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SLC26 TRANSPORTERS, CFTR AND EPITHELIAL Cl^- AND HCO_3^- TRANSPORT

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Many members of the SLC26A transporters family are expressed in the luminal membrane of epithelia and transport Cl^- and HCO_3^- to mediate the critical function of epithelial Cl^- absorption and HCO_3^- secretion. The mode of transport and its regulation determines the capacity of the transporters expressed in a particular tissue to mediate Cl^- and HCO_3^- transport. Examination of the transport mode of SLC26A3 and SLC26A6 revealed that these are coupled, electrogenic transporters with isoform specific Cl^-/HCO_3^- stoichiometry. All SLC26 transporters examined are activated by the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) and regulate CFTR channel function. Biochemical and functional assays mapped the reciprocal regulation of the transporters to the CFTR R domain and the SLC26 transporters STAS domain. Interaction between the domains required phosphorylation of the R domain and was essential for the mutual activation of the transporters. The mutual regulation plays important role for regulation of HCO_3^- secretion and Cl^- absorption in vivo. Deletion of slc26a6 in mice revealed that slc26a6 mediates a large fraction of stimulated HCO_3^- secretion by the pancreatic duct. Furthermore, in the resting state slc26a6 inhibit CFTR function but in the stimulated state slc26a6 activates CFTR. The two modes of regulation of CFTR activity by slc26a6 determine the modes of HCO_3^- secretion by the resting and stimulated pancreatic duct. The role of the other SLC26 transporters in epithelial Cl^- absorption and HCO_3^- secretion is being examined.