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Immune-System Cells May Promote Chronic Infections in Cystic Fibrosis

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DENVER — Cells sent to fight infections in the lungs of cystic fibrosis patients actually enhance the development of permanent bacterial infections, according to researchers at National Jewish Medical and Research Center. Infections with the bacteria *Pseudomonas* are a major cause of sickness and death in cystic fibrosis patients. The findings, published in the June issue of *Infection and Immunity*, suggest new treatment strategies for patients with cystic fibrosis.

"*Pseudomonas* can use the remnants of dead white blood cells to develop a protective biofilm, which helps the bacteria establish a permanent infection," said National Jewish pulmonologist Jerry Nick, MD, senior author on the paper. "So, ironically, the very cells sent to fight infection may contribute to our inability to eradicate the *Pseudomonas* infection in cystic fibrosis patients."

Cystic fibrosis (CF) is a genetic disorder affecting about 30,000 people in the United States, and is the most common genetic disorder among Caucasian people. People with CF produce abnormal mucus that obstructs the airways and leads to chronic lung infections. The disease is fatal, but life expectancy for patients has increased dramatically in recent years, from 14 years in the mid-1980s to 35 years today. National Jewish has one of the largest adult cystic fibrosis clinics in the nation.

Pseudomonas aeruginosa is widespread in the environment and repeatedly infects most CF patients. Aggressive treatment with antibiotics successfully fights most initial infections. Over time, however, *P. aeruginosa* infections often become permanent; more than 80% of adults with CF are chronically infected with *P. aeruginosa*. The chronic infection and inflammation associated with *P. aeruginosa* accelerate damage to the lungs, leading ultimately to respiratory failure and death.

Researchers believe that *Pseudomonas* establishes a chronic infection in the airway of CF patients by creating a biofilm, a three-dimensional structure composed of bacteria encased in an extracellular matrix. Other examples of bacterial biofilms include the plaque that forms on teeth and the "slime" that forms on rocks in a stream. Bacteria in biofilms take on distinctly different characteristics from those floating free in a "planktonic" form. Once *Pseudomonas* develops a biofilm it becomes significantly more resistant to both antibiotics and the immune system.

The immune system attempts to eradicate *Pseudomonas* by sending in massive numbers of cells called neutrophils. The short-lived cells die after a short time and cellular debris accumulate in the airway of CF patients.

In a series of experiments with neutrophils and *Pseudomonas*, Dr. Nick and his colleagues found that the contents of dead neutrophils, particularly DNA and a filament called actin, provide a scaffolding for *Pseudomonas* to construct a biofilm. In the presence of neutrophils, the development of *P. aeruginosa* biofilms increased by two and a half to three times compared to *P. aeruginosa* cultures without neutrophils.

"As the neutrophils die and fall apart, their contents provide an excellent substrate for the development of biofilms," said Nick. "In turn these biofilms allow *Pseudomonas* to survive despite intense medical treatment."

The researchers also found that an enzyme known as DNase, which breaks apart strands of DNA, inhibits the development of biofilms. DNase is already used to break up the thick mucus that develops in the lungs of CF patients. Nick believes that it might also be useful in preventing the development of *Pseudomonas* biofilms.

"Once the biofilm develops, *Pseudomonas* infections become almost impossible to eradicate," said Nick. "If we could prevent the development of these biofilms, with DNase or other treatments, we could possibly prevent chronic infections, reduce damage to the lungs of cystic fibrosis patients, and extend their lives."

Dr. Nick and his group are now using genomic analysis to better understand how the presence of neutrophils changes the response of *Pseudomonas*. They hope to discover mechanisms *Pseudomonas* uses to avoid eradication by the immune system, which could suggest new therapies to prevent *Pseudomonas* infections from developing in CF patients.

National Jewish Health is the leading respiratory hospital in the nation. Founded 120 years ago as a nonprofit hospital, National Jewish Health today is the only facility in the world dedicated exclusively to groundbreaking medical research and treatment of patients with respiratory, cardiac, immune and related disorders. Patients and families come to National Jewish Health from around the world to receive cutting-edge, comprehensive, coordinated care. To learn more, visit the media resources page.

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