

DESCRIPTION FOR THE GENERAL PUBLIC

Asthma is the most common chronic respiratory disease with recurrent acute episodes of airway inflammation and subsequent cycles of tissue repair triggering structural alterations of the lung tissue leading to progressive worsening of lung function. It is believed, that the chronic inflammation in asthma is result of dysregulated immune response to environmental factors. Consequently, several immune effector cells are activated in the airways including T cells, mast cells, eosinophils, basophils, macrophages as well as airway epithelial cells as well as smooth muscle cells. In this complexity, T cells emerge as the key players in asthmatic inflammation, by orchestrating both innate and adaptive immune response. For many years it was believed that in asthmatic patients, airway inflammation is driven by T cells with the most important role attributed to T helper type 2 (Th2) cells and their cytokines. Nowadays is growing evidence that not only Th2 cells have been associated with development and progression of asthma, but also T helper 17 cells (Th17) might be involved. In addition, regulatory T (Tregs) cells are also recruited to site of inflammation to dampen excessive response. However, data on the function of Tregs in asthma in humans are largely incomplete and quite inconsistent.

Our previous study revealed major changes in frequency of Tregs and expression of transcription factors FOXP3 and Helios during acute asthma episodes. Asthma exacerbations were characterized by reduced frequency of Tregs when compared to control group and stable asthma. In control group and stable asthmatics, majority of Tregs were FOXP3+Helios+ and positively correlated with FEV1%. In addition, inter-correlation of these two transcription factors was very high. In contrast, during acute asthma episodes the frequency of Tregs expressing both transcription factors were reduced. Interestingly, Tregs FOXP3+Helios- as well as both FOXP3- and Helios- were expanded in acute asthma episodes, and both subsets were negatively correlated with FEV1%. Based on these data it can be assumed that the stability of Tregs is determined by interaction between FOXP3 and other transcription factors.

The aim of this project is to study the alterations in phenotypic stability of the Tregs in asthma. It is hypothesized that Tregs of asthmatic subjects exhibit distinct profile of molecules involved in maintenance their stable regulatory phenotype. Such Tregs are prone to the action of cytokines produced by airway epithelium exposed to factors such as allergens, viruses and environmental pollutants that trigger in asthmatics conversion of FOXP3+ Tregs to exTregs (exhibit conventional T cells phenotype). As a result, exTregs acquire effector-like phenotype and failed to inhibit inflammation in lungs and contribute to acute asthma episodes.

At the first stage of the study transcriptome of Tregs will be analyzed using next generation sequencing. The aim of this part of the study is to identify a specific pattern of gene expression in asthmatic subjects, which contributes to the loss of stable phenotype of Tregs. In second stage, the impact of cytokines produced by activated airway epithelial cells on stability of regulatory phenotype of Tregs will be evaluated to prove hypothesis that Tregs in asthmatics are prone to phenotype changes. In last part of the project, Tregs will be co-cultured with human bronchial epithelial cells (HBECs) in the presence of blocking antibodies specific to airway epithelial cell-derived cytokines. At this stage we will be able to confirm that cytokines produced by airway epithelium are responsible for conversion of Treg cells to conventional T cells.

We assume that the data obtained in the project will essentially contribute to the extension of knowledge on the complexity of Tregs function in the immune pathology. Scientific information elaborated during the course of this study, will contribute to the further diagnostic and therapeutic strategies in asthma. The results will be also useful in better understanding of other immune pathologies including autoimmune disease.