IL-13 as a therapeutic target for allergic asthma tested in human precision-cut lung slices

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Introduction

Asthma is a chronic inflammatory disorder affecting nearly 300 million people. Patients with severe asthma are insensitive to inhaled corticosteroids and require novel therapeutic treatments. Interleukin (IL)-13 is considered as a key cytokine in the pathogenesis of asthma and is a pharmacological target for the treatment of airway inflammation and hyperresponsiveness. In the present study, the effect of IL-13 on cytokine release and methacholine-induced bronchoconstriction was evaluated in human precision-cut lung slices (PCLS). Antagonists for IL-13 and IL-13 receptor were evaluated as new anti-inflammatory therapeutics.

Methods

PCLS were prepared from human lung tissue. Human lung slices were incubated with 1-100 nM IL-13 with or without increasing concentrations of four different antagonists directed against IL-13 or the IL-4Rα chain of the IL-13 receptor. Induced cytokines were measured by ELISA. PCLS containing airways were pre-incubated with IL-13 and bronchoconstriction was induced by addition of methacholine. Bronchoconstriction was visualized by videomicroscopy.

Results

IL-13 induced cytokine release
It could be shown that human IL-13 stimulates the secretion of eotaxin-3 and TARC in human lung tissue after 24 h. Both cytokines are biomarkers for eosinophil and T-cell recruitment into lung tissue (Figure 2).

Inhibition of IL-13 induced cytokine release
Chemokine expression could be inhibited almost completely in a dose-dependent manner by addition of specific inhibitors acting either on the IL-13 ligand itself or the IL-4Rα chain of the IL-13/IL-4 receptor complex. The concentration of IL-13 for the inhibition experiments were chosen based on the titration of IL-13 shown in Figure 3.

Human IL-13 receptor
The presence and location of the IL-13 receptor in PCLS was confirmed in lung sections used for functional ex vivo studies. The results are presented for human (Figure 4).

IL-13 induced hyperreactivity
Pre-incubation with IL-13 induced hyperreactivity in human PCLS indicated by decreased EC₅₀ values and an increase in maximum bronchoconstriction after methacholine provocation (Figure 5).

Conclusion

This study shows that PCLS can be used to mimic IL-13 induced inflammation and airway hyperreactivity in human lungs. The effect of different inhibitors developed as asthma therapeutics could be compared on reduction of eotaxin-3 and TARC in human lung tissue.

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