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Cystic-Fibrosis Treatment Hope Emerges

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University of Pennsylvania Medical School researchers have discovered that a bacterial enzyme may play a role in lung damage in cystic-fibrosis patients, a finding that eventually could lead to a new treatment.

The researchers from Penn's physiology department reported in a recent edition of the Proceedings of the National Academy of Sciences that the enzyme, produced by respiratory-tract bacteria, further helps to shut down a protein that is defective in cystic-fibrosis patients.

The findings about the effects of the enzyme, sphingomyelinase, or SMase, might lead to a new treatment to improve patients' length and quality of life, if the researchers find an inhibitor for the enzyme. Such a treatment could potentially hold benefits for noncystic fibrosis patients with lung-damaging infections as well.

"We hope that application of an inhibitor, in conjunction with effective antibiotic treatment and supportive measures, will provide a significant therapeutic improvement," researcher Dr. Zhe Lu, a physiology professor at Penn, said.

The research is only at an early, conceptual stage of development now, with support from the National Institute of General Medical Sciences, part of the National Institutes of Health. No drug companies are involved at this point.

Some 70,000 adults and children world-wide, including 30,000 in the U.S., have cystic fibrosis, an inherited chronic disease that affects the lungs and digestive system, according to the Cystic Fibrosis Foundation. The foundation, which sponsors research on the disease and cites a drug-development pipeline with more than 25 therapy candidates, including gene and protein-repair therapy, wasn't involved with the Penn study.

A defective gene and the protein it produces tell the body to make a very thick mucus that congests the lungs, leading to life-threatening infections. The mucus also blocks the pancreas, making it difficult for the body to absorb food, the foundation says. Advances in treatments, including antibiotic therapy, have increased the median life span of cystic-fibrosis patients to nearly age 37 today. In 1955, children with the disease in the U.S. usually didn't survive long enough to attend elementary school, the foundation says. Current treatments include oral, intravenous and inhaled antibiotics and inhaled medications to treat symptoms, among other measures. **Genentech** Inc.'s inhaled Pulmozyme helps thin the mucus by acting on DNA left by infection-fighting white blood cells, and **Novartis** AG makes the inhaled antibiotic TOBI for cystic fibrosis patients.

"Obstruction by mucus predisposes CF patients to chronic infections and inflammation, which become gradually harder to control and eventually fatal," the Penn researchers noted in the scientific journal. Dr. Lu conducted the research with Yajamana Ramu and Yanping Xu.

In healthy people, a protein called cystic-fibrosis conductance transmembrane regulator, or CFTR, allows chloride ions to move in and out of cells that line the lungs, which helps keep the lungs clear.

The protein is defective in cystic-fibrosis patients, disturbing the salt balance in the body and making what should be a thin layer of mucus instead very thick, according to the Cystic Fibrosis Foundation. The Penn researchers, who conducted their work in a lab, reported that the SMase enzyme produced by infecting bacteria further suppresses the defective protein.

These findings, combined with other research not previously tied to cystic fibrosis, "compellingly suggest that SMases play a critical role" in the pathogenesis, or development, of lung injuries from bacterial infection and inflammation in cystic fibrosis patients, according to the study. This may help explain why the severity of lung damage in cystic-fibrosis patients doesn't correlate well with the type of genetic mutation that causes the disease.

The research implies that the SMase enzyme breaks down lipids on cells lining the airways, which would further suppress function of the defective protein. The Penn researchers also noted that important studies not previously linked to cystic fibrosis have established that the products of lipid breakdown trigger inflammation and cell death.

Although correcting the genetic defects remains the ideal cure for cystic fibrosis, application of medicines against various bacterial "virulence factors" like the SMase enzyme, in conjunction with other effective measures, might be a viable approach to improving length and quality of life, the paper said.

The researchers demonstrated the disruptive action of the enzyme in engineered frog egg cells. They plan next to develop chemical inhibitors to target the SMase and test them in laboratory animals.

It's too early to say where the research will lead, according to Bert Shapiro, an NIH program director overseeing the grant. The findings, he said, suggest the possibility of approaches that rather than trying to repair the genetic defect underlying cystic fibrosis, instead would seek to "ameliorate the effects of the genetic defect."

Christopher Penland, director of research at the Cystic Fibrosis Foundation, said the Penn researchers' findings about the enzyme's effects on CFTR are interesting, could have implications for cystic fibrosis and may be important for other diseases in which infections damage the lung. He questioned, however, whether targeting the enzyme would make a significant difference to most cystic-fibrosis patients.

Mr. Penland suggested that focusing on antibiotics to target the bacteria that releases the enzyme may make more sense, and noted that antibiotics already play an important role in treating cystic-fibrosis patients. Bacteria release a plethora of "virulence factors" that help the infection cause damage or illness, Mr. Penland noted, voicing skepticism about targeting just one of them.

"We don't really know the significance of this one virulence factor in relation to all the others," Mr. Penland said. "I'm not saying it's not important, but I don't know where it stands in a hierarchy of virulence factors that have been released."

Targeting the enzyme may be important in helping cystic-fibrosis patients with some CFTR activity to avoid further destruction of lung function, Mr. Penland said. "A vast majority" have little or no CFTR

activity from birth because of their particular gene mutation, however, so it's hard to say how significant the enzyme is in their disease, he said. For cystic-fibrosis patients with some CFTR activity, he said, the finding could be very important.

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