Cell Responses in Infected and Cystic Fibrosis Respiratory Epithelium

av

Rashida Hussain

Akademisk avhandling

Avhandling för medicine doktorsexamen i medicinsk vetenskap, inriktning biomedicin, som kommer att försvaras offentligt fredagen den 17 januari 2014 kl. 09,15 Bohmansalen, A-huset, Universitetssjukhuset Örebro

Opponent: Professor Hans Kollberg
Institutionen för kvinnors och barn hälsa,
Uppsala Universitet

Örebro universitet
Institutionen för hälsovetenskap och medicin

701 82 ÖREBRO
Abstract


Cystic fibrosis (CF) is caused by a mutation in a cAMP-activated chloride (Cl⁻) channel (CFTR). Mortality and morbidity in CF is mainly due to the deregulated responses of the airway epithelial cells. The purpose of the thesis was to investigate the behaviour of the airway epithelial cells that are involved in maintaining the homeostasis in the airways.

Nasal brush biopsies obtained from anesthetized human nasal mucosa can be an easy source to establish primary epithelial cell lines (Paper I). We found that CF and non-CF cellular models cannot fully show the relation between CFTR and the phenotypic differences between CF and healthy cells (Paper II). The possibility to correct the Cl⁻ transport defect in CF by the use of stable NO-donors, and ambroxol was investigated. NO-donors stimulated Cl⁻ efflux, and decreased ENaC mRNA expression in CFBE cells (Paper III), while ambroxol increased Cl⁻ efflux from CFBE cells, and showed a positive effect on the bio-synthesis of CFTR (Paper IV). This suggests that these substances may be a potentially interesting group of compounds for the treatment of CF. Increased levels of IL-6 and IL-8 upon infection in CF cells can increase the susceptibility of *P. aeruginosa* infected CF cells to apoptosis and/or internalization of these bacteria in CF cells and hence, may have important roles in the pathology of *P. aeruginosa* infection in CF airways. If internalization is beneficial for the host then glucocorticoids (GCs) are not beneficial for the treatment of CF patients. However, GCs may improve airway hydration. Whether the benefits of GC treatment outweigh the negative effects is questionable, and further clinical studies need to be carried out (Paper V). The neonatal isolates *S. epidermidis* 94B080 and *S. aureus* 90B083 can modulate CFTR and ENaC expression in airway epithelial cells, which may disturb the ion transport in the respiratory epithelium upon bacterial exposure. Airway epithelial cells also show excessive inflammatory responses to these bacteria, which means that these bacteria may induce pulmonary inflammation (Paper VI).

*Keywords*: Airway epithelial cells, cystic fibrosis, bacterial infection, CFTR, ENaC, chloride transport, intracellular calcium, *P. aeruginosa* internalization.

Rashida Hussain, School of Health and Medical Sciences, Örebro University Hospital, Örebro University, SE-701 82 Örebro, Sweden, rashida.hussain@oru.se