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SIL-6R α amplified IL-6 signaling in bronchial epithelial cells defines a subgroup of asthma patients low in sputum eosinophils

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Background: Asthma is clinically stratified into type 2-high and type 2-low asthma. Limited success has been achieved in developing drugs that target type-2 low inflammation. Previous studies have linked IL-6 signaling to type 2-low asthma.

Objective: We sought to study the role of IL-6 signaling in asthma in further detail and to develop an IL-6 gene signature that may be used for diagnostic purposes to identify patients high in IL-6 signaling.

Methods: Human airway epithelial cells were stimulated with different combinations of IL-6, sIL-6R α , sgp130 (Olamkicept), and anti-IL6 (Tocilizumab) to assess their effect on signaling pathway activation, epithelial barrier integrity, and gene expression. The gene signature was used to identify IL-6 high patients in a clinical cohort.

Results: The presence of sIL-6R α amplified the activation of the IL-6 pathway, shown by stronger gene induction in airway epithelial cells compared to IL-6 alone. Olamkicept and Tocilizumab effectively inhibited the effect of IL-6 and sIL-6R α on gene expression. We developed an IL-6/sIL-6R α gene signature and observed enrichment of this signature in bronchial biopsies but not nasal brushes from asthma patients. Patients high in the IL-6/sIL-6R α gene signature had significantly lower levels of sputum eosinophils.

Conclusion: sIL-6R α amplifies IL-6 signaling in bronchial epithelial cells. We find evidence for higher local airway IL-6/sIL-6R α signaling in asthma patients with low sputum eosinophils. These findings provide a rationale for the evaluation of olamkicept as a potential drug to be repositioned for patients with non-eosinophilic IL-6 high asthma.

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