Tumor-infiltrating B cells and plasma cells influence early-stage lung cancer biology, immunotherapy responses

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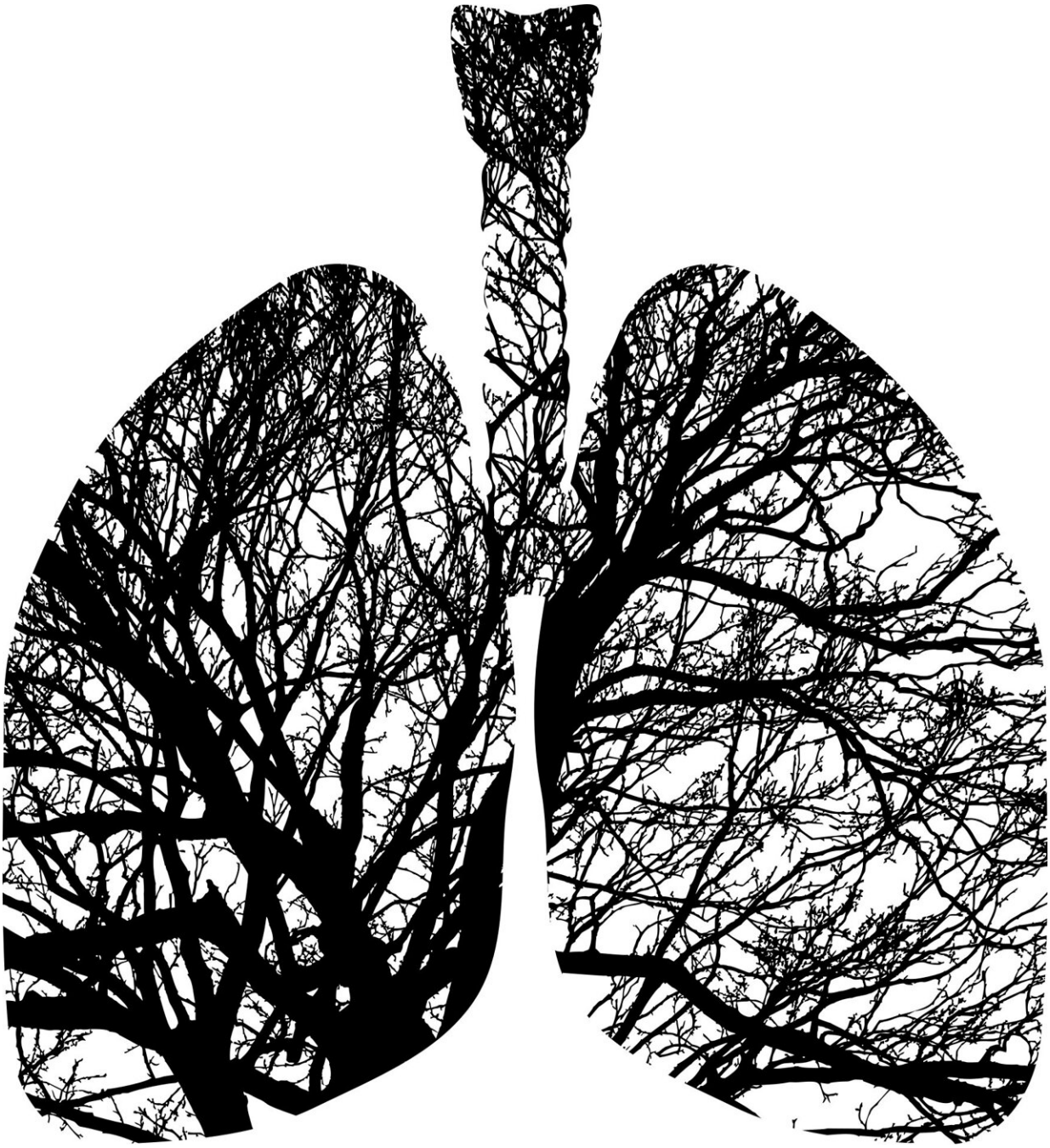

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Through extensive single-cell analysis, researchers at The University of Texas MD Anderson Cancer Center have created a spatial map of tumor-

infiltrating B cells and plasma cells in early-stage lung cancers, highlighting previously unappreciated roles these immune cells play in tumor development and treatment outcomes.

