Scientists develop synthetic molecules that can 'ferry' mucus-clearing ions blocked by cystic fibrosis

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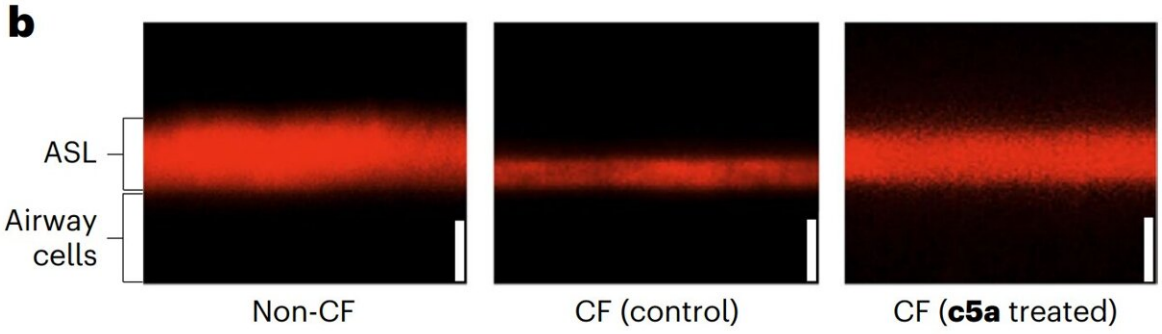

These microscopy images show the airway surface liquid of a non-cystic fibrosis cell, a cystic fibrosis control cell and a cystic fibrosis cell treated with the team's synthetic molecules. Credit: University at Buffalo *Nature Chemistry* (2023). DOI: 10.1038/s41557-023-01315-w

A University at Buffalo-led research team has developed molecules that could help unclog thick, sticky mucus from the lungs of people suffering from cystic fibrosis.

The chronic disease is caused by a defective protein channel that prevents chloride ions from leaving cells and creating the watery conditions necessary to clear mucus. Researchers' synthetic molecules

offer something of a detour by binding to ions and carrying them through the cell membrane.

This binding increased a liquid layer vital for mucus clearance in cystic fibrosis cells by 50%, according to a study published in *Nature Chemistry* .

"We found that these molecules can serve as an effective ferry to transport chloride across the cell and therefore restore the level of airway surface liquid, or ASL, to essentially that of a normal cell," says the study's lead author, Bing Gong, Ph.D., UB Distinguished Professor in the Department of Chemistry, within the College of Arts and Sciences. "One day, they could be leveraged into a drug that treats cystic fibrosis, a very painful and unpleasant disease."

The inability to clear mucus makes breathing difficult and risk of infection high for the nearly 40,000 Americans living with cystic fibrous. It is one of the most common fatal genetic diseases in the United States.

"It is exciting when scientific discoveries can be applied in ways that will potentially improve the health and well-being of people with complex conditions like cystic fibrosis that have limited treatment options," says co-author Daniel Miller, a UB Ph.D. graduate who is now assistant professor of chemistry at Hofstra University.

Helping chloride ions escape cells

In healthy lungs, chloride ions exit the cell via a tube-shaped protein channel called a cystic fibrosis transmembrane conductance regulator (CFTR). Once outside the cell, chloride ions attract water that helps tiny, hair-like cilia sweep out mucus from the airways.

In cystic fibrosis, the CFTR channel is either defective or nonexistent. Without chloride ions to attract water, mucus hardens and the cilia can't clear it.

Gong's lab previously developed synthetic binders for positively charged ions called cations, but chloride is a negatively charged ion, or anion.

"Synthetic anion binding is much more challenging because anions can be all kinds of shapes—spherical, octahedral, even tetrahedral," Gong says. "It's hard to tailor-make clothes for them, so to speak."

The solution turned out to be macrocycles, a form of molecule with a ring containing 12 or more atoms. Gong's team's nontoxic macrocycles are characterized by a star-shaped, rigid backbone that can selectively lock anions into place with its binding cavities.

Computational chemistry, conducted by Zurek and Miller, was used to illustrate the macrocycles and their anion binding on a molecular scale. Models confirmed the macrocycles' structure and positive charge of its binding activity.

"Our computations were able to provide a deeper understanding of the orientation and positioning of the macrocycle relative to chloride," Miller says.

Researchers found the macrocycles were not only effective binders—they were essentially bodyguards.

"The interior of a cell membrane is hydrophobic—it doesn't like positively or negatively charged ions—but our macrocycles actually gave anions a hydrophobic shield so they can travel to the other side of the cell membrane," Gong says.

When the macrocycles were applied to tissue taken from the airways of cystic fibrosis patients, ASL visibly thickened. In fact, cells treated with the macrocycles had an ASL 50% higher than that of the control cystic fibrosis cells.

The macrocycles do have some limitations. The fixed size of their binding cavity prevents them from binding with small or very large anions. Plus, only small quantities can currently be produced due to the required high-dilution conditions.

Gong's lab will now try to adjust the cavity size, as well as scale up production.

Life expectancy on the rise

Just a few decades ago, most cystic fibrosis patients died in their early adulthood. However, life expectancy is now approximately 56 and many with the disease live full life spans, thanks in part to advances in treatment.

These include a drug called Trikafta, which helps the CFTR channel funnel out ions like it's supposed to. However, the drug is expensive and, in certain countries, not even on the market.

"Developing new treatments for cystic fibrosis treatment remains a crucial effort," Gong says. "Our research in anion and cation binding can apply to not only cystic fibrosis, but a host of other channel diseases caused by defective ion channels."

More information: Ruikai Cao et al, Aromatic pentaamide macrocycles bind anions with high affinity for transport across biomembranes, *Nature Chemistry* (2023). DOI: 10.1038/s41557-023-01315-w

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