Weak immune response critical to disease that causes most infant hospitalizations

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The most common cause of infant hospitalization in the United States, respiratory syncytial virus, infects virtually all children by age two. Along with the influenza virus, RSV is a major contributor to the approximately two million infant deaths worldwide caused every year by respiratory infections, according to the World Health Organization. Worse yet, there's no safe and effective RSV vaccine available to prevent severe respiratory infections, and no specific antiviral therapy to treat them.

Normally RSV results only in a cold-like upper respiratory infection. But in some babies, it spreads deep into the lungs, where it prompts coughing, wheezing and extreme difficulty in breathing, a clinical syndrome known as bronchiolitis. In these cases, the child's survival may require immediate medical attention.

For the past four decades, medical science thought it knew how this dangerous condition arose from such a common virus. Scientists blamed an overreaction in the lungs by specific immune-system cells, T lymphocytes (also known as "T cells"), for the most severe symptoms of infection.

But now, researchers at the University of Texas Medical Branch at Galveston (UTMB), the State University of New York at Buffalo, the University of Chile, the Hospital Roberto del Rio in Santiago, Chile, the University of Texas Southwestern Medical Center, Dallas, and MedImmune Inc. of Gaithersburg, Md., have turned that dogma on its

head.

Instead of being caused by too strong an immune response, they've shown that severe RSV infections in the lower respiratory tract actually are associated with an inadequate immune reaction — a characteristic they share with fatal influenza infections, which were also studied by the group. Their findings have major implications for efforts to develop therapies for RSV and perhaps other viral respiratory infections during infancy.

"As part of our studies funded by the UTMB National Heart, Lung and Blood Institute Proteomics Center to study airway inflammation, we compared respiratory secretions from RSV-infected and influenza-infected babies, looking for proteins and cytokines — immune signaling molecules — made by T cells, and we saw no evidence that T cells had been activated in the RSV babies," said UTMB professor Roberto Garofalo, a senior author of a paper on the research scheduled to appear in the April 15 issue of the Journal of Infectious Diseases. "In fact, irrespective of RSV or influenza infection, the cytokines we found in these infants were mostly those made by other types of cells of the lung, such as macrophages or epithelial cells," Garofalo added.

Garofalo and his colleagues (including fellow senior author Robert Welliver of the State University of New York at Buffalo and UTMB postdoctoral research fellow Yashoda Hosakote) then put this data together with postmortem lung samples from autopsies of infant victims of severe RSV and influenza in Chile. (Although RSV causes extensive serious illness and a significant drain on medical resources in the United States, the widespread availability of advanced respiratory therapy makes U.S. RSV fatalities rare.) Analysis of the lung samples showed high concentrations of RSV and inflammatory signaling molecules associated with infection, but no sign of T-cell activity.

"This significantly changes the way we look at how we want to intervene in terms of therapy," Garofalo said. "We all agree that killing the virus with anti-viral drugs, which we still don't have, is important. But it looks like we also need to find a way to control unwanted inflammation and boost the disease-fighting T-cell response."

Garofalo attributed the long-lived but mistaken "hyperactive T-cell" explanation for severe RSV to a "bias in the literature" influenced by studies of infections that occurred in infants who had been given a flawed experimental RSV vaccine in the mid-1960s. Instead of preventing RSV infections, that vaccine actually made them worse, resulting in the deaths of two children in 1967.

"I think there was pretty strong evidence of increased T-cell response in the post-vaccine infections, and people started to think that even the natural primary infections of unimmunized babies had these characteristics, too," Garofalo said.

Source: University of Texas Medical Branch at Galveston