Airway cells exposed to IL-17 develop altered MMP-TIMP expression and squamous phenotype

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Background

Interleukin (IL)-17 is a Th17 cytokine that supports chronic, neutrophil dominated inflammation and airway remodeling. We have previously shown that IL-13 transforms cultured normal human bronchial epithelial (NHBE) cells into goblet cells that secrete mucus, leukotrienes, and inflammatory mediators.

We hypothesized that IL-17 will transform NHBE cells into a secretory goblet cell phenotype and that the signaling mechanisms responsible may be different from IL-13 induced goblet cell metaplasia.

Methods

We examined the effect of IL-17 on mucin production and growth of human airway epithelial cells.

Cell culture model

NHBE cells were cultured for 14 days at an air-liquid interface along with IL-13, IL-17 or both IL-13 and 17.

Histological analysis

Histochemical analysis was performed using H&E staining, periodic acid-Schiff (PAS) staining, and immunostaining for involucrin, transglutaminase (TGM)-1, transforming growth factor (TGF)-β, matrix metalloproteinase (MMP)-1, MMP-9, and tissue inhibitor of metalloproteinase (TIMP)-1.

RT-PCR & ELISA

TGF-β and MUC5AC synthesis were assayed by RT-PCR and ELISA.

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Discussion

We showed that IL-17 alone increases stratified multilayered cellularity; squamous metaplasia. This is confirmed with a robust squamous metaplasia marker, involucrin, and an enzyme that crosslinks the cornified envelope of mature keratinocytes, TGM-1.

IL-17 decreased MMP9 deposition and increased TIMP1 activity. There was no effect of IL-17 on TGF-β or MUC5AC expression. These findings suggest that IL-17 dose-dependently induces squamous metaplasia via changes in the MMP-TIMP balance rather than TGF-β production from bronchial epithelium.

Conclusions

IL-17 appears to induce squamous metaplasia by suppressing expression of MMP-9 and increasing involucrin, independent of TGF-β secretion.

This cell culture model of IL-17 induced airway remodeling that recapitulates changes seen in the airway of persons with COPD and obliterative bronchitis and it may be useful for screening potential immunomodulatory or anti-inflammatory drugs.