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Title: LSC 2013 abstract - Identifying a molecular defect in bronchial epithelial cells from 70% of mild asthmatics

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Body: Interleukin-17 (IL-17) synergizes with pro-inflammatory stimuli like TNF-α in an exaggerated production of inflammatory mediators by human primary bronchial epithelial cells (PBEC) which relates to a decreased decay of mRNAs encoding these inflammatory mediators. Recently, we have found that IL-17 coordinately attenuates both the ARE-mediated pathway of mRNA decay and that mediated by microRNA (miR)16 (submitted). Since airway IL-17 has been associated with asthma severity and steroid resistance and PBEC from asthmatics were recognized earlier to produce enhanced levels of inflammatory mediators we hypothesized that asthma PBEC have an aberrant mRNA decay. We found that PBEC from 70% of mild asthma patients (n=27), as opposed to 15% from PBEC of healthy individuals (n=19), exposed to IL-17 plus TNF-α showed enhanced IL-8, IL-6 and G-CSF production, which was not due to differential IL-17A receptor expression. In PBEC from these patients, miR16 levels were elevated, also when exposed to TNF-α alone indicative of a defective mRNA decay, which is independent of IL-17, but that additional exposure to IL-17 aggravates the consequences of the defective mRNA decay. In addition, miR16 negatively correlated with lung function. Intriguingly, inflammatory mediator responses by PBEC with a defective mRNA decay showed resistance to dexamethasone. In short we have uncovered a molecular defect in PBEC in about 70% of asthma patients which may represent asthmatics who are relatively resistant to corticosteroids and hyper-responsive to IL-17. We also show that these patients tend to complement those that have a dominant Th2 profile as exemplified by periostin expression. IL-8 production in PBECs from asthmatic and healthy individuals.

miR16 in PBECs from asthmatics and healthy individuals.