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Title: Co-ordinate regulation of vectorial cytokine release and paracellular permeability from polarized bronchial epithelium challenged with double stranded RNA (dsRNA)

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Body: Background: Respiratory virus infections, a common cause of asthmatic exacerbations, are associated with increased epithelial permeability and accumulation of inflammatory cells in airway lumen. We hypothesized that the innate anti-viral response of bronchial epithelium controls luminal inflammation by coordinating vectorial cytokine secretion with opening of tight junction (TJ) complexes. Methods: Human bronchial epithelial cells were challenged with dsRNA. Apical and basolateral secretion of IL-8 and TNF-α was measured by ELISA. Macromolecular and ionic paracellular permeabilities were measured by FITC-dextran and transepithelial electrical resistance (TER) respectively, while TJ integrity was assessed by immunofluorescent staining for ZO-1. Results: dsRNA induced apical and basolateral secretion of IL-8 and TNF-α, with a significant vectorial bias towards the apical surface; this was paralleled by an increase in both macromolecular and ionic permeabilities. These responses were completely blocked by dexamethasone. Neutralization of TNF-α partially inhibited IL-8 and TNF-α release and the increase macromolecular paracellular permeability but had no effect on TER. Inhibition of p38MAPK or JNK also inhibited IL-8 and TNFa secretion and prevented the increase in macromolecular permeability. Disruption of junctional ZO-1 induced by dsRNA was rescued by inhibition of p38 MAPK and JNK pathways. Conclusions: These findings suggest that bronchial epithelial cells control their inflammatory responses so that changes in macromolecular paracellular permeability are coordinated with vectorial secretion of chemokines and cytokines.