Impaired secretory IgA and mucosal immunity in cystic fibrosis: contribution to lung pathology and impaired defence against bacterial infection, and role of CFTR-related epithelial changes in the regulation of the receptor-mediated IgA transcytosis

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Background. Cystic fibrosis (CF) represents the most common lethal autosomal recessive disorder in the white population, mainly affecting the lungs. It affects the Cystic Fibrosis Transmembrane Regulator (CFTR) gene, which encodes a protein expressed on the apical membrane of airway epithelial cells, where it acts as a cAMP-dependent chloride channel and regulator of other channels, including the epithelial Na+ channel (ENaC). Airway colonization of the airways and lung infections are a hallmark of this disease, in particular with Pseudomonas aeruginosa (PA) that affects ~70% of CF patients and is associated with poor clinical outcomes. However, the mechanisms underlying the persistence of pathogens in CF airways, remain largely unclear. Secretory-immunoglobulin A (S-IgA) is a major line of mucosal defense, through so-called immune exclusion of inhaled / ingested antigens and pathogens. Following synthesis of polymeric (mainly dimeric) IgA by subepithelial mucosal plasma cells, IgA is transported across the epithelium by a transcellular routing mediated by the polymeric immunoglobulin receptor (pIgR).

Hypothesis and objectives. This project aims to investigate whether the production of secretory IgA (S-IgA) is impaired in the CF lung, through which mechanisms, and whether this defect contributes to the pathogenesis of CF by impairing immunoprotection against respiratory pathogens such as PA.

Methods. pIgR expression was assessed in CF and control lung explants by immunohistochemistry. S-IgA and PA-specific antibodies were assessed by ELISA in CF and control sputum, and correlated to the microbial status according to Lee's criteria. The regulation of pIgR expression following CFTR disruption by selective inhibitors was also assessed in primary cultures of human bronchial epithelial cells (HBEC).

Results. Broncho-epithelial pIgR expression was upregulated in CF lungs as compared to controls. Accordingly, total IgA and PA-specific IgA were increased in sputum from CF patients, as compared to control subjects. In contrast, pIgR/SC production by cultured HBEC was inhibited following CFTR inhibition. Altogether, these data indicate that lung S-IgA immunity is preserved in CF, whereas in vitro CFTR disruption leads to pIgR downregulation. The mechanisms of CFTR-pIgR interactions will be explored, as well as the relevance of these findings to CF pathogenesis.

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