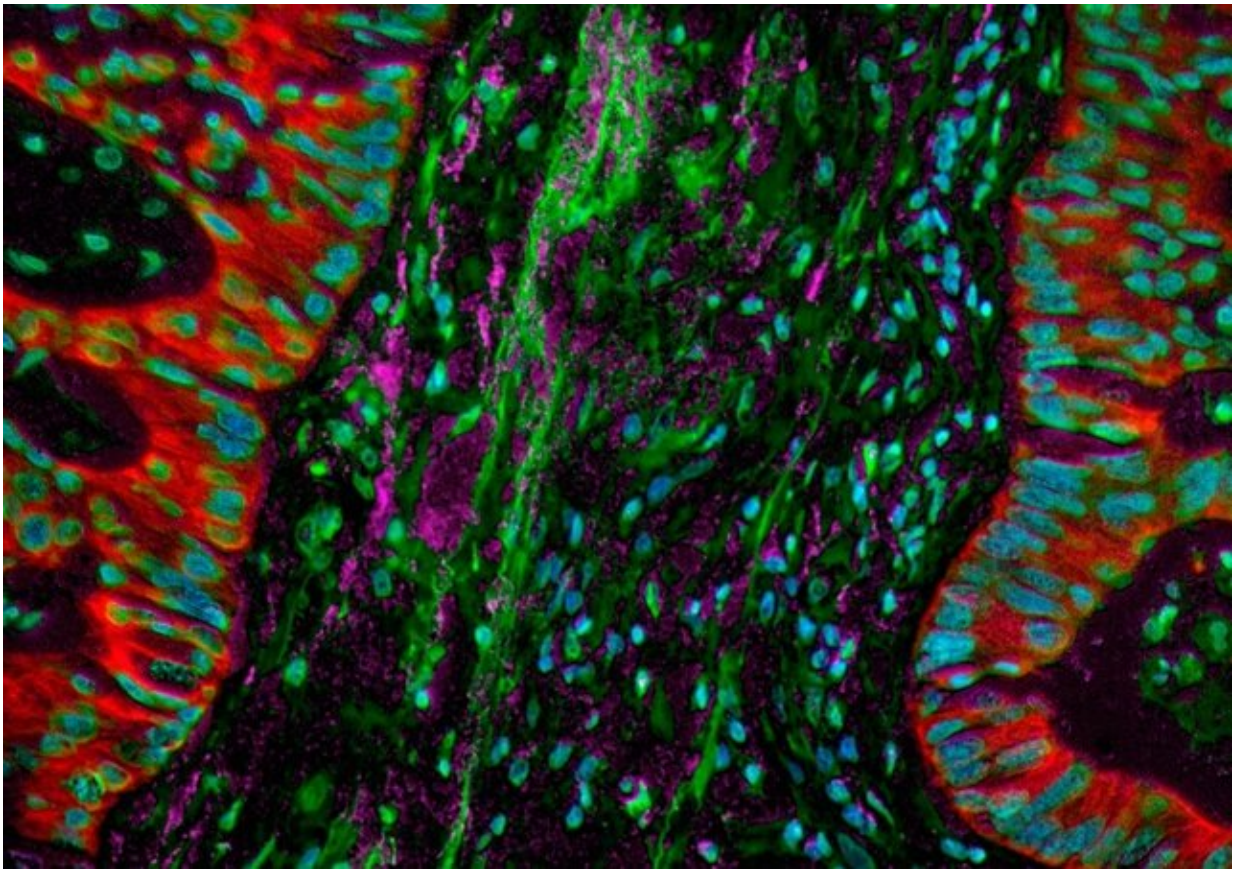
Lung cancer's molecular features shed light on immunotherapy response

April 19 2023, by Karen Zusi-Tran



Cancer cells (red), cell nuclei (cyan), stroma/desmoplasia (green), active stroma-specific marker (purple). Credit: National Cancer Institute \ Fox Chase Cancer Center, Neelima Shah and Edna Cukierman

One of the newest types of cancer drugs, immunotherapies called

immune checkpoint inhibitors, has transformed the treatment of lung cancer over the last decade—dramatically improving the survival of some patients with the most common form of this disease, non-small cell lung cancer (NSCLC). However, only about 20% of patients experience a benefit from these immunotherapies.

