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Increased susceptibilty to allergic airway inflammation in βENaC-overexpressing mice

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Mucociliary clearance (MCC) is an important defence mechanism of the lung, and its impairment is a feature of chronic airway diseases including asthma. MCC is mediated by ciliary beating, airway surface liquid (ASL) hydration and mucus production. The βENaC-transgenic (βENaC-Tg) mouse is a model of ASL depletion, which causes impaired mucus clearance and chronic lung disease including spontaneous allergic airway inflammation in juvenile mice with Th2 biased immune system.

We hypothesized that reduced mucus clearance in βENaC overexpressing mice plays an important role in the pathogenesis of allergic airway disease. To test this hypothesis, we challenged WT and βENaC-Tg mice with a natural allergen, *Aspergillus fumigatus* extract (aspergillus) and compared the severity of allergic airway inflammation, airway mucus obstruction and goblet cell metaplasia. Further, we generated double mutant

Stat6-/- βENaC-Tg mice to study the relationship between Stat6 signaling, mucociliary dysfunction and allergic airway inflammation.

We demonstrate that intrapulmonary sensitization with aspergillus causes exaggerated allergic airway inflammation with increased airway eosinophila and IL-13 level in bronchoalveolar lavage (BAL) from βENaC-Tg mice compared to WT littermates. By using immunohistochemistry, we identified that airway epithelium as a major source of aspergillus-induced IL-13 expression. Allergic sensitization caused goblet cell metaplasia (GCM) and mucus hypersecretion in WT mice, but did not exaggerate mucus obstruction in βENaC-Tg mice. However, βENaC-Tg Stat6$^{-/-}$ mice were protected from both aspergillus-induced allergic airway inflammation and airway mucus obstruction.

In summary, these studies in the βENaC-Tg mouse demonstrate that (i) ASL depletion can produce spontaneous allergic airway inflammation, and exaggerated allergic airway inflammation following exposure to a specific allergen, (ii) the airway epithelium is a major source of IL-13 production in allergen-induced airway inflammation, and (iii) Stat6 signaling plays an important role in mediating ASL depletion induced allergic airway inflammation *in vivo*. We concluded that ASL depletion plays an important role in the pathogenesis and potentially as a novel therapeutic target in allergic airway disease.