

Defective signaling pathway sheds light on cystic fibrosis

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In a study that could lead to new therapeutic targets for patients with the cystic fibrosis, a research team from the University of California, San Diego School of Medicine has identified a defective signaling pathway that contributes to disease severity. In the study, published in the journal *Nature Medicine*, the researchers report that defective signaling for a protein called the peroxisome proliferator-activated receptor- γ (PPAR- γ) accounts for a portion of disease symptoms in cystic fibrosis, and that correction of the defective pathway reduces symptoms of the disease in mice.

In the paper published in the February 14 edition of the journal, lead investigator Gregory Harmon, MD, study supervisor Christopher Glass, MD, PhD, professor of cellular and molecular medicine, and colleagues show that both mice and cells from patients with [cystic fibrosis](#) have a defect in signaling for PPAR- γ , as a result of reduced levels of prostaglandins that activate the receptor.

Cystic fibrosis is the most common, potentially lethal genetic disease among whites, occurring in one in 3,000 births. The disease is a multisystem condition that leads to progressive lung failure, pancreatic failure and gastrointestinal obstruction, or blockage.

"Cystic fibrosis results from a genetic mutation in a channel, or membrane pore, that facilitates the transport of chloride and bicarbonate electrolytes from inside the cell to the spaces outside the cell," said Harmon. "Loss of the cystic fibrosis pore channel results in

inflammation and mucus accumulation. It also results in dehydration of the cell surfaces that make up the lining spaces inside the lungs and other affected organs, such as the intestinal tract."

Exactly how the process occurs has been a matter of intense scientific scrutiny; yet despite numerous therapeutic advances, individuals with the disease continue to endure a shortened lifespan. "Someone born in the 1990s with cystic fibrosis is expected to live to an age of around 40," Harmon added.

Working with isolated cells from mice and human cell lines from patients with the disease, Harmon identified that multiple genes affected by PPAR- γ were reduced in cystic fibrosis. When the researchers treated mice with cystic fibrosis with the drug rosiglitazone, a thiazolidinedione drug that binds and activates PPAR- γ , gene expression was largely normalized and survival improved. The drugs also corrected part of the inflammatory process in the tissue. Deleting the PPAR- γ [protein](#) in the intestine of mice worsened the disease, leading to mucus accumulation in the intestine. Additionally, the researchers found that activating PPAR- γ could increase bicarbonate production in the intestinal tissue by increasing the activity of bicarbonate-producing enzymes called carbonic anhydrases.

"For the first time, we are able to use a drug that activates bicarbonate transport without affecting chloride transport, and see improvement in the disease," Harmon said. The results provide support for the hypothesis of experts in the field such as UCSD's Paul Quinton, PhD, who has written that increasing bicarbonate in cystic fibrosis tissues could be a relevant target for future therapies.

"The finding of the reduced PPAR- γ activating prostaglandin in cystic fibrosis is exciting since it could serve as a marker to identify which patients might benefit from treatment with PPAR- γ activating

drugs," said Glass.

Provided by University of California - San Diego

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