Scientists find key mechanism of childhood respiratory disease

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Researchers have identified a critical part of the process by which one of the world's most common and dangerous early childhood infections, respiratory syncytial virus, causes disease.

The discovery could lead to badly needed new therapies for RSV, which in 2005 was estimated to have caused at least 3.4 million hospitalizations and 199,000 deaths among children under five worldwide.

By analyzing samples taken from infected infants and data from laboratory-mouse experiments, University of Texas Medical Branch at Galveston scientists determined that RSV interferes with airway cells' ability to produce enzymes that keep highly damaging molecules known as reactive oxygen species under control. The virus does this by preventing the activation of a single protein needed for the expression of a variety of detoxifying enzymes. Reactive oxygen species then accumulate, causing cell-killing oxidative stress and inflammation in both infected and uninfected airway cells — a major factor in the damage done by RSV infection.

"The role of oxidative stress has been studied in everything from aging to asthma, but this is really the first study to implicate it in lung inflammation associated with viral infections," said Dr. Antonella Casola, an associate professor at UTMB Health and lead author of a paper on the research, published online March 4 in the "Articles in Press" section of the *American Journal of Respiratory and Critical Care Medicine*. "We've been working on this project for a while — starting in

cells, then moving to animal models and finally getting results in patients — so we're very excited about this paper."

The UTMB Health researchers followed up earlier studies in human cell cultures with experiments that showed a substantial reduction in the expression and activation of antioxidant enzymes in the lungs of RSV-infected mice. Further investigations revealed that mice infected by RSV had much lower levels of a protein called Nrf2 — a "transcription factor" needed to prompt the production of enzymes that clean up reactive oxygen species.

"What was really striking is that Nrf2 is a kind of master switch controlling the machinery of these antioxidant enzymes, and it appears the virus blocks its activity," said UTMB Health professor Dr. Roberto Garofalo, also a lead author on the study. "This is interesting because genetic factors have been shown to be associated with other airway diseases, and the obvious question now is do the children who develop the most severe disease in response to RSV also have an Nrf2 gene that favors a low level of expression of these antioxidant enzymes? Are we seeing a combination of two hits, one from the virus and one from genetics?"

The apparent involvement of Nrf2 also opens an intriguing therapeutic possibility, Garofalo said, because compounds that induce cells to make more of the transcription factor are already in clinical trials as potential cancer therapies. Another possibility is the delivery of short-term genetic therapy via a genetically engineered virus licensed by the National Heart, Lung and Blood Institute.

Any such intervention will have to await further human studies like the one described in the AJRCCM paper. In that part of the investigation, the researchers measured biochemical markers of reactive oxygen species and levels of antioxidant enzymes in nasal samples from 30

infants with RSV infections. The severity of the babies' disease ranged from relatively minor upper respiratory tract infections to full-blown lung disease requiring respiratory support from a ventilator.

"Our findings in patients were very consistent with what we saw in mice, " Garofalo said. "We found a significant increase in markers of oxidative injury and a significant decrease in antioxidant enzyme expression corresponding to the severity of the disease."

Because the study was conducted in a relatively small number of human subjects, Garofalo and Casola plan to conduct larger human investigations under the auspices of UTMB Health's Institute for Translational Research. In future research, they also hope to examine the possible role of other viruses in inhibiting antioxidant enzymes, produce a more detailed profile of virus-induced changes in antioxidant levels and detail the magnitude and type of oxidative damage done to airways by RSV infection.

More information: http://ajrccm.atsjournals.org/articlesinpress.dtl

Provided by University of Texas Medical Branch at Galveston