Scientists find gene that modifies severity of cystic fibrosis lung disease

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Researchers have discovered a gene that modifies the severity of lung disease in people with the lethal genetic condition, cystic fibrosis, pointing to possible new targets for treatment, according to a new study in *Nature*.

Deleting this gene in mice confirmed its role in regulating inflammation and disease. After the animals' airways were infected with the bacterium that is a major cause of lung infection in cystic fibrosis, the mice experienced less inflammation and disease, said senior investigator Christopher Karp M.D., director of Molecular Immunology at Cincinnati Children's Hospital Medical Center.

Posted online by the journal Feb. 25 in advance of publication, it the first published study to use a genome-wide approach to look for genes that modify the severity of cystic fibrosis lung disease.

After analyzing the genetic makeup of nearly 3,000 people from two groups of cystic fibrosis patients - one from Johns Hopkins University and the other from the University of North Carolina and Case Western Reserve University - the researchers found that small genetic differences in a gene called IFRD1 correlate with lung disease severity. While probing how the gene might alter the disease's course, researchers discovered the protein encoded by IFRD1 is particularly abundant in a type of white blood cell called neutrophils, and that it regulates their function.

Part of the immune system, neutrophils are known to cause inflammatory damage to the airways of people with cystic fibrosis.

"Neutrophils appear to be particularly bad actors in cystic fibrosis," said Dr. Karp. "They are important to the immune system's response to bacterial infection. In cystic fibrosis, however, neutrophilic airway inflammation is dysregulated, eventually destroying the lung."

Although it's been known for 20 years that cystic fibrosis is caused by mutations in the CFTR gene, the molecular mechanisms that link these mutations to the generation of lung disease still remain unclear. Increasingly evident in recent years is that variations in other genes also play a role in controlling cystic fibrosis lung disease severity.

Prior to the current study, IFRD1 wasn't on the radar screen of researchers looking for genetic modifiers of disease severity, although the gene had been linked to stress responses in muscle and other tissues, Dr. Karp said.

To further explore IFRD1's role in the disease process, the researchers studied mice in which the IFRD1 gene was knocked out. Researchers infected the airways of these animals with Pseudomonas aeruginosa, a common cause of airway infection in cystic fibrosis. The absence of IFRD1 resulted in delayed clearance of bacteria from the mice's airways, but also resulted in less inflammation and disease.

Although deleting IFRD1 blunted the inflammatory response of neutrophils to infection, it did not appear to affect other blood cells or compromise the overall functioning of the immune system. Also unaffected was the ability of mice to make blood cells, including neutrophils. Bone marrow transplantation studies in mice revealed that IFRD1 expression in blood cells, or the lack thereof, was central to these findings.

Researchers also studied blood samples from healthy human volunteers to verify the impact of genetic differences in IFRD1 on neutrophil regulation. They found that the same IFRD1 variations that modified cystic fibrosis lung disease severity also altered neutrophil function in the healthy volunteers.

In a finding that may be the basis for novel approaches to treating cystic fibrosis, the investigators also determined that IFRD1's regulation of neutrophil function depends on its interaction with histone deacetylases - enzymes important for regulating gene transcription. Additional research is needed to better understand this interaction before its potential role for treatment is known.

"It's possible that IFRD1 itself could become a target for treatment, but right now it's a signpost to pathways for further study," Dr. Karp said. "We want to find out what other genes and proteins IFRD1 interacts with, and how this is connected to inflammation in cystic fibrosis lung disease."

According to the National Cystic Fibrosis Foundation, cystic fibrosis is an inherited chronic disease that affects the lungs and digestive systems of about 30,000 children and adults in the United States and 70,000 worldwide. The defect in the CFTR gene causes the body to produce unusually thick, sticky mucus that clogs the lungs and leads to life-threatening lung infections. It also obstructs the pancreas and stops natural enzymes from helping the body break down and absorb food.

In the 1950s, few children with cystic fibrosis lived to attend elementary school. Today, advances in research and medical treatments have allowed people to live into their 30s or 40s. Despite these advances, the norm remains an ongoing decline in pulmonary function.

Source: Cincinnati Children's Hospital Medical Center