CFTR ACTIVITY AFFECTS AIRWAY MUCUS PROPERTIES

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Cystic fibrosis (CF) is a letal genetic disease caused by mutations in the *CFTR* gene, coding a ionic channel protein. This disease is characterized by the buildup of thick and viscous mucus obstructing the lungs. Mucus stagnancy promotes infections and chronique inflammation ultimately leading to organ failure and patient's death in the absence of transplantation. Gel-forming mucins are responsible for the viscoelastic properties of mucus and play a key role in CF pathogenesis. In the CF lung, abnormal MUC5B and MUC5AC properties drive airway obstruction but the pathophysiologic link with CFTR dysfunction is unclear. Mutations within CFTR reduce transepithelial Cl- and HCO3- secretion, which leads to ionic imbalance and volumedepletion. Airway dehydration causes mucin hyperconcentration, increasing the interactions between mucin monomers (i.e., mucin entanglement). CFTR dysfunction is also associated with oxidative stress, which may increase disulfide bond formation (i.e., mucin crosslinking). Additionally, deficient bicarbonate secretion affects Ca2+ chelation, which may compromise mucin unfolding/expansion (i.e., mucin compaction). Understanding the dominant biochemical change(s) (i.e., mucin entanglement, covalent crosslinking, electrostatic compaction) caused by CFTR malfunction is critical to identify new therapeutic targets aimed to "reverse" mucus abnormalities in CF.