



**Mechanisms of innate immunity involvement in asthma exacerbations:
Experiments with in vitro models of human airway epithelial cells (EpiAirway™)
and epithelial cell/fibroblast co-cultures (EpiAirway-FT™).** P. J. HAYDEN, G. R.
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Abstract #1567260:

Respiratory viral and bacterial infections are a major cause of asthma exacerbations. The airway epithelium is known to express innate immune responses to these agents via toll-like receptors (TLRs). The current studies investigated the effect of TLR stimulation in well differentiated in vitro models of human airway epithelium consisting of normal airway epithelial cells (AEC) (EpiAirway™) and AECs co-cultured with normal airway fibroblasts (EpiAirway-FT™). Both models display a well-differentiated mucociliary phenotype similar to in vivo airway epithelium and are cultured at the air-liquid interface. RT-PCR experiments confirmed expression of TLR 1, 2, 3, 5, 6, and TOLLIP by the models. Apical stimulation with TLR agonists resulted in decreased barrier function as determined by measurement of transepithelial electrical resistance (TEER), concomitant with secretion of numerous cytokines and chemokines. Forty-four cytokines, chemokines and growth factors were evaluated by bead based multiplex assays and/or ELISA assays. High levels of IL-8, fractalkine, G-CSF, IL-1 α , IL-1ra, IL-6, IL-8, IP-10, MIP-1 α , MIP-1 β , MIP-3 α , RANTES, TNF α and VEGF were observed after TLR stimulation. Moderate amounts of eotaxin-3 but only slight amounts of eotaxin-1 were detected in the absence of fibroblasts. However epithelial cell/fibroblast co-cultures produced high levels of eotaxin -1 after apical TLR stimulation. The most potent inducer of chemokine secretion was poly (I:C) (TLR3 ligand). Weaker induction was observed with PAM (TLR 1/2), Flagellin (TLR5) and FLS-1 (TLR6/2). TH2 cytokines that are characteristically associated with asthmatic disease (e.g. IL-13) synergized with Poly (I:C) in production of IL-8 and eotaxin-1. These data provide additional evidence of mechanisms by which epithelial/fibroblast TLR activation synergizes with TH2 conditions to produce chemokines that promote influx of neutrophils and eosinophils into the airway, hallmark features of asthmatic disease.

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