European Respiratory Society
Annual Congress 2013

Abstract Number: 7201
Publication Number: P2101

Abstract Group: 7.3. Cystic Fibrosis
Keyword 1: Infections **Keyword 2:** Bacteria **Keyword 3:** No keyword

Title: High expression of midkine in the airways of patients with cystic fibrosis

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Body: Mutations in the CFTR gene result in impaired host defense during cystic fibrosis (CF), where Pseudomonas aeruginosa becomes a key pathogen. We investigated the expression pattern of the antibacterial growth factor midkine in CF and possible interference with its activity by the altered airway microenvironment. High midkine expression was found in CF lung tissue compared with controls, involving epithelium of the large and small airways, alveoli, and cells of the submucosa (i.e. neutrophils and mast cells). In CF sputum, midkine was present at 100-fold higher levels but was also subject to increased degradation, compared with midkine in sputum from healthy controls. Midkine had a bactericidal effect on P. aeruginosa but increasing salt concentrations and low pH impaired the activity. Molecular modeling suggested that the effects of salt and pH were due to electrostatic screening and a charge-neutralization of the membrane, respectively. Both neutrophil elastase and elastase of P. aeruginosa cleaved midkine to smaller fragments, resulting in impaired bactericidal activity. Thus, midkine is highly expressed in CF but its bactericidal properties may be impaired by the altered microenvironment as reflected by the in vitro conditions used in this study.