Editorial

# Understanding the mechanisms of immune-evasion by lung cancer in the context of chronic inflammation in emphysema

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*Comment on:* Kerdidani D, Magkouta S, Chouvardas P, *et al.* Cigarette Smoke-Induced Emphysema Exhausts Early Cytotoxic CD8(+) T Cell Responses against Nascent Lung Cancer Cells. J Immunol 2018;201:1558-69.

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Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disorder that constitutes the third leading cause of death worldwide. The presence of COPD is associated with an increased incidence of lung cancer, even after correction for the risk associated with cumulative tobacco exposure (1). Furthermore, the severity of COPD, as defined by the degree of airflow obstruction or the severity of radiographic emphysema, portends a worse prognosis in patients with lung cancer (2). Although our understanding of the pathophysiology of COPD and lung cancer is rapidly evolving, the underlying mechanisms of the epidemiologic link between COPD and lung cancer remain obscure (3). Accumulating evidence suggests that smoke-induced chronic airway inflammation could serve as a potential link between these two disease processes.

Dysregulated immune function is implicated in the pathogenesis of COPD. The destruction of the alveoli in emphysema was initially thought to be driven by the increased proteinase burden associated with an overcharged innate immune response. This hypothesis is consistent with the high prevalence of emphysema observed in patients with deficiency of the alpha-1 antitrypsin (A1AT) enzyme, which is an inhibitor of neutrophil elastase (4). However, emerging evidence also implicates the dysregulation of adaptive immunity in the pathogenesis of COPD. T-helper cell type 1 (Th1) and Th17 polarization, decreased programmed death ligand-1 (PD-L1) expression in alveolar macrophages, and increased production of IFN-γ by $CD8^+$ T cells in the lungs of patients with emphysema facilitate cell-mediated destruction of the host tissue (3). At the same time, increased numbers of T regulatory cells (Tregs) and myeloid-derived suppressive cells (MDSCs), which inhibit cell-mediated host responses against pathogens and render the host susceptible to recurrent infections, have been observed in COPD lungs (5).

The interplay between the immune system and lung cancer development is also complex (6). While genetic mutations are critical for the malignant transformation of epithelial cells, evidence suggests that chronic airway inflammation influences the lung microenvironment to facilitate cancer initiation and progression. Leukocyte infiltration into the lung can induce DNA damage in cells through the generation of reactive oxygen species. Furthermore, an environment rich with inflammatory cells can foster altered signaling pathways, such as the nuclear factor kappa B (*NF-κB*) pathway, and aberrant expression of cytokines, chemokines, growth factors, and DNA damage-promoting agents to promote carcinogenesis (7). Consistent with these findings, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) revealed that IL-1β inhibition with canakinumab decreased both the incidence and mortality of lung cancer in patients with atherosclerosis (8).

In contrast, host immunosurveillance plays an integral antitumor role during the evolutionary course of lung cancer (9). Non-small cell lung cancers (NSCLCs) possess

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high somatic tumor mutational loads, which can potentially generate neoantigens (10). Appropriate presentation of these tumor neoantigens by professional antigen-presenting cells, such as dendritic cells (DCs), in the context of autologous major histocompatibility complex (MHC) molecules, positive co-stimulatory signals, and pro-inflammatory cytokines can induce robust tumor-specific T cell responses. Indeed, a recent study identified $CD8^+$ tumor-infiltrating lymphocytes that are reactive to tumor clonal-neoantigens in patients with early-stage NSCLC (11). Abundant tumor infiltration of mature DCs, tertiary lymphoid structures, and cytolytic $CD8^+$ T cells (CTLs) has also been implicated as a positive prognostic indicator in patients with lung cancer (12). The importance of professional APCs at the tumor site is also supported by preclinical studies documenting the therapeutic benefit of cytokine gene-modified DCs injected intratumorally (13). This approach is being explored clinically in NSCLC in which intratumoral injection of autologous CCL21 gene-modified DC has demonstrated local and systemic immune responses, including $CD8^+$ T cell infiltration of the tumor and systemic recognition of autologous tumor antigens (14). Furthermore, treatment of advanced NSCLC patients with PD-1/PD-L1 checkpoint inhibitors, which augment the effector function of tumor-specific T cells, has demonstrated an overall survival benefit with evidence of durable immune-mediated responses in a subset of patients (15,16).

Yet, the majority of NSCLCs evade detection and elimination by the immune system through a variety of mechanisms. During cancer development, tumor cells often interact with their microenvironment to establish an immunosuppressive milieu characterized by an abundance of inhibitory molecules and an accumulation of suppressive mediators, such as Tregs and MDSCs. Tumor cells can also directly inhibit the effector function of tumor-specific T cells by upregulating checkpoint inhibitors such as PD-L1, which binds to PD-1 on tumor-infiltrating T cells and promotes T cell exhaustion (17). In addition, antigen presentation is often deficient in lung cancer patients, resulting in a state of suppressed cell-mediated immunity. Loss of heterozygosity in human leukocyte antigen (HLA) was found to occur in 40% of patients with NSCLC and is associated with a high burden of subclonal neoantigens (18). In addition, genomic variation in MHC-I has recently been implicated to restrict the capacity of the host immune system to direct immunosurveillance for certain epitopes, suggesting a primary role of the tumor antigen-presenting function in tumor progression (19). Consistent with these findings is a recent study that utilized single-cell analyses of NSCLC tumors, and revealed a paucity of functional antigen-presenting DCs as well as a limited number of activated $CD8^+$ T cells within the tumor microenvironment (TME) (20).

