Unraveling a new regulator of cystic fibrosis

September 19 2011

Cystic fibrosis (CF), a chronic disease that clogs the lungs and leads to life-threatening lung infections, is caused by a genetic defect in a chloride channel called cystic fibrosis transmembrane conductase regulator (CFTR). Although scientists do not fully understand how or why this defect occurs, a team of researchers at The Hospital for Sick Children (SickKids) in Toronto, Ontario, Canada has found a promising clue: a protein called ubiquitin ligase Nedd4L.

In a study led by Daniela Rotin, PhD, senior scientist at SickKids and professor of biochemistry at the University of Toronto, mice specially bred to lack Nedd4L in the lung developed cystic fibrosis–like lung disease. Dr. Rotin, the lead author of a number of recently published studies on this topic, will discuss the team's findings at the 7th International Symposium on Aldosterone and the ENaC/Degenerin Family of Ion Channels conference sponsored by the American Physiological Society.

Previous studies have shown that CF results when a genetic mutation in CFTR interferes with its ability to deliver signals and instructions for cells to execute. In the case of the mutated gene, the lung cells absorb too much salt via a protein known as epithelial sodium channel (ENaC). Airways become dry and hamper the lungs' ability to clear away mucus and filter out foreign matter and bacteria. As a result, the person with CF becomes susceptible to debilitating infection and disease.

Nedd4L and ENaC

Previous CF research has shown that Nedd4L suppresses ENaC. To confirm the link, Dr. Rotin and her team genetically engineered mice to be born without Nedd4L in the lungs. The mice developed lung disease similar to cystic fibrosis, including inflammation and obstructed airways, and died within 3 weeks of birth. When the researchers sampled tissues from deceased mice, they found that there had been increased ENaC activity.

According to Dr. Rotin, the results indicate options for developing treatments for CF. "If you can enhance Nedd4L function or increase the amount of Nedd4L in the lungs, that may be useful in alleviating symptoms of the disease. Another option is to inhibit ENaC."

Provided by American Physiological Society