34* Tracheal structure abnormalities in Cftr−/− knockout mice

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In contrast to CF patients, respiratory tract of Cftr−/− mice exhibit few pathologic changes. Among them, we have observed limitations of the respiratory airflow. The aim of this study was to characterize the airflow reduction and to investigate whether this alteration could be explained by morphologic changes in the upper airways structure. Experiments were performed on adult Cftrtm1Unc knockout mice (Cftr−/−) and their control littermates (Cftr+/+). Ventilation was measured in conscious mice breathing room air using body-plethysmography. Results show that minute ventilation was lower in Cftr−/− than in Cftr+/+ mice because of a lengthening of both inspiratory and expiratory durations. Subsequently, study of the tracheal structure was carried out by in situ morphometric analyses and histological examination of tracheal rings. The length of the trachea/body and the number of tracheal rings were similar. However, most Cftr−/− mice exhibit striking abnormalities localised in the proximal part of the trachea with a severe narrowing, elliptical deformities and numerous frontal disruptions of the cartilage rings. Histological analysis of tracheal sections revealed marked disorganization of cartilaginous rings confirming previous macroscopic observations. Similar tracheal structure alterations were observed in Cftr−/− newborn mice. These findings suggest that the reduced respiratory airflow can be explained by tracheal constriction and incomplete cartilage rings of the proximal trachea. These tracheal abnormalities already present in newborn strongly suggest malformations questioning on the molecular mechanisms governing tracheal development.

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35* Disruption of CFTR-dependent Lung and Intestine Organogenesis Results in Adult-Onset Diseases

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Cystic fibrosis transmembrane conductance regulatory (CFTR) is highly expressed in the lung and other organs during development. The role of CFTR in organogenesis and the effect of its absence on lung structure and function have been largely overlooked in the pathophysiology of cystic fibrosis. Recently, we demonstrated that transient in utero loss of CFTR can have significant effects of lung and intestine function in the adult and that CFTR is involved in stretch induced differentiation of both the lung and intestines.

In work to be presented we show that the developmental effect of transient in utero CFTR deficiency in the lung and intestines results in progressive disease. The lung function degenerates over time, intestinal metabolic activity is altered, and CF related diabetes occurs. These changes are shown to be directly related to changes in cell function due to immaturity and developmental arrest. Type II cell function is altered and changes in surfactant production occurs in the presence of a normal CFTR phenotype postnatally. In the intestines changes in metabolic activity lead to altered glucose metabolism and degeneration of pancreatic function.

These late onset pathologies following transient in utero inhibition of CFTR are consistent with CF belonging to a group of diseases we have termed “Peter Pan Diseases”. Failure to complete organogenesis due to a deficiency of CFTR results in retention of a immature cell phenotype that leads to decreased functionality and disease in the adult.

36 Feasibility of airway surface liquid (ASL) height measurement in human nasal and bronchial biopsies

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Measurement of ASL in man would be useful both for understanding of CF pathophysiology as well as a potential biomarker for therapeutic trials. We have assessed the feasibility of measuring ASL in CF and non-CF nasal (NB) and bronchial biopsies (BB). We analysed 16 non-CF and 6 CF NB, assessing 20–30 sections per biopsy. ASL height could be measured in all non-CF samples and approximately 50% of the CF biopsies, the rest not having adequate areas of ciliated epithelium. However, in addition, a stable cumulative mean derived from the number of cells available for counting, could only be achieved in 45% of the biopsies irrespective of genotype. Thus, only approximately one quarter of CF nasal biopsies taken were available for analysis. We also assessed 28 non-CF and 17 CF BB. 50% of biopsies from either genotype were suitable for ASL height assessment. Subsequently, a stable cumulative mean could be derived from only 20% of samples. Thus, only approximately one tenth of CF bronchial biopsies taken were suitable for analysis. Analysis of ASL height is also very labour intensive, requiring approximately 2 days of laboratory time per biopsy. We conclude that this assay will require both large patient numbers (approximately 50 biopsies/group) and extensive manpower, to confirm the approximately 0.5 μm reduction in ASL height observed by our group, and others, in the CF mouse nose.

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37 Effect of mist tent on ion content of nasal fluid in patients with cystic fibrosis

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Mist tents were recommended for CF patients in the 1960s and 1970s in order to hydrate their viscous mucus. However, the efficiency of the method was doubted and its use largely discontinued. We have measured the effect of sleeping in a mist tent on the ion content of nasal airway surface liquid (ASL) in CF-patients and healthy controls by using a recently available method. The CF patients and controls spent 8 h in a mist tent. Samples of the nasal ASL were taken with Sephadex G-25 beads mounted on filter paper, and analyzed by X-ray microanalysis in the scanning electron microscope, before the experiment, after 8 h in the tent, and then at each hour during 4 h after the persons had left the tent. In an initial experiment, samples were taken from a healthy control every 2 h during 8 h, and then every 24 h during two days.

CF patients had significantly higher levels of Na, Cl, and K in their nasal ASL compared to controls, in agreement with previous results. Immediately after and at 2 h after leaving the tent, the concentrations of Na, Cl, and K had decreased in CF-patients and in controls. At that time, there was no difference in elemental content between CF-patients and controls. However, at 4h after leaving the tent, the levels of K and Cl, but not of Na, were significantly increased in CF-patients, but not in controls. The levels of Cl and K in CF-patients were similar to the levels determined before the patient went into the tent. In the preliminary experiment on the control no major changes in ion content of the ASL occurred after 4 h.

Conclusion: sleeping in a mist tent lowers the ion content of the nasal ASL, which may improve its bactericidal properties, but the effect is short-lived.