Scientists find protein 'talks' to wrong partners in cystic fibrosis

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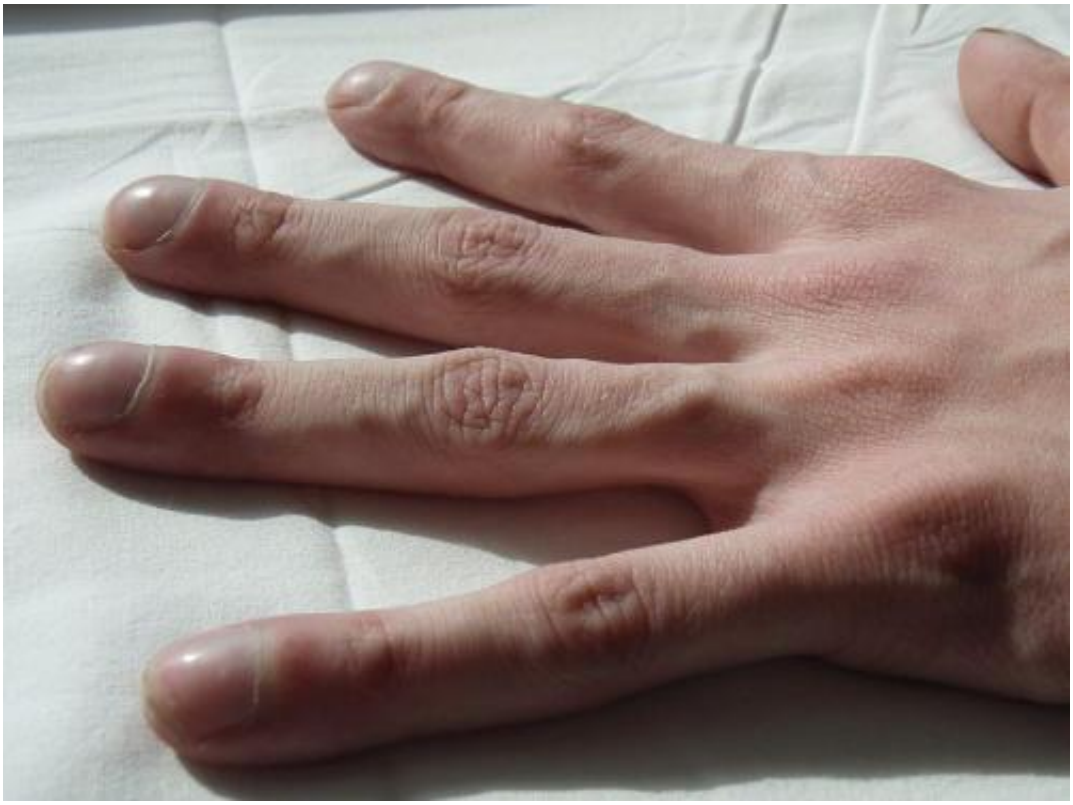

"Clubbing" of the fingers is a classic features of Cystic Fibrosis, although not present in many patients. Credit: Jerry Nick, M.D./ Wikipedia

Scientists at The Scripps Research Institute (TSRI) have found evidence that a mutant protein responsible for most cases of cystic fibrosis is so busy "talking" to the wrong cellular neighbors that it cannot function normally and is prematurely degraded.

By removing this chatter, researchers partially restored the protein's normal function. The findings suggest that therapies could one day treat the root cause of cystic fibrosis, not just the symptoms.

"The proteins and the interactions we've identified really fuel the pipeline for new drug targets to treat cystic fibrosis," said Casimir Bamberger, a research associate in the lab of TSRI Professor John R. Yates and co-first author of the new study with TSRI Staff Scientist Sandra Pankow.

The new study was published November 30, 2015, online ahead of print by the journal *Nature*.

The Root Cause of Cystic Fibrosis

People with cystic fibrosis suffer from persistent infections and mucus build-up in the lungs. While there are treatments to deal with the symptoms—such as antibiotics for infections—there are no therapies that fully restore lung function.

Bamberger, Pankow and their colleagues believe a better understanding of a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) could be the key to developing new treatments. Most patients with cystic fibrosis have a mutation, called ΔF508, in the gene that encodes CFTR, keeping CFTR from folding properly and being processed correctly in cells.

Interestingly, previous studies showed that mutant CFTR regains normal functions at low temperatures.

"Freezing people is not a practical treatment, of course, but this showed us mutant CFTR can be functional," said Pankow. "So the idea behind our new study was to find new drug candidates that could mimic what

we see at low temperatures."

Finding Drug Targets

In the new study, the researchers analyzed cell samples with a tool called Co-Purifying Protein Identification Technology (CoPIT), a new method they developed to identify proteins and analyze data. With CoPIT, they identified almost every protein CFTR interacted with—even tracking the secondary and tertiary protein interactions.

The results were surprising. While it was thought that most mutant proteins just lack one or two crucial interactions, the ΔF508 CFTR mutant had acquired an entirely new "disease-specific" interaction network.

"Three hundred proteins changed their level of interaction, and an additional 200 proteins interacted with the mutated CFTR," said Pankow. "It's like the wrong people are talking to the mutated CFTR all the time."

The researchers narrowed these mutant protein interactions to just eight key disruptive proteins. The team then used a gene silencing approach to remove or "knock down" those proteins and block the interaction of these proteins with ΔF508 CFTR. They found that without the additional interactions, ΔF508 CFTR partially returned to normal function.

Pankow and Bamberger said the next step in this research is to look for small molecule drug candidates that could target these disruptive proteins. The researchers have also released their raw CoPIT data publicly so other scientists can explore the clinical implications of CFTR interactions.

More information: ΔF508 CFTR interactome remodeling promotes

rescue of Cystic Fibrosis, *Nature*, DOI: 10.1038/nature15729