Cystic Fibrosis Research News

Title:
Electrochemical measurement of membrane cholesterol correlates with CFTR function and is HDAC6-dependent

Authors:
Binyu Lu¹, Li Li Molly Schneider², Craig A. Hodges², James A. Burgess³, and Thomas J. Kelley¹²

Affiliations:
¹Department of Chemistry, Case Western Reserve University
²Department of Pediatrics, Case Western Reserve University
³Department of Medical, Laboratory, Imaging and Radiologic Sciences, Augusta University

What was your research question?
We wanted to determine the mechanism by which CFTR function regulates cellular events. We know that membrane cholesterol levels are elevated in CF cells and reflect changes to cellular processes that relate to inflammation, but we seek to gain an understanding regarding the way that CFTR regulates these processes.

Why is this important?
It is not clear how CFTR function influences cellular events. If we can understand better the cellular consequences of losing CFTR function we can develop methods to monitor those consequences to more effectively evaluate new therapeutic interventions as well as develop new therapies.

What did you do?
We used CF mouse models where we could induce CFTR function to test whether the membrane cholesterol measurement was responsive to CFTR correction. The same approach was taken with primary CF bronchial epithelial cells treated with a CFTR corrector. We also multiple methods to inhibit a protein called HDAC6 that we hypothesize is the link between CFTR and cellular regulation changes seen in CF. We then used a cholesterol sensing electrode to measure changes in membrane cholesterol.
What did you find?
Results showed that either the induction of CFTR expression in a CF mouse or the use of CFTR correctors in CF cells resulted in normalization of the cholesterol measurement and restoration of the CFTR activity. Our findings show that this membrane cholesterol assay reflects CFTR-dependent cellular regulation. We also demonstrated that inhibition of the protein HDAC6 had the same normalization effect strengthening the case that HDAC6 is the link between CFTR and cellular regulation.

What does this mean and reasons for caution?
These results mean two things. First, the membrane cholesterol measurement is capable of monitoring CF cellular changes that are dependent on CFTR activity and that this method may be useful as a means to follow intracellular changes in CF. Secondly, these results point to HDAC6 as the mediator of CFTR-dependent changes to cell regulation. HDAC6 may represent a suitable target to effectively reverse CF-related changes to cell function without the need to optimally correct CFTR function. More detailed studies on HDAC6 regulation in CF need to be pursued.

What’s next?
Future studies will focus on defining the relationships between intracellular changes in CF and the membrane cholesterol measurement. The development of HDAC6 inhibitors as potential augmentative therapies in CF will also be pursued.

Original manuscript citation in PubMed
https://www.ncbi.nlm.nih.gov/pubmed/?term=Electrochemical+measurement+of+membrane+cholesterol+correlates+with+CFTR+function+and+is+HDAC6-dependent