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RESEARCH NEWS

CFTR gets together

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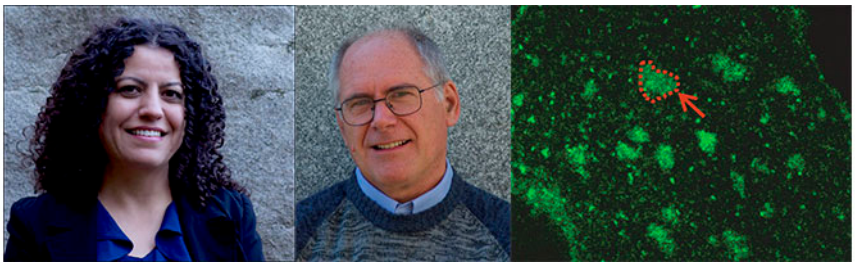
***JGP* study shows that pro-secretory agonists prompt CFTR to assemble into large lipid platforms.**

Cystic fibrosis is a heritable disease caused by mutations in CFTR, a protein expressed on the epithelial cells that line mucosal tissues throughout the body. Although its incidence varies according to ethnicity, the disease is fairly common, appearing in ∼1 in 3,500 people of northern European descent. Despite decades of research, fundamental questions about CFTR and the disease process remain. A *JGP* paper by Abu-Arish et al. details some unexpected findings regarding CFTR distribution and dynamics in the plasma membrane (1).



First author Asmahan Abu-Arish (left), senior author John Hanrahan (right), and colleagues show that agonists that stimulate secretion cause CFTR to assemble into large, ceramide-rich platforms on the surface of airway epithelial cells (outlined area in micrograph).

"CFTR is an ABC transporter family member that is unique in that it functions as an anion channel," explains John Hanrahan, a Professor of Physiology at McGill University in Montreal, Canada. "Disease-associated mutations cause a reduction in CFTR channel activity, which then leads to reduced chloride currents and fluid secretion, so mucus becomes viscous and isn't cleared properly from the airways."

For CFTR to function, it must be present at the cell surface. Little is known about how CFTR is distributed there, or how its distribution might change under different conditions. Prior work has shown that CFTR is located in specialized membrane domains at the cell surface called lipid rafts (2, 3). These dynamic structures are assembled from clustered lipids—principally, cholesterol and sphingomyelin—that form a spatially and biochemically distinct region to segregate certain membrane proteins within the plasma membrane.

As a postdoc in Hanrahan's lab, Asmahan Abu-Arish investigated CFTR's distribution in the cell membrane. Using a microscopy technique called k-space Image Correlation Spectroscopy (kICS), developed by Paul Wiseman's group at McGill, the group saw that CFTR resides in tiny lipid raft microdomains on the surface of resting epithelial cells (4). They became curious whether CFTR distribution changes when the channel is activated by exposure to agonists that stimulate secretion from airway epithelial cells, such as the neuropeptide vasoactive intestinal peptide (VIP).

"We were interested to understand what controls where CFTR goes on the cell surface and also the role of lipids in that process," says Hanrahan.

"We wanted to work with live cells because we wanted to see that behavior in real time and in a relevant living system," adds Abu-Arish, now a research associate working with Hanrahan.

To address this, Abu-Arish et al. again used kICS to observe CFTR molecules in live primary airway epithelial cells collected from human donors. They found that stimulation with VIP and other pro-secretory agonists prompted CFTR lipid raft microdomains to coalesce into large, ceramide-rich platforms. CFTR surface expression is known to increase after VIP stimulation (5), and Hanrahan speculates that CFTR inclusion in these lipid platforms may promote cell surface retention by preventing internalization.

"We believe the major mechanism for platform formation is diffusion," says Abu-Arish. "CFTR clusters can diffuse in the membrane, and when rafts containing ceramide meet, the ceramide molecules form strong bonds, and the rafts coalesce."

CFTR-containing platforms were located near cilia, and their formation depended on an increase in membrane ceramide content driven by the enzyme acid sphingomyelinase (ASMase). Most cellular ASMase is found in lysosomes. There, it can be activated by cell stress and then trafficked to the cell surface. However, Abu-Arish et al. found no evidence for such trafficking in VIP-stimulated epithelial cells.

"We think that there's probably a redox signaling mechanism that activates the acid sphingomyelinase on the outer surface of the cell," says Hanrahan. His laboratory is already working to identify this pathway. Because cell membrane lipid imbalances are a common feature of cystic fibrosis, they're also investigating whether common CFTR mutations affect the channel's distribution and dynamic behavior at the cell surface.

1. Abu-Arish, A., et al. 2019. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.201812143
2. Dudez, T., et al. 2008. *Cell Res.* 1783:779–788.
3. Wang, D., et al 2008. *Pflugers Arch.* 456:929–938.
4. Abu-Arish, A., et al 2015. *Biophys. J.* 109:85–94.
5. Chappe, F., et al 2008. *J. Pharmacol. Exp. Ther.* 327: 226–238.

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