An 'unconventional' path to correcting cystic fibrosis

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Researchers have identified an unconventional path that may correct the defect underlying cystic fibrosis, according to a report in the September 2nd issue of the journal *Cell*. This new treatment dramatically extends the lives of mice carrying the disease-associated mutation.

Cystic Fibrosis is caused by a mutation in a gene responsible for the transport of ions across cell membranes. This gene encodes a protein channel, called the cystic fibrosis transmembrane conductance regulator or CFTR, that is normally found on the surfaces of cells lining the airway and intestine. In patients with the disease, the channels don't make it from inside cells to their surfaces along the standard path. As a result ions and fluids fail to move in and out of cells as they should, causing mucus build-up and chronic lung infections.

The new study identifies an unexpected way to send the mutant proteins to the surface where they can restore ion transport. A protein normally localized to membranes inside cells, called GRASP65, is co-opted to escort mutant CFTR channels to the cell surface by following a "detour" route.

"Many have searched for the so-called CFTR correctors that can aid the surface expression of mutant CFTR through conventional trafficking," said Min Goo Lee, senior author of this study. Some molecules have shown promise in the laboratory, but none have led to the development of commercially available therapies so far.

"In this study, we discovered that CFTR surface trafficking can be rescued by an alternative route that former investigators had not expected."

Mice carrying the cystic fibrosis-linked mutation typically live for less than 3 months. In those that produce higher levels of GRASP65, only 1 out of 20 of the CFTR-mutant mice died in those first 3 months. Importantly, the transport of ions by CFTR in the animals' intestinal lining was also restored to more than 60 percent of the level seen in normal, healthy mice.

The findings may ultimately have real treatment implications for those with cystic fibrosis or other genetic diseases stemming from problems with the transport of proteins that are folded incorrectly.

"We made a small step in understanding cell biology," Lee says. "We hope this could turn out to be a giant leap in future clinical medicine, especially for treating human genetic diseases."

In the U.S., cystic fibrosis is the most common deadly inherited disorder, according to PubMed Health. One in 29 Caucasian Americans carry the cystic fibrosis mutation, and those with two copies of the mutant gene will develop the disease.

Provided by Cell Press

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