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Increase of Th17 cells in peripheral blood of patients with chronic obstructive pulmonary disease

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KEYWORDS
Chronic obstructive pulmonary disease;
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Summary
Background: Chronic obstructive pulmonary disease (COPD) is a progressive disorder characterized by an inflammatory response to cigarette smoke. A disorder in immune regulation contributing to the pathogenesis of COPD has been suggested, however, little is known about the involvement of $CD4^+$ T cells. To determine the distribution of different $CD4^+$ T cell subsets in patients with COPD, current smokers without COPD (CS) and healthy subjects (HS), and its correlation with pulmonary function.
Methods: Th1, Th2, Th17 and Treg, subsets, were quantified by flow cytometry in peripheral blood (PB) of 39 patients with COPD, 14 CS and 15 HS. Correlations were assessed with Spearman's rank test. The association between Th17 and lung function was evaluated with a multivariate logistic regression analysis.
Results: An increase of Th17 cells (median 9.7% range 0.8–22.5%) was observed in patients with COPD compared with CS (median 2.8% range 0.8–10.6) and HS (median 0.6% range 0.4–1%, $p < 0.0001$). Th1 and Tregs subsets were also increased in COPD and CS compared to HS. Inverse correlations were found between Th17 with FEV_1%p $r = -0.57$ and with FEV_1/FVC $r = -0.60$, ($p < 0.0001$ for both comparison). In addition, increase of Th17 predicted the presence [OR 1.76 (CI 95% 1.25–2.49, $p = 0.001$)] and severity of airflow limitation [OR 1.13 (CI95% 1.02–1.25, $p = 0.02$)].

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Conclusions: The increase of Th17 response and the lost of balance between $CD4^+$ T cell subsets, suggest a lack of regulation of the systemic inflammatory response that may contribute to pathogenesis in COPD patients.
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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive, largely irreversible condition characterized by airflow limitation.[1] Cigarette smoking is the main risk factor for the development of COPD.[2] Tobacco smoking elicits an inflammatory response in the lungs of all smokers, but in those who develop COPD it is enhanced and fails to resolve after cessation of smoking, which suggests that smokers who develop COPD have an abnormal regulation of the inflammatory response in the lungs. [3] However, the relationship between the inflammatory response in the lungs and the accelerated decline in forced expiratory volume in 1 s (FEV_1), which characterizes this disease, is far from clear. In this sense, by considering that COPD is associated with an abnormal inflammatory response in the lungs, Agustí et al., suggested that excessive inflammation is the key to susceptibility, supporting the notion that COPD has an autoimmune component.[4] Inflammation in COPD shows an increase in the total number of T cells in lung parenchyma, and peripheral and central airways.[5] $CD4^+$ and predominantly $CD8^+$ T cells infiltrates in lung tissue of COPD patients exhibit either a Th1 or a Th2 phenotype characterized by expression of interferon-gamma (IFN-γ) or interleukin-4 (IL-4).[6] Several groups have proposed that the alveolar tissue destruction observed in emphysema represents an autoimmune disorder implicating T cells as central to disease pathogenesis.[7–11] However, implication of T $CD4^+$ cells subsets involved in the inflammatory response may determine whether polarization of one of these cells is involved in perpetuating the inflammatory process that leads to the development of this disease.

IL-17A and IL-17F, two members of IL-17 family of cytokines, have been shown to induce neutrophilic airway inflammation by stimulation of neutrophil chemotaxis and mucin gene expression by bronchial epithelial cells.[12,13] Given the recent identification of Th17 cells, as a distinct effectors T cell subset, secreting IL-17A, IL-17F, IL-22 and TNF-α,[14,15] these TH17 cells have been implicated in the pathogenesis of autoimmune disorders.[16]

Based on the hypothesis of the autoimmune component in COPD and the important role of Th17 cells in the development of autoimmune disorders, we studied the distribution of this effectors subpopulation in peripheral blood (PB) of COPD patients, current smokers without COPD (CS) and healthy subjects who never smoked (HS).

Patients and methods

Patients

The study was carried out at the National Institute of respiratory diseases, in Mexico City. Included were 39 consecutive patients with a previous COPD diagnosis at least 1 year prior to the study, 14 CS who wanted to stop smoking, and 15 HS. The protocol was authorized by the ethics and research committees of the institution and all subjects signed a letter of informed consent. Patients belonged to a cohort of subjects with COPD who were evaluated in a clinically stable, exacerbation-free period 6 weeks prior. They had history of tobacco smoking of at least 10 pack/years.

Subjects who met the criteria for COPD but had a known alternative respiratory disorder (such as bronchiectasis or asthma) were excluded. The CS, was recruited when they attended the smoking cessation program of the Institute. Both CS and HS had normal lung function tests. Subjects from either group having additional comorbidities with some autoimmune component such as type 1 diabetes mellitus, or rheumatoid arthritis, among others, were excluded as well.

Diagnosis of COPD

COPD diagnosis was established according to the history of tobacco smoking, symptoms and pulmonary function tests with FEV_1/FVC post-bronchodilator lower than 70%,

Table 1 Demographic and clinical characteristics.

	COPD $n = 39$	CS $n = 14$	HS $n = 15$	*p Value
Age-yrs	66 ± 10	64 ± 7	68 ± 6	0.4
Gender, M/F	30/9	9/5	8/7	0.2
Tobacco, pack/yrs	45 ± 26	30 ± 26	–	0.35
FEV_1 ml	1.57 ± 0.7	2.7 ± 0.9	3.8 ± 0.4	<0.0001
FEV_1 % predicted	56.7 ± 23.1	99.5 ± 18.7	109.8 ± 12	<0.0001
FVC ml	2.9 ± 1.02	3.4 ± 1	4.03 ± 0.47	0.1
FVC % predicted	82.5 ± 20.3	98.2 ± 17	107.7 ± 11.3	0.002
FEV_1/FVC	53 ± 13.8	80.6 ± 5.3	80.5 ± 6.2	<0.0001

Definition of abbreviations: CS = Current smokers; HS = Healthy subjects Values are expressed as mean and standard deviation.
*ANOVA One way Analysis.

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