WS17.5 A new tool for CF diagnosis: short circuit current measurements in human nasal epithelial cells collected by nasal brushing

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Context: Diagnosis of cystic fibrosis (CF) is usually made by the presence of sinopulmonary disease with or without pancreatic deficiency, with abnormal sweat chloride values and/or the finding of two *CFTR* mutations. However, an emerging number of patients present with an atypical phenotype of the disease may have normal or intermediate range sweat chloride level and only one or no identified CF-causing mutations.

Currently, investigators use nasal potential difference (DPN) measurements to demonstrate abnormal function of CFTR in patients with atypical presentations. However, DPN can be problematic in CF patients with chronic rhinosinusitis. Then we investigate a new method to evaluate ion transports in upper airways *ex vivo*.

Methods: Human nasal epithelial cells (HNEC) from 5 healthy individuals, 5 CF and 5 atypical patients were collected by brushing inferior turbinates. HNEC cultures were analyzed by short circuirt current to measure amiloride (Isc_{am}) and AMPc (Isc_{F+I}) currents. All participants had been subjected to a complete genetic exploration of *CFTR* gene and DPN test.

Results: Isc_{am} was significantly different in atypical CF ($12.85\pm1.98\,\mu A/cm^2$) compared to CF patients ($43.6\pm7.7\,\mu A/cm^2$) ($p<0.05$) but was similar to healthy individuals ($14.4\pm4.5\,\mu A/cm^2$). Isc_{F+I} was significantly decreased in atypical CF ($1.35\pm0.59\,\mu A/cm^2$) compared to healthy individuals ($8.7\pm1.07\,\mu A/cm^2$) ($p<0.0001$) but very close to CF ($0.9\pm0.3\,\mu A/cm^2$) ($p=0.34$). DPN results were similar to those obtained by this new tool.

Conclusion: This study higlights that this new tool is a very reliable test for CF diagnosis and could allow evaluation of new therapies *ex vivo*.

WS17.6 Colonic mucus formation relies on bicarbonate secretion via apical Cl^-/HCO_3^--exchange

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Objective: Loss of CFTR mediated anion secretion results in mucus accumulation in organs that express CFTR and gelforming mucins. We have previously shown that CFTR mediated bicarbonate secretion is essential for mucus formation in the ileum, but whether the same principle applies to the colon is unknown.

Methods: Colonic tissues from wild type (WT) and F508del Cftr (CF) mice were mounted in perfusion chambers followed by measurements of mucus thickness, growth rate and adhesiveness.

Results: Baseline mucus growth rate and adhesiveness was similar in WT and CF colon. Since colonic bicarbonate secretion also occurs via apical Cl^-/HCO_3^- exchange, we tested the role of this pathway in colonic mucus formation. Inhibition of Cl^-/HCO_3^--exchange reduced baseline mucus growth and increased mucus adhesion in both models. The importance of the CFTR in secretagogue induced mucus formation was tested with prostaglandin E_2 (PGE_2), carbachol (CCh) and the combination of the two. WT colon responded to all treatments with an increase in mucus thickness similar in magnitude. The CF colon failed to respond to CCh, but had an intact PGE_2 response, while the combination of PGE_2 and CCh had additive effects on mucus thickness. Since Cl^-/HCO_3^--exchange was important for baseline mucus growth we tested whether the same pathway was involved in the CCh+PGE_2 response. Inhibition of Cl^-/HCO_3^--exchange did indeed reduced the CCh+PGE_2 effect of mucus growth in CF colon.

Conclusion: These results show that bicarbonate secretion plays an important role in regulation of mucus formation also in the colon, although the main route for bicarbonate secretion appears to be via apical Cl^-/HCO_3^--exchange.