Editorial

Immunoescape the link between emphysema and lung cancer?

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Chronic obstructive pulmonary disease (COPD) has been reported as a risk factor for lung cancer (LC) (1) independently of smoking and mainly related with the presence of emphysema, even in non-smokers (2). The mechanisms of this association are poorly understood. It has been hypothesised that the inflammation and oxidative stress present in COPD could facilitate carcinogenesis (3). More recently, several studies have shown the importance of cancer induced inflammation impairing the antitumoural immunity (4). It is accepted that LC avoids immunosurveillance by several mechanisms: (I) impairing the number and activity of T cells as a consequence of the hostile environment created by tumour (5) such as inflammation; (II) increasing the number of regulatory T cells (Treg) in lung tumour that downregulates the immune response against LC and contributes to its progression (6); (III) favouring the increase of myeloid derived suppressor cells (MDSC) that downregulates the function of T cells (7); and, (IV) preventing the activation of T cells by antigen presenting cells (APC), mostly dendritic cells (DC). Regulatory DC have shown to be induced by tumour derived factors and represent a potentially important player in supporting tumour progression suppressing the development of antitumour responses (8). Most of these phenomena, that may create favourable conditions for tumour growth, have been associated to COPD (7,9,10). However, this topic in emphysema is unknown.

To add evidence to this issue Kerdidani and colleagues, in a recent article published in the *Journal of Immunology* (11), evaluated the immunological responses that control growth of nascent lung cancer cells in an experimental model of mice emphysema. They postulated an impaired immunological response against tumoural cells in the microenvironment of pulmonary emphysema that creates the adequate conditions to escape immunity. To test their hypothesis, they implanted OVA-expressing cancer cells in the lungs of mice with cigarette smoke-induced emphysema evaluating the control growth and effector functions of cytotoxic T cells (CTLs), DC-T cells axis and finally, made a parallel analysis of the transcriptome of human lung tumours. First of all, they found that CTLs fail to control the growth of lung cancer cells in the presence of emphysema, probably due to a decreased number of CTLs and an increased expression of costimulatory inhibition through CTLA-4, PD-1 and TIM-3. A smaller percentage of intratumoural CTLs of emphysematic mice produced the cytokines TNF-α and IFN-γ. There was also an expansion of CD4 T reg cells. Second, emphysema suppresses the effector functions of cancer Ag-specific CTLs. To reach this conclusion they sorted and expanded CTLs from

tumour-infiltrated lymph nodes outside the emphysema microenvironment in the presence of IL-2. Then they tested their cancer specific cytotoxicity and proliferative response to secondary stimulation. Compared to control CTLs, emphysema associated CTLs showed impaired ability to kill OVA-Lewis lung cancer cells *in vitro* and proliferated less upon transfer in OVA cancer-bearing mice *in vivo*. These results suggest that the emphysema microenvironment severely impairs cancer Ag specific presentation to CD8-T cells. Third, the presence of higher percentages of immature $CD11c^{+}$ myeloid DCs, expressing inhibitory molecules (PD-L1) and immunosuppressive enzymes (IDO), failed to mount effector T cell responses against cancer-specific Ags, representing (DCs) a new and potentially important player in supporting tumour progression and suppressing the development of antitumour immune responses. Fourth, they also observed that antioxidants rescued splenic DCs from CD80/CD40/MHC suppression and PD-L1/IDO upregulation which suggests the implication of oxidative stress mechanisms in emphysema tumour-induced immunosuppression. And finally, they found a downregulation of differentially expressed genes involved in antitumour immunity in patients with mild emphysema in the transcriptome analysis of primary human lung tumours.

This study gives a better understanding of the biology of antitumour immunity in emphysema- associated cancer and highlights the role of the costimulatory inhibitory molecules (CTLA-3, PD-1, TIM-3), the effector functions of CTLs and the DC/T cells axis in the tumour microenvironment in emphysema and might help to identify which genes could be implicated.

Collectively, Kerdidani *et al.*'s very interesting results introduce an important link between emphysema and lung cancer that are the immunological mechanisms that block antitumoural immunity (immunoescape). Their findings could open a new opportunity to eventually prevent LC in patients with emphysema with immunotherapies that target immune suppressive regulatory pathways.

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Footnote

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