THE CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR AND ACID-BASE TRANSPORTERS OF THE MURINE DUODENUM

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ABSTRACT

The alkaline mucus barrier of the duodenum plays an important role in protecting the epithelium from acidic chyme entering from the stomach. Active HCO_3^- secretion involves the apical membrane activities of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel, the protein that is defective in cystic fibrosis (CF), and Cl^-/HCO_3^- exchangers. Under basal conditions, studies of CF patients and mouse models indicate that HCO_3^- secretion by anion exchange predominates. In addition, basal HCO_3^- secretion is reduced in the CF duodenum, but the specific pathophysiology for this deficiency has yet to be elucidated. Our studies reveal that Cl^- channel activity by CFTR facilitates apical membrane $Cl^-_{in}/HCO_3^-_{out}$ exchange by providing a Cl^- 'leak' and is responsible for the reduced rate of Cl^-/HCO_3^- exchange in the murine CF intestine. Using mice with gene-targeted deletions of the apical membrane Cl^-/HCO_3^- exchangers PAT-1, DRA, and AE4, PAT-1 was found to be the major Cl^-/HCO_3^- exchanger of the upper villus of the duodenum. Interestingly, these studies also revealed a novel role for PAT-1 as a base-importer (i.e., $Cl^-_{out}/HCO_3^-_{in}$) whereby it interacts with carbonic anhydrase II (CAII), the most widely expressed isozyme of the small intestine, during H^+/peptide transport to minimize intracellular acidification and sustain nutrient absorption.