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POSTER PRESENTATION Open Access

IL-13Rα2/AP-1 complex signalling mediates airway epithelial repair without effects on remodeling pathways

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Objective/purpose

The airway epithelium serves as a physical defense barrier to the external environment for the underlying tissue and suffers frequent injury. The response to injury is inflammation followed by debris clearance and repair. Although IL-13 is known to be a key cytokine in mediating inflammatory and remodeling responses *via* signal transducer and activator of transcription 6 (STAT6) and early growth response protein 1 (Egr1), our laboratory has demonstrated that IL-13 is critical to airway epithelial repair *via* the release of heparin-binding epidermal growth factor (HB-EGF) and activation of epidermal growth factor receptor (EGFR). IL-13 signals through two receptors, IL-13Rα1/IL-4R and IL-13Rα2. IL-13Rα2 has previously been thought to act exclusively as a decoy receptor, however our findings show that IL-13Rα2 can act as a signaling receptor and is involved in mediating airway epithelial repair. Differential signaling via IL-13Rα1 or IL-13Rα2 may determine a remodeling versus repair response to injury in airway epithelium.

Methods

IL-13Rα1 and IL-13Rα2 functions were disrupted in Human Airway Epithelial (1HAEo-) cells using specific IL-13Rα1 and IL-13Rα2 blocking antibodies and small interfering RNAs (siRNAs). 1HAEo- cells were also transfected with activator protein 1 (AP-1) specific and scramble siRNA. Following specific antibody blocking or siRNA transfection, 1HAEo- cells were either stimulated with IL-13 (10 ng/ml) or mechanically injured. Supernatants and protein lysates were collected at different time points. Expressions of phospho-STAT6, STAT6, Egr1, and AP-1 were detected via Western blotting, while HB-EGF release in supernatants was quantified using ELISA. Furthermore, AP-1 activity in 1HAEo- cells after IL-13 stimulation or mechanical injury was measured using an AP-1-luciferase assay.

Findings

IL-13 stimulation resulted in upregulation of phospho-STAT6, Egr1 and AP-1 expression. AP-1 expression correlated with activity as determined by AP-1 luciferase assay. Following mechanical injury, the expression of phospho-STAT6 and Egr1 was inhibited when IL-13Rα1 function was disrupted, while induction of AP-1 expression is unchanged. In contrast, when IL-13Rα2 function was disrupted, HB-EGF and AP-1 expression was inhibited while STAT6/Egr1 signaling remains intact. Gene silencing of AP-1 had no effect on phospho-STAT6 expression in response to injury, however HB-EGF expression was significantly inhibited compared to scramble siRNA treated cells.

Deliverables

Our data indicates that IL-13 mediates repair of airway epithelial cells *via* IL-13Rα2 and AP-1, while remodeling responses downstream of STAT-6 and EGR-1 are signaled *via* IL-13 Rα1.

Relevance

Strategies directed towards augmentation of the IL-13Rα2/AP-1 pathway may lead to novel therapies which target the dysfunctional repair phenotype in asthmatic epithelium without adverse effects on airway remodeling.

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