

# Neutrophils dominate the immune landscape of non-small cell lung cancer

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Cancer may evolve and progress by evading the immune system that would naturally prevent this process. Cancer immunotherapy is a strategy that aims to modulate the patient's endogenous immune system to recognize and clear cancer cells. Immune checkpoint therapy class of immunotherapy has demonstrable efficacy in patients with cancer, including non-small cell lung cancer (NSCLC). The response rate from phase I–III trials testing the efficacy of immune checkpoint inhibitors anti programmed death-1 (PD-1)/PD-ligand 1 (PD-L1) antibodies in NSCLC have shown response rates from 16% to 50% (1). To improve this response, several clinical trials combining these agents with novel immunotherapeutics have been initiated. However, most of these studies are somehow empiric and lack clear scientific rationales. Further research to identify alternative therapeutic strategies for the NSCLC patients intrinsically resistant to immune checkpoint inhibitor therapy is warranted.

Kargl and colleagues have recently reported that the immune cell composition varies among the different NSCLC subtypes, and that neutrophils are the most prevalent immune cell type identified in NSCLC, suggesting a potential novel immunotherapeutic target in NSCLC (2).

Lung adenocarcinoma and squamous cell carcinoma (SCC) subtypes have been comprehensively profiled

performing messenger RNA, microRNA and DNA sequencing that allowed whole-exome and whole-genome characterization of somatic alterations, integrated with copy number, methylation and proteomic analyses. However, a comprehensive profile of immune cell composition and function present in NSCLC (3-5) is currently unknown. Kargl *et al.* (2) employed a flow cytometry based assay composed of 27 markers that can identify 51 unique immune cell types and functional subpopulations from single-cell suspensions derived from lung cancer tissue and non-adjacent lung.

The key finding in this study is that Tregs and neutrophils are the most prevalent immune cell types in NSCLC, accounting for nearly 20% of all immune cells, and are potential immune suppressive in this disease. Gentles and colleagues (6) recently identified that, of any immune cell type, tumor-associated neutrophils are the strongest predictor of mortality in a large cohort of NSCLC patients. Nevertheless, based on transcript abundance neutrophils were estimated to be just 2% of all immune cells in NSCLC.

A second key feature of this study is the unique identification of immune signatures associating with NSCLC histological subtype (adenocarcinoma as compared with SCC), highlighting the heterogeneity inherent in immune responses to cancer. The results show that tumor-

associated T-cell clones are nearly ubiquitous in NSCLC, though their expansion is variable. A combination of a T-cell receptor beta sequencing and functional tumor-infiltrating lymphocyte experiment allowed Kargl and colleagues (2) to predict that tumor reactive T cells exist in 75% of SCC but in <35% of adenocarcinoma tumors and that, despite these results, the immune cell composition is more heterogeneous in adenocarcinoma than SCC lung subtype. One potential explanation of these results is that cigarette smoke consumption and the presence of key driver mutations is more variable in adenocarcinoma than in lung SCC. Although SCC tumors frequently possess clonal T-cell populations, it has been found that they contained twice as many Tregs as adenocarcinoma cases, with concomitant reductions in Th17 and Th1 lymphocytes.

Another key finding of this manuscript is that NSCLC specimens displayed increased composition of 37 distinct immune cell types and subtypes, including B cells, T cells, CD4<sup>+</sup> cells and CD8<sup>+</sup> cells compared with adjacent normal lung tissue. This expansion of B cells, 7-fold compared with normal lung tissue, is the largest fold-change increase for any immune cell type described to date. The composition of CD4<sup>+</sup> subsets differed as well, as evidenced by a statistically significant increase in Tregs, and decrease in Th1 cells.

The findings by Kargl *et al.* (2) highlight the need for strategies that combine immune checkpoint inhibitors with agents that can deplete neutrophils population. This is particularly relevant as there are a number of clinical trials underway that combine anti-PD-1 antibodies with agents that theoretically deplete Tregs. The discovery that neutrophils dominate the immune landscape of NSCLC and given the intrinsic heterogeneity in the immune cell response to NSCLC, there is an urgent need to develop novel immune diagnostics that could guide the initial choice of immunotherapy and devise a secondary strategy

to address treatment failures. In summary, these findings provide investigators with a comprehensive profile of immune cell composition present in NSCLC and help the design of new clinical trials employing immune-based therapeutics.

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### Footnote

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

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