Genotype-agnostic Rescue of Cystic Fibrosis with Small Molecule Bicarbonate Channels

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Cystic fibrosis (CF) is caused by loss-of-function mutations in the CFTR anion channel. The corresponding reduction in apical bicarbonate transport leads to decreased pH, increased viscosity, and decreased antibacterial activity in airway surface liquid (ASL), contributing to the chronic infections that shorten the lives of CF patients. Restoration of this anion transport deficiency using small molecule-based ion channels would provide a CFTR-independent alternative to existing small molecule modulators of mutant CFTR. Here we report that bicarbonate-permeable channels formed by the small molecule amphotericin B restore ASL pH, viscosity, and antimicrobial activity in primary cultured lung epithelia derived from CF patients with a range of different CFTR mutations. This increase in pH matches that caused by pharmacological potentiation of mutant CFTR, persists for at least 48 hours, and is invariant with increasing concentration of detoxified small molecule channels. It also requires both small molecule channel-mediated bicarbonate transport and activity of the basolateral Na^+/K^+ ATPase. These findings suggest that small molecule-based channels are functionally interfaced with a robust ion transport network that drives sufficient transepithelial bicarbonate movement through an unregulated and unselective surrogate for CFTR. They also demonstrate that the non-channel-based activities of CFTR, including regulation of other apical ion transporters, are not required for maintaining these key parameters of ASL physiology. These results collectively illuminate a potential path for genotype-agnostic rescue of CF.