Immune cells play surprising role in cystic fibrosis lung damage

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Immune cells once thought to be innocent bystanders in cystic fibrosis may hold the key to stopping patients' fatal lung disease. New findings from the Stanford University School of Medicine and Lucile Packard Children's Hospital show that white blood cells called neutrophils respond strongly to conflicting signals from cystic fibrosis patients' lungs, setting up a molecular fracas that may explain the patients' severe lung damage.

"Cystic fibrosis patients have a problem with turning down the inflammatory response in the lungs," said senior study author Rabindra Tirouvanziam, PhD, an instructor in pediatric pulmonary medicine. "We've found that patients' neutrophils become kind of schizophrenic, doing a number of things that are opposite to the textbook view of neutrophils' role."

The research, which will be published online March 23 in the Proceedings of the National Academy of Sciences, opens up new targets for cystic fibrosis treatment, Tirouvanziam said.

Cystic fibrosis is a genetic disease of the lungs and digestive system that affects about 30,000 people in the United States. Patients used to die in childhood, but the life expectancy for a child born today with cystic fibrosis is now 50 to 60 years. Although modern medications and dietary treatments do a good job of controlling the digestive aspects of the disease, patients still suffer serious lung problems. Thick, sticky mucus builds up in their lungs, and chronic inflammation and bacterial

infections lead to the breakdown of lung tissue.

For years, scientists believed that cystic fibrosis patients' lung problems started when bacteria became trapped in the excess mucus in their lungs. Neutrophils showed up at the lungs in response to the invasive bacteria, the thinking went. Neutrophils are supposed to engulf and destroy bacteria, but something went wrong and the neutrophils quickly died in the lung, releasing tissue-destroying enzymes, scientists thought.

"This paradigm makes sense in a superficial way, but it has very little to do with clinical reality," Tirouvanziam said. Careful clinical testing in infants with cystic fibrosis has shown that lung inflammation with neutrophils occurs even in the absence of detectable infection. And Tirouvanziam's earlier research showed the immune cells stay alive in the lung for quite a while after they arrive.

So what are the live neutrophils doing in patients' lungs? The new findings surprised Tirouvanziam's team. After collecting fresh neutrophils from cystic fibrosis patients' sputum and analyzing them with fluorescence-activated cell sorting, the team discovered that signals from the patients' lung tissue were reprogramming live neutrophils with conflicting messages. The first set of signals switches on what Tirouvanziam calls "an ancient happiness pathway" — a chain of commands that tell the neutrophils that nutrients are plentiful, and that it's a good time to translate the cell's library of genes into new protein. The second pathway is a cellular alarm system associated with inflammation and stress.

"They're receiving a lot of signals at same time, and we think the happiness signals are messing them up completely," Tirouvanziam said.

His team now suspects the inappropriate activation of the "happiness signal" — the molecular target of rapamycin, or mTOR, cell signaling

pathway — may trigger neutrophils to release large quantities of human neutrophil elastase, the enzyme that destroys the elastic fiber of lung tissue. In healthy individuals, neutrophils never release destructive human neutrophil elastase into nearby tissue.

Understanding the sequence of events that release the tissue-chewing enzyme in cystic fibrosis is important, Tirouvanziam said, because it could help researchers find new disease therapies. Drugs now given to improve patients' lung function target symptoms such as difficulty breathing, but don't do anything to alter neutrophils' behavior. Tirouvanziam hopes that will soon change.

Source: Stanford University Medical Center (news : web)