At last, a living model for an important body channel

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(PhysOrg.com) -- Ion channels provide a way for key molecules to cross into cells, are the means for many swift physical reactions and regulate the movement of fluid across internal cavities in our bodies. When chloride ions cross a cell membrane they may also bring sodium and water along. In the airways, when the channels don't function well, the mucus that covers the surface becomes very thick and breathing is difficult, as seen in the disease cystic fibrosis (CF).

Researchers at the Duke University Medical Center and University of California at San Francisco (UCSF) used funding largely from an NIH Innovator Award Grant and a pilot project from the Cystic Fibrosis Foundation to identify and isolate a gene in zebrafish that when mutated leads to a sudden influx of fluid and causes a dramatic expansion of the gut tube. The findings may be helpful to people with CF as research continues, said Michel Bagnat, Ph.D., lead author and assistant professor of cell biology at Duke.

"This work establishes the zebrafish as a forward-genetics model system in which to study ion channel biology," Bagnat said. Forward genetics is a process that starts with an observed trait (sudden water in the gut) that leads through investigation to the gene or genes responsible for the trait.

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Bagnat and colleagues at Duke and UCSF, under the leadership of Didier Y. R. Stainier, Ph.D., of the UCSF Department of Biochemistry

and Biophysics, showed that this phenotype in zebrafish embryos resulted from uncontrolled activation of CFTR (cystic fibrosis transmembrane conductance regulator), a chloride channel. Using several different techniques, they showed that the Cse1l protein is a negative CFTR regulator -- it prevents CFTR-dependent fluid secretion. Thus, when there is a mutation in the cse1l gene, water crosses into the gut without any brakes.

In addition to being useful way to study CFTR regulation, the model has direct implications to conditions like diarrhea, the opposite of the CF problem. The CFTR channel plays a role in secretory diarrheas like cholera, where the cholera bacteria's toxin physically binds to the small intestine lining and rapidly leads to the activation of CFTR channel, causing the epithelial cells to secrete chloride ions and fluid into the intestine, with rapid dehydration.

"You can either have too much or too little fluid secreted, and we hope this model will help us learn more about the controls on this critical balance," Bagnat said.

The researchers also showed that the fish studies could be translated into work with mammalian cells. In dog kidney cells Cse1l also functions as a brake on CFTR activity, which could be a promising finding for people with CF.

"This work demonstrates the importance of fluid homeostasis in development," Bagnat said. "It establishes the zebrafish as a model for studying CFTR regulation in living creatures."

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