A new study led by researchers at the Broad Institute of MIT and Harvard and Massachusetts General Hospital (MGH) reveals key molecular features of lung tumors that could explain why some patients respond to these treatments while others do not. The team has pinpointed several genetic and other biological factors that may influence the response of NSCLC patients to immunotherapies that inhibit the PD-1 or PD-L1 proteins.

Published in *Nature Genetics*, this work is the first joint analysis of the Stand Up To Cancer-Mark Foundation cohort, a large dataset gathered through a multi-institution effort to expand the molecular understanding of treatment response in NSCLC.

The research team examined whole-exome sequencing and RNA-sequencing data from tumor samples contributed by nearly 400 NSCLC patients before treatment, along with information about their clinical responses to anti-PD-(L)1 therapy. This is one of the largest multi-omic datasets from NSCLC patients who have been treated with these medicines, enabling the scientists to identify a suite of molecular features that are associated with improved treatment outcomes.

These results demonstrate the complexity of the biological factors that determine immunotherapy response, and suggest why existing methods of predicting treatment outcomes in NSCLC patients, which look at only a small number of molecular features, aren't always accurate. The researchers said their study points to the potential for improving these predictions or even developing more personalized approaches to

treatment based on a patient's molecular profile.

"Right now, long-term disease control is only achievable for some patients," explains co-senior author Justin Gainor, director of the Center for Thoracic Cancers at MGH and associate professor at Harvard Medical School (HMS). "This analysis offers a deeper understanding of cancer and immunobiology, which we hope could be harnessed to make these treatments effective for a broader population. And as this collaboration continues to grow, it will further increase our understanding of the relevant molecular changes."

"This work also demonstrates the importance of collaborations that enable aggregating data from large cohorts of patients," adds Gad Getz, an institute member at Broad and faculty at HMS and MGH. "Collectively, we aim for this richly annotated dataset to serve as a useful resource to the field at large, beyond our first analysis."

"We hope that the stratification of tumors by mutations and gene expression patterns will provide principles and mechanistic hypotheses underlying immunotherapy, and in this way, encourage specific mechanistic studies," explains Nir Hacohen, institute member at Broad and director of the Center for Cancer Immunology at MGH.

The work was additionally led by co-first authors Arvind Ravi, Matthew Hellmann, and Monica Arniella of the Broad Institute, Dana-Farber Cancer Institute, and Memorial Sloan Kettering Cancer Center.

Building molecular profiles

The PD-1/PD-L1 immune checkpoint is a protein interaction that normally suppresses the immune system. Cancer cells use this mechanism to evade the body's defenses. Anti-PD-(L)1 agents work by blocking this interaction, stimulating the immune system to attack cancer

cells.

The research team set out to comprehensively profile this molecular landscape in patient samples. Among their findings, they identified specific genetic alterations that disabled the DNA-repair gene ATM and were associated with favorable responses to immunotherapy. They also found genomic changes that could increase expression of the TERT gene, which correlated with negative outcomes. And they identified another key predictor in the expression of genes that encode certain immunoproteasome subunits.

By integrating the clinical, genomic, and transcriptomic data, the researchers uncovered two overall collections of features that correlated with a favorable treatment response: an "immune activated/exhausted" environment, in which the immune cells displayed signatures of previously high activity that had waned; and a signature defined by high levels of neoantigens, or foreign proteins displayed on the surface of the tumor cells.

A third category—a "wound healing" microenvironment, in which the immune system appeared dampened, similar to how it would behave in the early stages of healing a physical injury—was associated with an unfavorable response to treatment.

The team additionally identified a fourth "other" category, which had a mix of signatures correlating both positively and negatively with treatment outcomes.

"These features could provide the ability to stratify patients in a more nuanced way," explains Ravi. "We found that patients whom you would expect to respond well to therapy based on traditional predictors may actually respond poorly, due to the presence of additional unfavorable factors that are not usually assessed in routine clinical care.

Understanding this complex architecture will continue to be critical as we investigate how to improve outcomes in all patients."

More information: Arvind Ravi et al, Genomic and transcriptomic analysis of checkpoint blockade response in advanced non-small cell lung cancer, *Nature Genetics* (2023). DOI: 10.1038/s41588-023-01355-5

Provided by Broad Institute of MIT and Harvard