Cystic fibrosis gene typo is a double whammy

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An imbalance of salt and water in patients with cystic fibrosis makes their lungs clog up with sticky mucus that is prone to infection. The cause of the offending imbalance is a well-known genetic error, one that blocks the molecular expressway for tiny chloride ions to move across the surface of the lungs.

But how does that same gene mutation upset a parallel roadway controlling the flow of the other component of salt, sodium ions? Now, researchers at the University of North Carolina at Chapel Hill School of Medicine have found the answer, demonstrating that the gene mutated in cystic fibrosis not only controls traffic on the chloride highway, but also keeps the sodium highway from being overused.

The finding suggests that the infamous mutation – in a gene called CFTR – is a double whammy, affecting the flow of two different ions that are important to keep the mucus on the surfaces of the airways hydrated. Clarifying this link between the genetic defect and the thick sticky mucus in cystic fibrosis lungs could help researchers develop better therapies.

"It is very important to slow down this sodium channel when it is overactive before it leads to dehydration of the mucus in patient airways," said Martina Gentzsch, PhD, assistant professor of cell and developmental biology at UNC and lead author of a study published Oct. 15 in the *Journal of Biological Chemistry*. "If we can understand the mechanism of how CFTR does that, it might give us a new approach to treat the disease."

Cystic fibrosis is one of the most common genetic diseases in Caucasians, affecting approximately 1 in 3500 births in the United States. It is caused by a defect in the gene that codes for a protein called cystic fibrosis transmembrane conductance regulator or CFTR. Cystic fibrosis patients with the most severe disease have very little of the CFTR protein, and this affects the way chloride ions move across many tissues in the body. A number of scientists have hypothesized that CFTR also controls the movement of other ions, such as through the epithelial sodium channel or ENaC.

This channel has been shown to be overactive in transporting sodium ions in the airways of cystic fibrosis patients, so Gentzsch and her colleagues set out to determine why. First, they looked at the effects of the CFTR gene on the sodium channel in xenopus oocytes, commonly known as frog eggs. They found that when the CFTR gene was intact, the sodium channel was kept in check.

The researchers followed up with a number of biochemical and electrophysiological experiments and showed that the chloride channel and the sodium channels interact. Gentzsch and her colleagues also confirmed their results in human primary airway epithelial cells from healthy volunteers and patients with cystic fibrosis, showing that the sodium channel was in fact more active when there was no functional CFTR.

Now that they know that the chloride channel can actually influence the function of the sodium channel, Gentzsch is trying to find out how.

"We don't know if it is doing this by basically acting like a roadblock, physically interfering with the proteases that activate ENaC, or if it is doing it by some indirect means," said Gentzsch. "That is what we are investigating at the moment, so there are a lot of more questions to be answered."

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