Editorial

Transcriptional programs of tumor infiltrating T-cells provide insight into mechanisms of immune response and new targets for immunotherapy

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Provenance: This is an Invited Editorial commissioned by Section Editor Dr. Long Jiang (Department of Thoracic Oncology, Second Affiliated Hospital, Institute of Respiratory Diseases, Zhejiang University School of Medicine, Hangzhou, China).

Comment on: Ganesan AP, Clarke J, Wood O, *et al*. Tissue-resident memory features are linked to the magnitude of cytotoxic T cell responses in human lung cancer. Nat Immunol 2017;18:940-50.

Submitted Sep 13, 2017. Accepted for publication Oct 01, 2017.
doi: 10.21037/jtd.2017.10.35
View this article at: http://dx.doi.org/10.21037/jtd.2017.10.35

Early 2015 marked the first major clinical success of immunotherapy in lung cancer, resulting in the FDA approval of nivolumab (an anti-PD-1 antibody) for metastatic squamous non-small cell lung cancer (NSCLC). A little over a year later, two additional PD-1 blocking agents were approved, atezolizumab and pembrolizumab, for use in the treatment of metastatic NSCLC. Pembrolizumab was approved as a first line therapeutic option if a patient's tumor was found to contain at least 50% of tumor cells expressing PD-L1. While immunotherapeutic advancements in lung cancer are promising, response rates to anti-PD-1 therapy in NSCLC have been poor, ranging from 15–50% (1-3), even when prospectively screening tumors for PD-L1 expression before therapeutic intervention. Likewise, clinical response has been observed for anti-PD-1 agents independent of a tumor's baseline PD-L1 status (4-6), which further complicates clinical decision making in the assessment of optimal therapy for NSCLC. A great deal of additional research is necessary to determine the best use of checkpoint inhibitors in lung cancer and the best set of tumor-immune features for determining durable clinical response.

The recent publication by Ganesan *et al.* in *Nature Immunology* (7) highlights the need for a deeper understanding of the immunological state of lung tumors to determine how the immune landscape of lung tumors may predispose patients for better or worse outcomes. The authors investigated the molecular features associated with robust anti-tumor immune responses by extracting tumor-infiltrating and adjacent-normal T cells from surgically resected NSCLC specimens and utilizing RNA-seq to analyze the transcriptional programs of these immune cells. Marked differences in the transcriptional landscape were found in tumor infiltrating T cells when compared to their adjacent-normal T cell counterparts. Likewise, they characterized similar transcriptional program profiles in tumor-infiltrating T cells derived from head and neck squamous cell carcinoma (HNSCC), ultimately validating their T cell findings and further suggesting that a core set of regulatory programs may define tumor-infiltrating leukocytes across multiple tumor types. Major players in the active transcriptional programing of tumor-infiltrating T cells appeared to be related to T cell exhaustion, cell-cycle regulation, and T cell receptor activation. Most significantly, exhaustion signatures were found to be upregulated in the tumor-infiltrating T cells, a gene set containing the clinically relevant immunotherapeutic targets such as PD-1, CTLA-4, and TIM-3.

The authors also noted significant heterogeneity in the expression of these clinically relevant T cell exhaustion targets among the tumor-infiltrating T cells, which they highlighted may account for the person-to-person variability

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in immunotherapeutic responses in NSCLC. Furthermore, the observation of the heterogeneous expression of checkpoint molecules in tumor-infiltrating T cells suggest that precision immunotherapy would greatly benefit from utilizing personalized tumor-immune profiling. However, additional clinical studies will be necessary to determine the optimal drug combinations for these individual tumor-immune profiles.

The authors also found *PD-1* expression to be closely correlated with *4-1BB* expression (another immunotherapeutic target currently under investigation in clinical trials) and found both to be dependent on the number and density of infiltrating T cells in these tumors. Expression of *PD-1* and *4-1BB* was not found to be dependent on the clinical/pathological features of tumors, nor patient characteristics such as age, sex, performance status, or smoking status. On the other hand, tumors containing high T cells densities, which concurrently demonstrated increased *PD-1* and *4-1BB* expression, were found to contain a greater number of tissue-resident memory CD8+ T cells (T_{RM} cells) which were marked by the unique expression of CD103, CD69, and CD49a.

This led the authors to determine how these promising CD8+ T_{RM} features might have an impact on patient survival in an independent, retrospective NSCLC cohort. Ultimately, they found that patients with tumors containing a high density of CD103+ CD8+ T_{RM} cells had significantly better survival than those with tumors containing a low density of CD103+ CD8+ T_{RM} cells. Likewise, two other recent studies have demonstrated a similar link between CD103+ CD8+ T_{RM} cells and patient prognosis in lung cancer (8,9). These survival findings further implicate tumor-infiltrating T cell responses as a crucial component of the tumor-immune microenvironment and identify a unique subset of T cells, CD103+ CD8+ T_{RM} cells, which are likely responsible for the previously reported survival outcomes linked to tumor-infiltrating T cell densities.

What remains to be seen, however, is the role tumor-infiltrating T cell transcriptome profiles play in patients' responses and outcomes in the context of NSCLC immunotherapy. The authors could not assess the impact of these T cell features on immunotherapy outcomes. The retrospective NSCLC cohort included early stage patients diagnosed between 2007 and 2016. During this time frame, NSCLC patients were not expected to have received immunotherapy outside of clinical trials until its approval for use in NSCLC in late 2016. Moreover, immunotherapy has been demonstrated as an effective agent in late-stage metastatic lung cancer, but has not yet proven to be an effective early stage treatment when compared with the current standards of care involving surgery, radiation, and adjuvant therapy for early stage disease. Nevertheless, this publication provides a useful paradigm in the characterization of the molecular signatures of effective T cell mediated anti-tumor responses and these data should be strongly considered in future clinical investigations as a means to better determine optimal patient stratification, in addition to monitoring disease progression and immunotherapy response.

Acknowledgements

Funding: The authors would like to acknowledge the following sources of funding: National Institute of Health and National Cancer Institute (T32CA009531; P30CA022453; U01AI95776; R21AI122256), and the Burroughs Wellcome Fund grant (1013738).

Footnote

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

References

1. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
2. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
3. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med 2017;376:2415-26.
4. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372:2509-20.
5. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non–small cell lung cancer. Science 2015;348:124-8.
6. Le DT, Durham JN, Smith KN, et al. Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-13.
7. Ganesan AP, Clarke J, Wood O, et al. Tissue-resident

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memory features are linked to the magnitude of cytotoxic T cell responses in human lung cancer. Nat Immunol 2017;18:940-50.
8. Djenidi F, Adam J, Goubar A, et al. CD8+ CD103+ Tumor–Infiltrating Lymphocytes Are Tumor-Specific Tissue-Resident Memory T Cells and a Prognostic Factor for Survival in Lung Cancer Patients. J Immunol 2015;194:3475-86.
9. Koh J, Kim S, Kim MY, et al. Prognostic implications of intratumoral CD103(+) tumor-infiltrating lymphocytes in pulmonary squamous cell carcinoma. Oncotarget 2017;8:13762-9.

Cite this article as: Watza D, Purrington KS, Chen K, Schwartz AG. Transcriptional programs of tumor infiltrating T-cells provide insight into mechanisms of immune response and new targets for immunotherapy. J Thorac Dis 2017;9(11):4162-4164. doi: 10.21037/jtd.2017.10.35

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