Study shows important role gut microbes play in airway health in persons with cystic fibrosis

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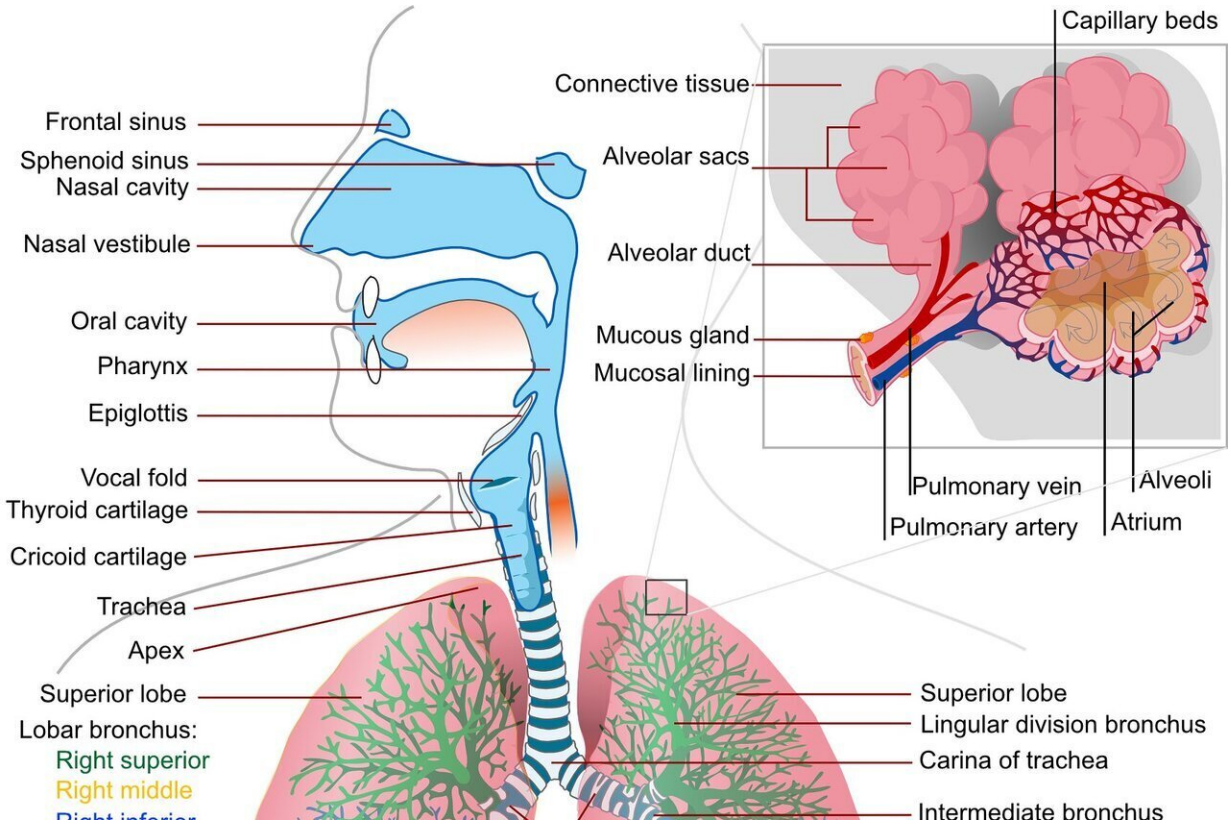

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Findings from a new study conducted by a team of researchers at Dartmouth's Geisel School of Medicine and published in the journal *mBio* reflect the important role that the gut microbiome (communities of bacteria) plays in the airway health of persons with cystic fibrosis.

Cystic fibrosis is an inherited disease that causes sticky, thick mucus to build up in the lungs and other organs, causing persistent infections that can be deadly. Until relatively recently, CF microbiology research has largely been focused on microorganisms in the lungs since most CF-related deaths have been due to respiratory complications.

But interest in the CF gut microbiome and its influence on the health of organs like the lungs has grown as the role of the gut microbiome in broader health outcomes has become more apparent.

For George O'Toole, Ph.D., and his colleagues at the Dartmouth Cystic Fibrosis Research Center(DartCF), the journey to better understand the gut-lung connection began more than 10 years ago, as part of a collaboration with physician-scientist Juliette Madan, MD, MS, who studies children with CF at Dartmouth Hitchcock Medical Center (DHMC).

"One of the key observations that Dr. Madan made early on was that, surprisingly, the best predictor of how a kid's airway would function actually turned out to be the microbes in their gut rather than the microbes in their airway," explains O'Toole, the Elmer R. Pfefferkorn, Ph.D., Professor of Microbiology and Immunology at Geisel and anchor author on the study. "We also had noticed that kids with CF were depleted for Bacteroides, a microbe known to be important in programming gut function and the immune system early in life."

The findings prompted them to do some experiments in which they were able to show that secreted products from these Bacteroides strains could reduce inflammation in gut-derived cell lines grown in the lab. In further experiments, they were able to narrow down the molecule that was important for that process—a short-chain fatty acid known as propionate.

To reinforce their hypothesis, the team did experiments in mice with the same CF mutation as humans which showed that those mice that had Bacteroides introduced into their guts had less inflammation in their blood and airways after being exposed to Pseudomonas aeruginosa—a common bacterium in CF infections—than other similar mice that were not given Bacteroides. Importantly, a Bacteroides variant that could not make propionate could not reduce inflammation.

"We think this establishes the idea that changes in the gut are causing a reprogramming of the immune system in such a way that the body isn't as sensitive to subsequent airway infections, so you don't have as much disease burden," says O'Toole. "The other exciting finding is that this actually provides, we think, a proof of concept that probiotics could be beneficial to kids with CF, so it could have important implications for treatments."

O'Toole is quick to credit his colleagues at Geisel and at DHMC for their contributions to the study, which in addition to Madan's clinic involved three labs in the CF Center and utilized microbiology experiments, tissue culture work, and animal studies. The Bliska, Cramer, and Ross groups at Geisel contributed to this study.

"There were a lot of moving parts to this project, so we needed a lot of help to get it all done," he says. "We're grateful, not only for the expertise that people provided but also for their willingness to participate. The culture of collaboration is core at DartCF, I think, to the

success of our group and this is just a nice example of that."

More information: Courtney E. Price et al, Intestinal Bacteroides modulates inflammation, systemic cytokines, and microbial ecology via propionate in a mouse model of cystic fibrosis, *mBio* (2024). DOI: 10.1128/mbio.03144-23

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