Mapping Genetic Diversity of Lung Tumors Over Time

Results revealed vast cellular diversity in both lung tumors and the tissue surrounding the tumor.

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Lung cancer often responds to an initial course of treatment but re-emerges after becoming drug-resistant, making it the deadliest form of cancer worldwide. In developing a treatment plan for a patient, doctors must rely on genetic tests on biopsied tumors in bulk rather than individual cells, which fails to capture the full extent of cellular diversity within tumors. A more complete picture of what is happening in a lung cancer tumor could yield clues for effective therapies that may benefit patients.

Doris Duke-Damon Runyon Clinical Investigator Collin Blakely, MD, PhD, and colleagues at the University of California, San Francisco, have developed a way to assemble genetic profiles of individual lung cancer cells obtained from patients at different times during treatment. The results revealed vast cellular diversity in both lung tumors and the tissue surrounding the tumor. This also provided a window into the evolution of individual cells within the tumor's ecosystem.

Picturing the cellular diversity of lung cancer

Starting with 49 biopsies obtained from 30 lung cancer patients, the researchers used single-cell sequencing to map the landscape of gene activity in over 23,000 individual lung cancer cells at three stages: before treatment, after the tumors stabilized or went into remission during treatment, and after the cancer, despite continuous treatment, surged back in a treatment resistant form.

These single-cell profiles revealed the presence of tumor cells that harbored cancer-driving genetic mutations distinct from those that were identified by the various clinical tests that the patients received during their treatment. Though these mutations were present in only a fraction of cells in each tumor, patients whose tumors carried two or more of these mutations had significantly lower overall survival rates than patients with fewer than two.

The researchers also found that when lung tumors stabilized or went into remission in response to treatment, some malignant cells were able to survive by switching on genes associated with injury repair and survival that are normally only active in healthy lung cells. When these genes are active, the cancer cells enter a hibernation mode to avoid cell death.

The study also provided key insights into how the cells and tissue that surround a lung malignancy – the tumor microenvironment – create conditions that prevent the immune system from attacking the tumor. The tumor microenvironment was hostile to immune activity both before treatment and after a tumor had evolved drug resistance. However, during treatment, when the cancer is in the "hibernation mode", the researchers found that immune cells were able to infiltrate the tumor microenvironment and appeared to be switched on. This suggests that a limited window of opportunity exists during which conventional cancer therapies can be combined with immunotherapies – a class of cancer treatments that has largely failed against the types of lung tumors profiled in this study – to produce better overall survival rates.

The researchers suggest that the single-cell analysis proposed is feasible in real-life clinical tumors and may help usher in a new era in the clinical management of tumors during therapy.

Read more: Cell

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