

**Early airway inflammation in allergic asthma:
Aspects of pulmonary innate immunity**

AKADEMISK AVHANDLING

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ABSTRACT

Allergic asthma is a chronic disease in which allergen-induced inflammatory processes of the airways contribute to the development of symptoms and eventually may lead to remodeling of the airway tissue.

In the present work low-dose allergen inhalation challenges of individuals with asthma were used as a model to delineate inflammatory events occurring in an early phase of the allergic airway inflammation associated with asthma. The thesis focuses on studies of the pulmonary innate immune system in this context, specifically alveolar macrophages and their mediators as well as anti-inflammatory and antibacterial peptides and proteins.

Low-dose allergen exposure of asthmatic subjects induced an asymptomatic allergic airway inflammation, characterized by increased bronchial reactivity and increased numbers of total cells and eosinophils in BAL fluid, accompanied by raised levels of ECP in serum.

The macrophage expression of surface antigens as well as the expression of cytokines by BAL cells enriched for alveolar macrophages was investigated using flow cytometry and RT-PCR respectively. An altered alveolar macrophage phenotype pattern consistent with an increased proportion of monocytes within the population and increased mRNA levels of IL-13 were found following allergen exposure.

The feasibility of induced sputum as a method to recruit and study pulmonary macrophages was evaluated. Induced sputum retrieved from healthy individuals was found to provide a lower total number of cells showing a differential distribution of cell populations and a differing macrophage phenotype pattern compared to material collected with BAL.

To identify disease-associated alterations of the BAL fluid polypeptide pattern after induction of allergic airway inflammation, BAL fluid enriched for polypeptides was fractionated and investigated using RP-HPLC, Western blot and structural analyses. Decreased post-challenge levels of the anti-inflammatory protein CC16 were found, indicating a loss of anti-inflammatory activity in the airways in an early phase of the airway inflammation in asthma.

To investigate effects of an induced allergic inflammation on parts of the pulmonary antimicrobial defense system, antibacterial components in BAL fluid derived from asthmatics and controls were analyzed using an *in vitro* bio-assay and structural analyses. Similar levels of antibacterial activity were found and several active components were identified in BAL fluid retrieved from asthmatics before and after allergen challenges. Comparing antibacterial profiles of non-challenged asthmatics to that of healthy individuals, we found a larger number of antibacterial components together with higher levels of baseline activity in the patients, indicating that allergic asthma is associated with an augmented pulmonary expression of antibacterial components.

In conclusion, early stage allergic airway inflammation is associated with an altered balance of pro- and anti-inflammatory effectors of innate immunity, likely to be of importance in the further development of airway inflammation in asthma.

Key words: Allergic asthma, low-dose allergen challenge, induced sputum, alveolar macrophage, cytokine, CC16, antibacterial activity, antibacterial peptide

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