The study, published today in *Cancer Discovery*, represents the largest and most comprehensive single-cell atlas on tumor-infiltrating B cells and plasma cells to date, which can be used to develop novel immunotherapy strategies.

"We know the tumor microenvironment plays an important role in regulating tumor growth and metastasis, but we have an incomplete understanding of these interactions. So far, most of the focus has been on T cells," said co-corresponding author Linghua Wang, M.D., Ph.D., associate professor of Genomic Medicine. "Our study provides much-needed understanding of the phenotypes of B cells and plasma cells, which also play critical roles in early lung cancer development."

Improved screening approaches have increased the proportion of lung cancers diagnosed at early stages. Surgery is curative for some patients, but new treatment approaches are needed because many still experience a recurrence of their disease. Understanding the early interactions between cancer cells and immune cells could reveal opportunities to block cancer growth or boost the anti-tumor immune response.

Previous research co-led by Wang and her colleagues discovered that B lineage cells are critical for responses to immunotherapy in patients with melanoma. Additionally, a study jointly led by Wang and Humam Kadara, Ph.D., associate professor of Translational Molecular Pathology, found that B cells and plasma cells were enriched in early-stage lung cancers relative to normal lung tissue. Plasma cells are terminally differentiated B cells responsible for antibody production.

To better understand the roles of these cells in early lung cancer

development, the researchers performed single-cell analysis on 16 tumors and 47 matched normal lung tissues. The analysis was led by Dapeng Hao, Ph.D., and Guangchun Han, Ph.D., in the Wang laboratory, together with Ansam Sinjab, Ph.D., in the Kadara laboratory.

The researchers performed single-cell RNA sequencing on roughly 50,000 unique B cells and plasma cells to analyze their gene expression profiles. They also completed single-cell B cell receptor sequencing on more than 70,000 cells to understand the repertoires of B cell receptors, the membrane-bound proteins on the cell surface that recognize antigens.

The study identified 12 different cell subsets, with more differentiated states (memory B cells and plasma cells) being highly enriched in the tumors relative to adjacent normal tissue.

"This level of detailed analysis highlights the dynamic interplay between the tumor and its surrounding immune microenvironment," said Kadara, co-corresponding author on the study. "Our data reveal the importance of environmental factors, such as exposure to cigarette smoke, and molecular features of the tumor in contributing to the landscape of infiltrating B cells and plasma cells."

For example, tumors from smokers had elevated plasma cells and decreased B-cell clonality compared with those of non-smokers. Further, lung tumors with *EGFR* mutations had lower levels of plasma cells and higher levels of less-differentiated B cells when compared to those with *KRAS* or other mutations.

By studying the single-cell data together with spatial information from the tumors, the researchers also demonstrated that most B cells and plasma cells were recruited to sites with high levels of CXCL13. Levels of this signaling molecule increase as tumors progress from pre-cancerous lesions to invasive lung cancer.

The varied landscape of B cells and plasma cells in the tumor also appear to influence patient outcomes and treatment responses in early-stage lung cancers. Specifically, an enrichment of plasma cells in the tumor was associated most strongly with improved survival and responses to anti-PD-1/PD-L1 immune checkpoint inhibitors.

"Most previous studies have treated tumor-infiltrating B cells or plasma cells as a homogeneous population, but our in-depth analysis highlights the heterogeneous nature of these cells and their crosstalk with other components of the tumor microenvironment," Wang said. "Further studies are needed to fully understand their roles in tumor pathogenesis, but the evidence suggests the plasma cell signature may be a valuable biomarker to predict immunotherapy outcomes. Our findings also can be leveraged to identify new targets for immunotherapy that focus on tumor-infiltrating B cells and plasma cells."

Future studies will build on the foundation provided by this study to clarify the precise roles of B cells and plasma cells in early lung tumor progression and to identify the most promising therapeutic strategies.

More information: *Cancer Discovery* (2022). aacrjournals.org/cancerdiscove … 2159-8290.CD-21-1658

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