Bacterial 'sabotage' handicaps ability to resolve devastating lung inflammation

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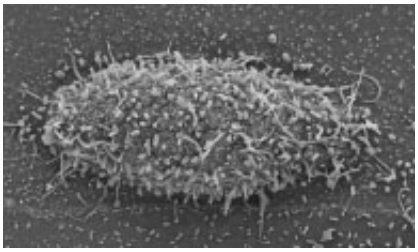


A human neutrophil migrating through an epithelial cell junction. Credit: Becca Flitter and Donna Stoltz

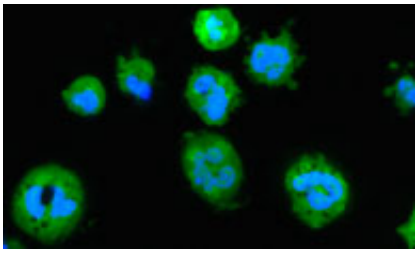
The chronic lung inflammation that is a hallmark of cystic fibrosis, has, for the first time, been linked to a new class of bacterial enzymes that hijack the patient's immune response and prevent the body from calling off runaway inflammation, according to a laboratory investigation led by the University of Pittsburgh School of Medicine.

The discovery, published today by the *Proceedings of the National Academy of Sciences*, gives scientists two avenues to explore for the creation of therapies that could interrupt or correct this interference by the opportunistic bacterium *Pseudomonas aeruginosa*, which disproportionately infects people with cystic fibrosis.

"There are about 30,000 patients in the U.S. with cystic fibrosis, and hundreds of thousands more with other chronic lung diseases. Once

these diseases progress to the point that the patient is chronically infected with *P. aeruginosa*, current antimicrobial therapies are no longer effective and there are very few treatment options left," said Jennifer M. Bomberger, Ph.D., assistant professor in Pitt's Department of Microbiology & Molecular Genetics and senior author on the study. "Lung damage from these chronic *P. aeruginosa* infections, coupled with a robust but unproductive inflammatory response to the infection, will eventually lead to respiratory failure in the patient and the need for a lung transplant."

Cystic fibrosis is caused by a genetic mutation that makes it difficult for patients to clear infections, allowing microorganisms to repeatedly infect the respiratory tract. By the time they reach adulthood, most cystic fibrosis patients are chronically infected with *P. aeruginosa* because this particular bacterium has an exceptional ability to outcompete other microorganisms and establish a stronghold in the lungs.



Human neutrophils isolated from peripheral blood. Multi-lobed nuclei are stained in blue and the cytoplasm of living cells are stained in green. Credit: Becca Flitter

Aiding its ability to outfight other infections, *P. aeruginosa* thrives when the body creates an inflammatory response aimed at isolating foreign invaders and attracting white blood cells to fight them. The body's own

inflammatory response to fight infection is a major part of what actually damages a cystic fibrosis patient's lungs to the point that they no longer function.

Bomberger's team, in collaboration with Dean Madden, Ph.D., at the Geisel School of Medicine at Dartmouth, discovered that *P. aeruginosa* perpetuates inflammation by secreting an enzyme called Cif that sabotages the body's ability to make a key molecule called a "pro-resolving lipid mediator" and put a stop to the inflammatory response it started.

The scientists confirmed this mechanism by analyzing secretions drawn from the lungs of cystic fibrosis patients seen at Children's Hospital of Pittsburgh of UPMC and linking their findings to patient records. Patients with higher Cif levels in their lung secretions had reduced biological signaling to stop inflammation and increased levels of IL-8, a marker for inflammation. Increased Cif levels also correlated with reduced lung function, which leads to disease progression in patients.

Previous studies in mice indicated that artificially boosting the levels of the pro-resolving lipid mediator reduces the inflammatory response and promotes clearance of *P. aeruginosa* in a pneumonia model. Bomberger and Madden, in collaboration with colleagues at the University of California, Davis, are exploring an alternative strategy to inhibit Cif activity, stopping the problem before it begins.

"It will be key to devise a way to remove *P. aeruginosa*'s ability to capitalize on the body's natural inflammatory response, without eliminating that response," said Bomberger. "Inflammation is happening for a reason—to clear infection. We just need it to temper the response when it is not effectively doing its job or is no longer needed."

More information: Pseudomonas aeruginosa sabotages the generation

of host proresolving lipid mediators, www.pnas.org/cgi/doi/10.1073/pnas.1610242114

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