Molecular prosthetics & CFTR modulators additively increase host defenses in cystic fibrosis airway epithelia

Nohemy Celis , Martin D. Burke

Cystic Fibrosis (CF) is caused by loss-of-function mutations in the CF transmembrane conductance regulator (CFTR) protein, an anion channel predominantly expressed on the apical surface of epithelial cells. CFTR modulators that restore the function of the CFTR channel improve lung function in people with responsive CF mutations. However, this approach is inherently limited by the less than wild type-like quantity and functional activity of modulator-rescued CFTR protein that reaches the apical membrane. An alternative approach is to replace CFTR with small molecule ion channels that act as molecular prosthetics (MPs). An important strength of this approach is that MPs operate independently of CFTR, and thus their benefit is not constrained by CFTR availability or activity. We hypothesized that MPs could thus complement CFTR modulators, driving additive benefit. We found that pre-treatment of CF airway epithelia with CFTR modulators alone left a residual driving force for HCO_3^- secretion. Accordingly, subsequent treatment of CFTR modulator-treated CF airway epithelia with MPs resulted in an additive increase of HCO_3^- efflux and ASL pH. Revealing untapped potential for further improvements of airway host defenses in modulator-treated airway epithelia.