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Gene network restores CF protein function

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Researchers at the University of Iowa Carver College of Medicine have discovered a genetic process that can restore function to a defective protein, which is the most common cause of cystic fibrosis (CF).

Cystic fibrosis is an inherited disease caused by mutations in a gene that adversely affect its protein product. In its correct form and cellular location, this protein, cystic fibrosis transmembrane conductance regulator (CFTR), functions as a channel for ions to move across cell membranes, and is critical for maintaining cellular salt and water balance.

The most common CF-causing genetic mutation, known as delta F508, disrupts the process whereby the CFTR protein is folded into its correct shape and shipped to the membranes of cells that line the airways and other organs. Most of the defective CFTR protein is misprocessed and gets degraded. The lack of normal CFTR ion channels leads to numerous problems, including lung infection and inflammation, the major causes of disease and death in cystic fibrosis.

Despite its importance, how the CFTR protein is made and delivered to cell membranes in its functioning form is not well understood. The UI team led by Paul McCray, M.D., professor of pediatrics and microbiology with UI Health Care and the Roy J. Carver Chair in Pulmonary Research and Vice Chair for Research in Pediatrics, investigated the role of microRNAs -- small non-coding stretches of RNA -- in regulating expression of CFTR.

In their research, McCray and colleagues discovered that one particular microRNA, called miR-138, helps control the biosynthesis of CFTR by regulating a network of genes involved in the production and processing of the protein. The study, published online the week of July 30 in the Proceedings of the National Academy of Sciences (*PNAS*) Early Edition, shows that that miR-138 acts on the other genes to orchestrate a cellular program that increases production of CFTR and increases the amount of the protein that is transported to the cell membrane where it functions as an ion channel.

"We first wanted to determine how this gene network impacts the CFTR protein produced in people who don't have cystic fibrosis," says lead author Shyam Ramachandran, Ph.D.. "We identified a novel regulatory circuit, but then asked ourselves if any of this affected the mutant protein."

Surprisingly, the researchers found that when the gene network was activated by miR-138, it not only increased the amount of the mutated protein, but also partially restored the protein's function.

By manipulating the microRNA network, the UI team was able to change the fate of the misfolded CFTR from being degraded in the cell to functioning as an ion channel in the cell membrane.

"This was a very surprising finding," Ramachandran says. "It unexpectedly helps rescue the function of the mutant protein."

Because most people with CF have one or two copies of the delta F508 mutation, interventions that overcome the CFTR protein-processing problems caused by this mutation might have important implications for new ways of treating CF.

"In the field of CF therapeutics there's great interest in identifying ways

to restore the function of this misprocessed protein," McCray says. "We were very surprised that manipulating this microRNA regulated gene network had this rescuing effect. This opens up a new avenue for the development of CF therapies."

Provided by University of Iowa