S 7-1

ROLE OF CFTR IN EPITHELIAL BICARBONATE TRANSPORT

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Bicarbonate in the exocrine fluids plays an important role in many physiologic processes. In duodenum and pancreas, bicarbonate neutralizes gastric acid and provides an optimum pH environment for digestive enzymes. An overlooked function of bicarbonate secretion is that bicarbonate is a chaotropic ion that is important for the solubilization of macromolecules to prevent the aggregation of dissolved proteins and mucins in epithelial fluids. Accumulating evidence suggests that aberrant bicarbonate transport caused by genetic defects in cystic fibrosis transmembrane conductance regulator (CFTR) protein is associated with a wide spectrum of respiratory, pancreatic and fertility disorders including classical type of cystic fibrosis. Recent findings from our research group and others demonstrate that CFTR plays a key role in transepithelial bicarbonate transport; 1) CFTR activates Cl-/HCO3- exchangers, possibly a member of SLC26 family transporters. 2) CFTR lowers intracellular Cl- concentrations, which facilitates electroneutral and electrogenic HCO3- efflux at apical membrane. 3) CFTR may itself have a HCO3- channel activity in physiologic conditions. 4) CFTR regulates overall epithelial HCO3- transport by interacting with other HCO3- transporters.

Key Words: Bicarbonate, CFTR, Epithelial, Transport

S 7-2

REGULATION OF LUNG ALVEOLAR EPITHELIAL ION TRANSPORT

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Active Na absorption across the lung alveolar epithelium, populated by both alveolar epithelial type I (ATI) and type II (ATII) cells, creates an osmotic gradient that drives alveolar fluid reabsorption, thus keeping alveolar airspaces relatively dry for efficient gas exchange. Apical Na entry into alveolar epithelial cells has been shown to occur via both amiloride-sensitive epithelial Na channels (ENaC) and amiloride-insensitive nonspecific cation (NSC) channels. Basolateral extrusion of Na in alveolar epithelium takes place via ouabain-inhibitable Na/K-ATPase, primarily comprised of $\alpha 1$ and $\beta 1$ subunits. Expression of α, β and γ subunits of ENaC at RNA and protein levels in both freshly isolated rat ATI and ATII cells has been reported along with confirmation of ENaC activities by patch clamp techniques. In cultured type II cells, ENaC activity is relatively low, but can be induced under certain culture conditions, including air-interface and presence of humoral factors (e.g., glucocorticoids). A very recent patch clamp study utilizing lung slice techniques demonstrated ENaC activities in ATI cells *in situ* that were stimulated by dopamine. Knockdown studies using an αENaC siRNA approach in rat lungs indicate a small decrement in basal lung fluid clearance, with almost completely abolished β-agonist responsive lung fluid clearance. A potential role for CFTR has been indicated in recent studies of fluid clearance across the distal lung epithelium of various animal species, although CFTR expression in human alveolar epithelium is reported to be very low. Overexpression of human CFTR in alveolar epithelium of rats and mice led to an increase in alveolar fluid clearance. The relative contributions and regulation of active ion transport afforded by ATI and ATII cells to overall transalveolar epithelial fluid clearance (and active ion transport) in both *in vitro* model(s) and *in vivo* lungs remain poorly defined to date.