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Title: Synthetic response of stimulated respiratory epithelium: Modulation by prednisolone and iKK2 inhibition

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Body: Background: The airway epithelium plays a central role in wound repair & host defence & is implicated in the immunopathogenesis of asthma. Whether there are intrinsic differences between the synthetic capacity of epithelial cells derived from asthmatics & healthy controls & how this mediator release is modulated by anti-inflammatory therapy remains uncertain. Aims: We sought to examine the synthetic function of epithelial cells from different locations in the airway tree from subjects with & without asthma & to determine the effects of anti-inflammatory therapies upon this synthetic capacity. Methods: Primary epithelial cells were derived from 17 asthmatics & 16 controls. The release of 13 mediators from nasal & bronchial basal & air-liquid interface differentiated epithelial cells before & after stimulation with IL-1β, IL-1β & IFNγ or Poly-IC (TLR3 agonist) were measured using MSD or ELISA & the effects of prednisolone, rosiglitazone, & an inhibitor of nuclear factor K-β2 (IKK2i) were determined. Results: The pattern of release of cytokines & chemokines was significantly different between nasal & bronchial basal & differentiated epithelial cells, but not between health & disease. Stimulation of the epithelial cells caused marked up-regulation of most mediators which were broadly corticosteroid unresponsive, but attenuated by IKK2i. Conclusion: Synthetic capacity of primary airway epithelial cells varies between location & degree of differentiation, but is not disease specific. Activation of epithelial cells by pro-inflammatory cytokines & TLR3 agonism is attenuated by IKK2i, but not corticosteroids suggesting that IKK2i may represent an important novel therapy for asthma.