airway. "We hypothesized that since RSV and PIV3 are very similar viruses these different effects must be due to differences in the types of genes that RSV expresses," Pickles said.

There aren't many genes in RSV, and by generating mutant viruses in the laboratory, Pickles' team found that a specific RSV gene – the NS2 gene – was responsible for the balling up of RSV-infected airway cells. In experiments led by UNC graduate student Rachael Liesman, the researchers decided to engineer PIV3 to express the RSV NS2 gene. When Liesman infected human airway cells in the lab with this re-engineered virus, she saw infected cells ball up and puff out of the airway epithelium. "The cells infected by PIV3 expressing the NS2 gene of RSV looked exactly like RSV-infected cells," Liesman said.

Pickles and Liesman then used their reengineered PIV expressing RSV NS2 in animal models to provide more clinical relevance for their findings. They found that infection of the narrowest airways of the lung by PIV3 alone caused moderate levels of inflammation, but after infection by PIV3 expressing RSV NS2, the epithelial cells lining the narrow airways were shed rapidly into the airway lumen. The shedding

occurred at such a great rate that the shed cells obstructed the airway lumen, resulting and caused excessive inflammation.

Pickles said that these findings in animal models were almost identical to what has been found in human infants who had died because of RSV infection. Pickles said, "I'm convinced that the RSV NS2 gene is a major driver for the well-recognized increased ability of RSV to cause lung disease, especially in the extremely narrow small airways of human infants."

Pickles is now on the trail of a human biomarker that would tell doctors if an RSV-infected infant is at greater risk of developing severe lung disease. A biomarker would be key in the development of a needed diagnostic tool and would aid clinical trials that aim to develop anti-RSV therapeutics.

Michelle Hernandez, MD, a pediatric immunologist at UNC, said, "When young children arrive at the hospital with an RSV infection, it's challenging and frustrating to guess which children you can safely send home, versus those you should admit to the hospital because they might require supportive care in an intensive care unit. Any information that will help us make these decisions not only helps us ensure that we provide the best care for these kids, but also helps us use health care resources more wisely."

Using animal models, Pickles has already found candidate molecular biomarkers that indicate if the epithelial cells in the tiniest airways are expressing the RSV NS2 protein. He is now initiating studies to look for the same biomarkers in human infants infected with RSV.

"If we can find biomarkers informing us that the most vulnerable parts of the lung have already been infected by RSV, then it could be possible to identify much more quickly the children at more risk for developing

severe lung disease and to get those babies in a treatment protocol at an earlier time," Pickles said.

Regarding whether these findings could lead to better RSV treatments, Pickles said it may be possible to suppress the ability of NS2 to shed the airway epithelial cells. Thwarting this shedding effect wouldn't stop infection or stifle the typical symptoms of RSV infection, but it might limit the virus's ability to spread into the tiniest airways, which are the most likely to be obstructed by cells shed during infection. This would lead to a less severe infection and fewer hospitalizations.

Pickles added that suppressing the effects of the RSV NS2 protein may also allow our immune system more time to deal with the RSV [infection](#) before the small airways become clogged with cells shedding from the lining of the airway. He said, "These are questions we are aiming to answer in studies already underway."

Provided by University of North Carolina Health Care

Citation: Researchers find genetic trigger for RSV-induced infant hospitalizations (2014, April 8) retrieved 8 May 2023 from <https://medicalxpress.com/news/2014-04-genetic-trigger-rsv-induced-infant-hospitalizations.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--