Persistence of systemic inflammation in COPD in spite of smoking cessation

La persistenza dell'infiammazione nella BPCO nonostante la cessazione dal fumo

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Cigarette smoking, which exposes the lung to high concentrations of reactive oxygen species (ROS), is the major risk factor for chronic obstructive pulmonary disease (COPD) [1]. ROS are responsible for lipid peroxidation, protein oxidation, DNA alterations, and cell damage. Coupled with oxidant/antioxidant imbalance, these changes lead to lung inflammatory responses through multiple pathways, among which the activation of stress kinases (c-Jun activated kinase, extracellular signal-regulated kinase, p38 kinase) and redox-sensitive transcription factors, such as nuclear factor (NF)-kappaB and activator protein-1, resulting in the expression of kinase- and NF-κB-dependent proinflammatory cytokines and chemokines [2].

COPD is related to smoking habit in the majority of cases, and smoking cessation is the single most beneficial and effective way to reduce COPD morbidity, hospital admissions and disease progression [1]. However, persistent inflammation in the airways of COPD subjects may continue after smoking cessation, as shown by studies showing a similar number of airway inflammatory cells, including CD4+ and CD8+ lymphocytes, in the bronchial biopsies of both current smokers and ex-smokers with COPD [3], and by other studies analyzing the composition of induced sputum, which showed a persistent increase in the number of airway neutrophils and lymphocytes one year after smoking cessation [4]. A persistent overall burden of non invasive markers of oxidative stress has also been found in the airways after smoking cessation [5]. Also systemic markers of inflammation were found elevated in the serum of COPD patients [6,7]. Taken together, these studies indicate that, in COPD patients, ongoing inflammation is persistent in spite of smoking cessation: this phenomenon is considered one of the determinants of the progressive decline in lung function.

This issue of *Multidisciplinary Respiratory Medicine* features an article by Serapinas et al. [8] on the presence of markers of systemic inflammation in a sample of 320 COPD patients according to their smoking status. The authors devoted their attention to the serum concentrations of the following set of oxidant markers: C-reactive protein (CRP), alpha-1 antitrypsin (AAT), tumor necrosis factor-α (TNF-α), and soluble tumor necrosis factor receptor (sTNFR)-1 and sTNFR-2. The markers were analyzed in relation to current smoking (n = 202) and ex-smoking (n = 61), as well never-smoker (n = 57) status. Mean (SD) forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) (%) was 54.8 (10.7), while mean (SD) pack/years in smokers and ex-smokers was 22.7 ± 12.9. The main result of the study was that AAT, CRP and sTNFR-1 concentrations were significantly increased in both smokers and ex-smokers as compared to never-smokers.

This study adds to the number of reports showing the presence of systemic and airway inflammation in COPD patients, irrespective of whether they were current or ex-smokers. Although inflammation is also present as a consequence of smoking in the airways of asymptomatic smokers, a significant decrease of oxidant markers occurs after smoking cessation in these subjects [4]. It is not known why - at variance with what occurs in asymptomatic smokers - inflammation persists after quitting smoking in

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COPD patients [1].
One of the leading explanations is the altered regulation of inflammatory gene expression, even though epigenetic mechanisms are implicated too. In a recent study it has been shown that smoking *per se* modulates the expression of genes from all the inflammatory functional groups except for the matrix metalloproteinases group [10]. The inflammation related genes (except TNF-a) were found to be up-regulated, while genes from the growth factor/receptor group, adhesion molecules and vessel tone/maintenance factors were down-regulated in smokers.
It is notable that all of these genes exhibited a similar profile in patients with moderate COPD, suggesting a crucial role of cigarette smoking in the genesis of these changes. However, one of the most significant changes associated with COPD was the increased expression of matrix metalloproteinases [10]. Although the COPD puzzle is still far from being solved, multidisciplinary research linking the different expertise of epidemiological, biological, translational and clinical nature is believed to be the best response to such a difficult task.

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