Insights into a new therapy for a rare form of cystic fibrosis

29 October 2012

Scientists at the Hospital for Sick Children in Toronto have established that a drug recently approved by the U.S. Food and Drug Administration to treat a rare form of cystic fibrosis works in an unconventional way. Their results reveal new possibilities for treating various forms of cystic fibrosis.

Cystic fibrosis is an inherited disease afflicting about 70,000 people around the world. Cystic fibrosis patients carry a defective gene that disables or destroys its protein product, which normally regulates the transport of ions across cell borders. When that transport is disrupted, the viscosity of the mucus coating certain organs becomes too thick. A characteristic feature of the disease is thick mucus buildup in the air passages, which causes difficulty breathing and recurring infections.

While the FDA approved the drug VX-770 (also known by the trade names Kalydeco and Ivacaftor) to ease breathing in people with cystic fibrosis caused by a particular mutation in the CFTR protein (the acronym is short for cystic fibrosis transmembrane conductance regulator), exactly how VX-770 worked in those patients was unknown.

Scientists have understood for some time that normal CFTR regulation requires modification of the protein and binding of a small, energy-providing molecule – adenosine triphosphate, or ATP. But, in their recent Journal of Biological Chemistry "Paper of the Week," Christine Bear and colleagues report that the drug opens both normal and mutant CFTR channels without ATP. Their results indicate that the compound binds to a different site on CTFR than ATP. Significantly, this finding may be useful in developing therapies for cystic fibrosis caused by various CFTR mutations that, like the G551D mutation that was studied, impair ATP-mediated channel regulation.

Bear's group determined how VX-770 works after developing a new experimental system that may have potential for discovering drugs that target the basic defects caused by CFTR mutations, Bear says. The system is useful for identifying compounds that interact with rare mutations such as G551D as well as the major CFTR mutant F508del, she said.

Provided by American Society for Biochemistry and Molecular Biology