Genetics and Regulation of Anion Exchange

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Transmembrane exchange of chloride for bicarbonate serves to control cell and lumenal pH, volume, and [Cl⁻], as well as to drive secondary active transport of other anions. Anion exchangers are encoded by the SLC4 and SLC26 gene families. The SLC4 family includes the Na-independent, electroneutral anion exchangers AE1, AE2, and AE3, as well as electrogenic and electroneutral Na-bicarbonate cotransporters, and Na-dependent anion exchangers. All polypeptides in this gene family encode a long N-terminal cytoplasmic domain, a transmembrane domain spanning the lipid bilayer 12-14 times, and a short C-terminal cytoplasmic tail. Erythroid AE1 (eAE1, band 3) is the major intrinsic membrane protein of the red cell, and serves to increase the capacity of the blood to carry CO2 from tissue capillaries to the lungs for expiration. AE1 is a homodimer in detergent solution. The N-terminal cytoplasmic domain of eAE1 interacts with multiple cytoskeletal proteins and with glycolytic enzymes. Ankyrin binding is a property of tetrameric AE1. The transmembrane domain suffices to mediate halide exchange, but bicarbonate transport requires binding to the C-terminal cytoplasmic tail of carbonic anhydrase 2. CA2 bound to one subunit within an AE1 homodimer can provide the permissive function for Cl-/HCO₃⁻ exchange by the other subunit of the homodimer, but unbound cytoplasmic CA2 cannot serve this function.

AE1 polymorphisms in the ectoplasmic loops of the protein encode minor blood group antigens. AE1 mutations distributed throughout the length of the protein cause the dominant erythroid conditions spherocytic anemia and ovalocytosis. An N-terminally truncated form of AE1 (kAE1) is expressed in the basolateral membrane of Type A intercalated cells of the kidney collecting duct. A distinct set of AE1 mutations causes recessive and dominant forms of distal renal tubular acidosis. Recessive AE1 mutations are associated with normal or near-normal eAE1 abundance and function due to the presence in the erythrocyte of the AE1-binding protein, glycophorin A. Glycophorin A coexpression can rescue surface expression and function of recessive dRTA mutant forms of kAE1 in Xenopus oocytes. Defective function of these mutants in intercalated cells is attributed to their lack of expression of the red cell-specific glycophorin A. Dominant dRTA mutant forms of kAE1 exhibit little or no dysfunction when expressed in Xenopus oocytes. Although their behavior in cultured cells is still being defined, these dominant mutants appear to be either dominant negative for surface membrane trafficking or for targeting. eAE1 abundance and function in red cells is also normal in dominant dRTA. Thus, defective urinary acidification either requires the absence of the N-terminal 65 amino acids present in eAE1 but lacking in kAE1, or reflects yet-to-be-defined differences in AE1-binding proteins in kidney cells and erythrocytes.

SLC4 Cl⁻/HCO₃⁻ exchangers differ in their acute regulation. These differences are particularly marked between AE1 and the more widely expressed electroneutral anion exchanger, AE2 (SLC4A2). AE2 is acutely
activated by ammonium and by hypertonicity, whereas AE1 is not sensitive to these stimuli. Residues in both N-terminal cytoplasmic and transmembrane domains are required to manifest these regulatory responses. A region of approximately 12 amino acids in the middle of the N-terminal cytoplasmic domain, highly conserved among polypeptides of the SLC4 gene family, is required for the wildtype pattern each of these regulatory responses. Mutation of corresponding residues in other SLC4 proteins can similarly alter regulatory responses. Domains within the AE2 transmembrane domain which are important for these regulatory responses are being sought.

SLC4 homologs are expressed in plants, worms, and yeast. In plants, one of the SLC4 homologs seems to mediate borate efflux from root cells into xylem (perhaps via borate/bicarbonate exchange) to supply the essential nutrient borate to distant parts of the plant.

The SLC26 family includes anion exchangers of broad specificity for monovalent and divalent anions. DTD/SLC26A2 mutations cause chondrodysplasias. DRA/SLC26A3 mutations cause congenital chloride diarrhea, and pendrin/SLC26A4 mutations cause congenital deafness with variably penetrant goiter. Pendrin is expressed in the apical membrane of Type B intercalated cells. Isolated perfused cortical collecting ducts from bicarbonate-loaded knockout mice exhibit impaired upregulation of bicarbonate secretion. SLC26 anion exchangers of the apical membrane can be regulated by CFTR activity.