C16

Coordination of Pancreatic HCO_3^- Secretion by Protein-Protein Interaction between CFTR and Luminal NHE

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Increasing evidence suggests that protein-protein interaction is essential in many biological processes including epithelial transport. In this report, we present the significance of protein interactions to HCO_3^- secretion in pancreatic duct cells. In pancreatic ducts HCO_3^- secretion is mediated by CFTR-activated luminal Cl^-/HCO_3^- exchange activity and HCO_3^- absorption is achieved by Na^+-dependent mechanisms including NHE3. We found biochemical and functional association between CFTR and NHE3. In addition, protein biding through PDZ modules is needed for this regulatory interaction. CFTR affected NHE3 activities in two ways. Acutely, CFTR augmented the cAMP-dependent inhibition of NHE3. In a chronic mechanism, CFTR increases the luminal expression of Na^+/H^+ exchange in pancreatic duct cells. These findings reveal that protein complexes in the plasma membrane of pancreatic duct cells are highly organized for efficient HCO_3^- secretion.