



Emphysema assessment for personalized immunotherapy response prediction in lung cancer patients

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Sauleda J, Verdú FJ, Scrimini S, Sala E, Pons J. Immunescape the link between emphysema and lung cancer? *J Thorac Dis* 2019;11:S329-30.

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After editorial request, we considered the expert opinion on the link between emphysema, immune suppression and lung cancer, expressed in two invited editorials on our published article entitled “Cigarette Smoke-Induced Emphysema Exhausts Early Cytotoxic CD8⁺ T Cell Responses against Nascent Lung Cancer Cells” (1). We reflected on both reviews, entitled “Understanding the mechanisms of immune-evasion by lung cancer in the context of chronic inflammation in emphysema” by Salehi-Rad *et al.* (2) and “Immunescape the link between emphysema and lung cancer?” by Saulea *et al.* (3). We would like to give responses to the issues that have been raised.

Both editorials address clinical implications of our findings for lung cancer patients. It has long been recognized that lung tumors develop more frequently in emphysematous lungs, but to date there are more diagnostic rather than therapeutic implications from identifying emphysema in patients who are being investigated for lung cancer. As such, emphysema confers increased risk for lung cancer in smokers (4) and in adults with a solitary pulmonary nodule (e.g., Brock University cancer prediction equation). Several meta-analyses on immune checkpoint inhibitor efficacy in non-small cell lung cancer (NSCLC) advocated a higher response rate in smokers, but there was no clear evidence for a link with smoke-induced emphysema/COPD (5). Our data put forward the hypothesis that chronic

inflammation in the context of emphysema suppresses adaptive immunity responses against cancer antigens and implicate the inhibitory molecules PD1/PD-L1 in this process. Apart from giving a deeper mechanistic insight on tumor-emphysema interactions, we point to PD1/PD-L1 immune checkpoint blockade as particularly promising for this group of lung cancer patients.

We acknowledge limitations of our orthotopic transplantation model. However, to date there is no laboratory-animal bioassay for lung tumor growth in the presence of cigarette smoke-induced emphysema: cigarette smoke exposed mice rarely develop lung tumors (1). Alternative genetically engineered mice models (GEMs) capture certain aspects of disease pathogenesis, but seem to represent specific patient phenotypes (6). Ovalbumin (OVA) indeed constitutes an artificial cancer antigen. Still, both emphysematous and control (healthy) lungs were inoculated with the same OVA-expressing cancer cell line and profound differences were observed not only in OVA specific, but also in total anti-tumor T cell responses between the two groups.

Despite limitations of existing *in vivo* platforms, three key factors testify to the extrapolation of our findings to the human system: (I) increased PD1/PD-L1 expression is observed in COPD/emphysema (7), (II) inhaled steroid-treatment decreases lung cancer risk in COPD, presumably

through dampening chronic inflammation (8), (III) two recent studies confirm that COPD patients respond better to checkpoint inhibitors (9,10).

There is an unmet need to develop precision immunology tools for clinical use. A number of factors, in addition to PD-L1 status, can affect response to immune checkpoint inhibitors: a high tumor mutational load, increased numbers of T and dendritic cells, a memory profile of CD8⁺ T cells. These emerging biomarkers show promise but have yet to be standardized and tested, prior to incorporation in the clinics. Pulmonary function testing and computed tomography (CT) of the chest, that can detect emphysema, are routinely performed in lung cancer patients and are thus ideal for personalized lung cancer therapy approaches. Our findings strongly propose the addition of emphysema severity scores (such as CT-emphysema score or DLco) in predictive algorithms of immune checkpoint inhibitor responses.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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