European Respiratory Society
Annual Congress 2013

Abstract Number: 437

Publication Number: P4741

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: Epithelial cell **Keyword 2:** Immunology **Keyword 3:** Animal models

Title: Airway surface dehydration confers susceptibility to allergic airway inflammation in vivo

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Body: Introduction: Recent evidence from mice lacking the epithelial Cl^- channel SLC26A9 and mice with airway specific overexpression of the amiloride-sensitive epithelial Na^+ channel (βENaC-Tg) suggests that airway surface dehydration is implicated in the pathogenesis of allergic airway disease (Anagnostopoulou et al., J Clin Invest 2012 and Mall et al., Am J Respir Crit Care Med 2008). We hypothesized that airway surface dehydration and reduced mucociliary clearance may increase the susceptibility for allergic airway inflammation due to reduced allergen clearance. Results: We demonstrate that airway surface dehydration in βENaC-Tg mice results into airway hyperresponsiveness as determined by lung function with the Flexivent system. Furthermore, intrapulmonary exposure to Aspergillus fumigatus extract significantly increased airway eosinophils and pulmonary IL-13 in βENaC-Tg mice. 11-color flow cytometry of BAL and lung tissue detected IL-13 secretion from Th2 cells, but also from other cells including recently discovered Lung Natural Helper cells and airway epithelium cells. IL-13 effector functions were further highlighted by introducing a genetic deletion of STAT6, a critical molecule for IL-13 signaling, to βENaC-Tg mice. These βENaC-Tg $STAT6^{-/-}$ mice were protected from airway eosinophilia, airway mucus obstruction and elevated IL-13 expression. Conclusion: Collectively, our results indicate that airway surface dehydration and impaired mucus clearance constitutes a risk factor for key pathologies in allergic airway disease including increased IL-13 production, eosinophilic inflammation and airway hyperresponsiveness. Acknowledgements: DFG (DFG MA 2081/3-2), BMBF (DZL 82DZL00401).