Although high-dimensional analyses of the tumor from NSCLC patients have begun to paint a more comprehensive picture of the immune contexture within the TME, the molecular mechanisms that link the origin of these immune cells to the extrinsic inflammatory microenvironment of the lung remain obscure. In a recent issue of *The Journal of Immunology*, Kerdidani and colleagues utilize orthotopic implantation of Lewis Lung Carcinoma (LLC) expressing exogenous chicken ovalbumin (OVA) in cigarette smoke-induced emphysematous lungs of mice to evaluate the emphysema-associated immunological mediators that potentiate tumor growth (21). The immune responses to known epitopes of the OVA antigen in the context of autologous MHCs are well characterized in the literature. OT-I mice that possess a high-affinity T cell receptor (TCR) for the $OVA_{257-264}$ peptide in the context of MHC-I, and OT-II mice that express a TCR for the $OVA_{323-339}$ peptide presented in the context of MHC-II are commercially available, providing a platform for the authors to quantify DC antigen-presentation and antigen-specific T cell function.

The authors observed enhanced growth of the trans-thoracically implanted tumors in mice with emphysema compared to those in the control group. Immunophenotyping of the TME revealed a decrease in total CTL infiltration with upregulated expression of the exhaustion markers (TIM-3 and PD-1) and diminished effector function (TNF-α and IFN-γ secretion), and a concurrent increase in Treg cells in mice with emphysema. Attempts to restore CTL function in OVA tumor-bearing mice with emphysema by adoptive transfer of OT-I T cells demonstrated no efficacy. Further interrogation of the adoptively transferred OT-I T cells in emphysematous mice revealed a T cell exhaustion phenotype with poor effector function, which was irreversible after sorting, expansion, and subsequent adoptive transfer. Next, the authors interrogated the myeloid compartment of the TME in tumor-bearing mice with emphysema and observed increased infiltration of $CD11c^+$ DCs with the inhibitory signal, PD-L1, and the immunosuppressive enzyme, IDO. *Ex vivo* functional analysis of sorted CD11c DCs revealed impaired capacity to prime the OVA-specific OT-I and

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OT-II T cells, and increased differentiation of $CD4^+$ T cells to natural Tregs. Consistently, adoptive transfer of OT-I T cells primed by emphysema tumor DCs was unable to halt tumor growth. Gene expression profiling of human lung tumors and tumor-free lungs of non-COPD and COPD patients revealed a decreased expression of positive regulators of immunogenic processes in patients with a high emphysema score.

The authors are to be commended for this study, which illustrates that cytotoxic T cell responses against developing lung cancers are dramatically impaired by emphysema. Their finding that the adoptive transfer of cancer antigen-specific naïve T cells fails to control tumor burden in mice with emphysema implicates immune dysregulation during multiple stages of T cell activation and regulation. First, the authors' observation that adoptively transferred T cells in mice with emphysema obtain an early exhaustion phenotype within the TME suggests that tumor-mediated checkpoints inhibit anti-tumor T cell responses. This finding is consistent with prior studies in NSCLC patients with COPD that reveal an increase in the number of exhausted $CD8^+$ T lymphocytes within the TME, and a longer progression-free interval in patients treated with immune checkpoint inhibitors (22,23). Secondly, their finding that tumors from mice with emphysema possess an increased number of PD-L1-expressing tolerogenic DCs strongly suggests that emphysema-associated inflammation impairs naïve T cell priming by DCs. Although prior studies have demonstrated that PD-L1 signaling is integrated into the priming phase of naïve T cells by DCs to restrain the acquisition of effector functions, the authors' documentation of this mechanism in emphysematous lungs that results in impaired antitumor CTL responses is novel (24). However, one of the limitations of this study is the use of overexpressed exogenous OVA antigen in murine lung cancer, which constitutes an artificial system that does not recapitulate the heterogeneous mutational landscape of human NSCLC. Also, as noted by the authors, the orthotopic model of tumor cell implantation in the lungs of mice with smoke-induced emphysema fails to capture the complex evolutionary course of lung cancer in humans, limiting the conclusions with respect to effect of emphysema-associated immunological mediators in the pathogenesis of lung cancer.

Further studies are needed to validate these preclinical results in human cohorts with emphysema and NSCLC. However, the work presented here introduces DCs as an important link between emphysema and lung cancer, and highlights the inhibitory role of PD-L1 during T cell priming and activation. These results have important implications for the design of novel future "immune enhancement" trials in lung cancer (25). Combination immunotherapy trials that utilize tumor vaccination with functional DCs to restore antigen presentation and effector T lymphocyte infiltration into the tumor hold promising potential to enhance the efficacy of checkpoint inhibitors in NSCLC patients with low baseline CTL infiltration and PD-L1 expression that are not anticipated to respond to anti-PD-1 monotherapy. Furthermore, rapid development of technologies that could reliably identify pre-malignant lung lesions is paving the way for introduction of immunotherapy trials that aim to enhance tumor-specific immune responses early in the course of the disease to intercept lung cancer progression.

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## Footnote

*Conflicts of Interest:* Dr. Dubinett: Early Diagnostics, Inc., T-Cure Bioscience, Inc. and J & J Lung Cancer Initiative. Dr. Salehi-Rad has no conflicts of interest to declare.

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