Karolinska Institutet

Institutionen för Medicin, Solna

Smoking and human airway inflammatory cells

Studies with focus on T cells in the development of COPD

AKADEMISK AVHANDLING
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ABSTRACT

Chronic obstructive pulmonary disease (COPD), the fourth leading cause of death worldwide, is characterized by persistent airflow limitation and a chronic inflammation of the lungs. One of the major risk factors is long-term exposure to cigarette smoking. The key inflammatory cells in the pathogenesis of COPD are macrophages, neutrophils and CD8+ T lymphocytes.

The heterogeneity of COPD and the need for identifying patient subgroups is becoming increasingly recognized. Besides, the differences in the immunopathology of current- and ex-smokers with COPD are uncertain. Characterizing the inflammatory mechanisms driving the disease in different subtypes of patients, including differences between men and women, will likely aid diagnostic procedures and tailoring of treatment strategies and caretaking.

To investigate the airway and systemic inflammatory profile and the role for T cells in smoke-induced inflammation and COPD, bronchoalveolar lavage (BAL) fluid, blood and chest high resolution computed tomographthy (HRCT) scans were collected from a gender- and age-matched cohort of 40 never-smokers, 40 smokers with normal lung function and 38 COPD patients (27 current smokers and 11 ex-smokers). BAL characteristics, including the distribution of inflammatory cells, were assessed. T cells subsets in BAL and blood were phenotyped using flow cytometry, and the levels of cytokines, chemokines and growth factors in BAL fluid were assessed with a multi-plex bead-based assay. HRCT images of the lungs were analyzed for the investigation of morphological patterns and correlated with the cellular inflammatory patterns of the lungs. In addition to univariate analysis, multivariate data analysis with OPLS-modeling was used for discovering within- and between group variations, and potential biomarkers.

The frequencies of several T cell subsets, including CD8+ T cells and NKT-like cells, both with cytotoxic capacities, and CD103+CD8+ T cells, were increased in BAL from smokers, regardless of airway obstruction. In COPD ex-smokers, the levels were similar to those of never-smokers. A more detailed phenotypic characterization of T cells revealed subsets specifically altered in smokers with normal lung function or COPD patients, including FOXP3+ regulatory T cells. A type 1 T cell-driven inflammation was indicated for female, but not male, COPD patients. Lung density, as measured by HRCT, was higher in smokers compared to both never-smokers and COPD patients and correlated with the cellular inflammation in the lungs.

Taken together, these findings suggest that current smoking status has a larger impact on the distribution of lymphocytes in BAL than does airway obstruction. A detailed characterization of T cell subsets is important for finding disease-specific alterations. Gender-specific differences among smokers and COPD patients can be detected on a cellular level.