Editorial

Immune phenotypes in lung cancer patients with COPD: potential implications for immunotherapy

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Lung cancer remains one of the most commonly diagnosed neoplasms, being responsible for the majority of cancer-related deaths worldwide (1,2). Chronic obstructive pulmonary disease (COPD) is also a major cause of morbidity and mortality globally. COPD underlies lung cancer in the majority of the patients. Despite that these two diseases are highly prevalent, share the main risk factor (tobacco smoking), and have a huge impact on public health, their pathophysiologic mechanisms are not yet fully understood (3,4). In lung cancer, the role of tumor-infiltrating immune cells (especially T-lymphocytes, TILs) and the immune checkpoints (particularly the PD-1/PD-L1 pathway) seems essential for the development of an adequate microenvironment for cancer initiation, development, and progression (5,6). In COPD patients, the elevated incidence of viral/bacterial infections and the reported increased risk of lung cancer strongly suggest the existence of an altered cell-mediated immune response, which may jeopardize the innate protective mechanisms against external agents or malignancy (7-9). The main immunologic alterations in COPD patients are two-fold: (I) dysregulation of T-cells in their lungs, mainly characterized by a lower proportion of $CD4^+$ along with an increased proportion of $CD8^+$ (10,11) and (II) T-cell exhaustion, represented by a loss of the effector function due to the chronic binding of immune checkpoints on T-cells; a phenomenon that is also frequently observed in chronic infections and autoimmune events. Importantly, the expression of PD-1 on T-cells and their subsequent exhaustion were shown to contribute to the dysfunction of the immune response that has been identified in patients with COPD (11,12).

The recent article published in the *American Journal of Respiratory and Critical Care Medicine* by Mark *et al.* (13) aimed to elucidate how the immune checkpoints and T-cell immunity could be interrelated in patients with COPD and non-small cell lung cancer (NSCLC) (13). The investigation was conducted on the basis of two different human cohorts. In the first cohort, patients with suspected NSCLC who were candidates for curative lung resection were prospectively included. Fresh tumor and non-tumoral lung specimens were obtained from all the patients. Immune cell composition was analyzed in all the samples (13). The majority of these patients also had COPD. Smokers with COPD and never smokers were also recruited in the investigation (13). All subjects had lung cancer. Interestingly, significantly higher proportions of $CD3^+$ (strongly related with the degree of airflow obstruction), $CD4^+$, and $CD8^+$ cells (in which IFN-γ levels were also increased) were detected in the lung specimens of the COPD patients with lung cancer compared to non-

COPD smokers (13). Increased levels of Th1-polarized $CD4^+$ lymphocytes were observed in the lung tissue specimens of the COPD patients, while no differences in regulatory T-cells (Treg) or Th17 differentiation program were detected between the COPD patients and non-COPD smokers (13). Nevertheless, a significant correlation was found between cigarette smoking and Th17 differentiation levels in the lung tissue of patients with COPD. Similar results were observed in a parallel animal model of tobacco exposure that was also conducted in the same study (13). These findings suggest that Th17 is induced in response to cigarette smoking rather than in response to airway obstruction in patients with underlying COPD.

No significant differences were found in the expression levels of the analyzed markers $CD4^+$, $CD8^+$ PD-1, or in myeloid cells PD-L1 in the lung tissue between the COPD and non-COPD patients (13). Additionally, Th-1 and T-Cells checkpoints (TIM-3 and PD-1 on $CD4^+$) were shown to be overexpressed in the tumor lung specimens of the COPD patients compared with the non-COPD smokers (13).

In the second study cohort, patients with advanced NSCLC who had been treated with immune checkpoint inhibitors (ICIs), either anti-PD-1 or anti-PD-L1 were retrospectively evaluated. Their clinical characteristics, progression-free survival (PFS), and overall survival (OS) were analyzed to assess whether changes in T-cell differentiation and the expression of immune checkpoints could influence prognosis following immunotherapy (13). Interestingly, patients with lung cancer and underlying COPD had much better PFS than lung cancer patients with no COPD, while no differences in OS were detected between the two study groups (13). PFS was also better in smokers or ex-smokers compared with non-smokers, and following a multivariate analysis COPD was the only variable that maintained statistical significance for a better prognosis (13). When ex-smokers were analyzed separately, patients with COPD showed not only a better PFS but also a significantly higher OS than those without COPD (13).

The study conducted by Mark *et al.* (13) confirms the relevance of immune imbalance in lung cancer patients with COPD and how the alterations in the immune equilibrium, especially those taking place in $CD4^+$ and $CD8^+$ T-cells and in the immune checkpoints, not only persist but are also present in the tumor cell composition, especially when both diseases coexist (13). These interesting findings strongly suggest the existence of an immunological link between both disorders. These authors also demonstrated an excess in the numbers of $CD8^+$ T-cells along with an overproduction of IFN-γ, as well as an important increase in Th1-polarized $CD4^+$ following stimulation *in vitro* with phorbol myristate acetate-ionomycin (13). Importantly, a specific COPD phenotype based on the increased expression of Th17 was not found (13). $CD4^+$ differentiation into Th17 is essential for maintaining mucosal antimicrobial immune defense and to control lung inflammation, while $CD8^+$ production of IFN-γ plays a major role in inflammation and viral infection control (14,15). Interestingly, all these findings are consistent with the natural history of COPD, characterized to some extent by the presence of chronic inflammatory events in the lungs and airways of the patients, who in turn, are exposed to a greater risk to viral infections (4). In line with these findings, in a previous study from our group, a relative predominance of Th1 cytokines and M1 macrophages was demonstrated in the blood and tumors of patients with underlying COPD (3). The reported findings showed that a stronger proinflammatory pattern exists in these patients. We concluded that inflammation should not be targeted systematically in all patients with lung cancer (3). We also suggested that screening for the presence of underlying respiratory diseases and identification of the specific inflammatory pattern should be carried out in patients with lung cancer, at least in early stages of their disease (3).

Despite that $CD8^+$ PD-1 levels were shown to be increased in lung tissues of patients with COPD in a previous study (10), such findings were not confirmed in the study conducted by Mark *et al.* (13). These discrepancies are probably due to differences in patients characteristics between the two studies. In the latter investigation all patients including those with COPD had lung cancer (13), which was not the case in the former investigation (10).

Finally, in the investigation conducted by Mark *et al.* (13), the most important result was the impact of COPD on advanced-stage lung cancer in the patients treated with ICIs (13). This finding is especially relevant as COPD is widely considered as a negative prognosis factor in lung cancer patients (16,17). Moreover, ICIs can potentially enhance the proinflammatory status in COPD patients, which in turn, may worsen lung cancer progression. However, the results recently demonstrated (13) are in contrast to this notion, which are in line with previous knowledge on the potential COPD-driven immunological imbalance in lung cancer (3,12). This scenario may lead to the overexpression of immune checkpoints in their T-cells, thus rendering the patients more prone to respond to

immunotherapy. Besides, it would be possible to speculate that immunotherapy may even have a beneficial effect in COPD alone with no lung cancer. Certainly, more studies are needed to better define the implications of cellular immunology and immune checkpoints in the potential links between COPD and lung cancer in patients as shown to occur with other biomarkers in patients (18-20). Elucidation of the most relevant molecular mechanisms will pave the way to predict the response to immunotherapy in patients with lung cancer with and without COPD.

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Footnote

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