Research project yields better understanding of the defective protein that causes cystic fibrosis

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Jeng-Haur Chen is a postdoctoral researcher at the University of Iowa's medical college and the lead author on a paper to be published in the Dec. 18 issue of the *Journal of Biological Chemistry.* Credit: Handout photo

A team of researchers studying the protein that, when defective or absent, causes cystic fibrosis (CF) has made an important discovery about how that protein is normally controlled and under what circumstances it might go awry.

"Understanding the regulation of salt transport in normal cells is critical for the development of new therapies for diseases, like CF, that disrupt salt movements across cell borders," said Jeng-Haur Chen, a postdoctoral

researcher at the University of Iowa Carver College of Medicine and the lead author on a paper to be published in the Dec. 18 issue of the Journal of Biological Chemistry.

Cystic fibrosis is an inherited chronic disease that affects many organs, particularly the lungs and digestive system. CF patients carry a defective gene that disables or destroys its protein product, which normally regulates the transport of salt across cell borders. As a result, the body produces thick mucus that blocks its ducts and tubes.

Blockage of air passageways causes chronic cough and lung infection; blockage of the pancreas prevents enzyme delivery to the intestine to break down food; and blockage in the intestine prevents food absorption.

About 70,000 people worldwide have the disease, the majority of whom are children and young adults.

The defective gene responsible for CF and its protein product, called cystic fibrosis transmembrane conductance regulator, or CFTR, were discovered only in 1989; but, thanks to early-detection techniques and improved therapies, the survival of CF patients has improved significantly over the past 40 years. Chen stressed that, despite big improvements, existing therapies for CF only ease symptoms by, for example, staving off lung infections with antibiotics, loosening mucus through chest physiotherapy and aiding in digestion with enzyme supplements.

Developing a true cure, he said, requires two things: first, when it is missing, delivering CFTR protein back to its correct location, on the cell border, and second, when CFTR is defective, restoring function to it.

"CFTR itself is a small passageway with a gate, called an ion channel, found on the surface of cells lining ducts and tubes, where it acts as a

pathway for the movement of chloride ions, one component of salt, and regulates the transport of bicarbonate, one part of soda," Chen explained.

By adjusting the transport of these molecules, he said, CFTR regulates the acid-base balance, or pH, of cells; and precise control of intracellular pH is vital for the function of all cells.

"In the case of cells lining ducts and tubes, intracellular pH regulates salt transport, protects the body against foreign invaders -- such as bacteria -- and controls cell survival," Chen said.

While scientists have had evidence that CFTR regulates pH in cells, it had been unknown how it detected changes in pH and knew when to adjust its activity. So, Chen set out to test his idea that CFTR activity is directly regulated by intracellular pH itself.

He successfully demonstrated that acid pH potently stimulates chloride transport by CFTR, whereas alkali pH inhibits it. To learn how pH regulates chloride transport via CFTR, Chen studied the function of the individual building blocks from which CFTR is assembled.

"The structure of CFTR resembles a turnstile -- it has a pathway for chloride movement across the cell border and a gate that controls access to this pathway. Turning of the gate is powered by adenosine triphosphate, or ATP, an energy source for all cells," explained David Sheppard, who oversaw Chen's work as a doctoral student in the department of physiology and pharmacology at the University of Bristol. "Jeng-Haur's work demonstrates that intracellular pH regulates ATP docking with the gate and the speed at which the gate turns."

Thus, intracellular pH determines the power level at the gate, which, in turn, regulates the transport of salt and bicarbonate. In the meantime, Sheppard said, if a cell needs to conserve energy, intracellular pH also

can tell enzymes when it's time to shut down CFTR activity.

"(Chen's) original insights into CFTR structure and function have been critical to advancing knowledge of how CFTR normally works and how it goes wrong in disease," Sheppard said. "The aim is to design and develop drug therapies that restore function to CFTR proteins disabled by CF mutations. By targeting the root cause of the disease, rather than the symptoms, new drug therapies for CF might stop disease progression and prevent the decline in health of individuals living with CF."

Chen's research was funded by the Cystic Fibrosis Trust, the U.K. charity for CF research and patient care. His article has been named a "Paper of the Week" by the *Journal of Biological Chemistry*, putting it in the top 1 percent of papers reviewed by the editorial board in terms of significance and overall importance.

"Jeng-Haur Chen richly deserves this accolade. He is an enormously talented and committed researcher," Sheppard said.

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