Genomic study points to new treatment approaches for advanced small-cell lung cancer

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A new study of advanced small-cell lung cancer (SCLC) led by researchers at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC—James) has identified molecular patterns linked to patients developing resistance to certain therapies.

This study, published in the journal *JTO Clinical and Research Reports*, examined more than 60 tumors from five patients. OSUCCC—James researchers identified distinct mutational and molecular changes in four SCLC subtypes. The findings provide new insights into the patterns treatment resistance and could offer new targets for the development of more effective immunotherapy and other therapies for advanced SCLC, which progresses quickly and is usually fatal.

SCLC accounts for up to 15% of lung cancer cases worldwide. The disease often responds well to chemotherapy when first diagnosed but then recurs in a lethal, treatment-resistant form.

"Advanced SCLC often does not respond as well to immune therapies that are effective in other types of lung cancer, and the reasons for this are poorly understood," says principal investigator Sameek Roychowdhury, MD, Ph.D., a medical oncologist and member of the OSUCCC—James Translational Therapeutics Research Program. He is also an associate professor in Ohio State College of Medicine's Division of Medical Oncology and medical director of the OSUCCC—James CLIA Cancer Genomics Laboratory.

"Our findings suggest that the causes of treatment resistances in advanced SCLC may be subtype-specific," says Roychowdhury. "They also highlight the importance of tumor genomic studies to identify the most effective therapies for these patients and to support development of new therapies for this often-fatal disease."

Genomics is the process of identifying specific cancer-related mutations that drive the growth and spread of cancers. Oncologists can gather specific genomic information from individual patients to help match patients with the best therapy based on their unique tumor characteristics. This concept is referred to as precision cancer medicine. This approach has important significance in metastatic and rare forms of cancer, where treatment options are often limited.

"Understanding the specific drivers of a person's cancer can help us identify potential alternative treatment options through clinical trials that would not have been possible otherwise," adds Roychowdhury.

For this study, Roychowdhury and his colleagues analyzed genomic DNA and total mRNA from tumor cells removed from five deceased patients with advanced SCLC, along with circulating tumor DNA. The tissue was obtained as part of a rapid research autopsy study, originally supported by a Pelotonia Idea Grant. Tissue was collected within 16 hours of each patient's passing, minimizing the molecular changes that occur in cells after death.

The five patients consented to undergo a research autopsy soon after death to allow the researchers to collect and evaluate many tumors. The researchers used sequencing technologies to identify genetic and molecular changes in four SCLC tumor subtypes. Many of the changes are associated with resistance to immune therapy and other treatments.

Key findings include:

- Feasibility for rapid research autopsy to provide in-depth insights into resistant lung cancers;
- Evidence that tumors have continue to evolve after patients receive treatment. Even a single patient may have six to eight genetically distinct subtypes of their cancer ¬¬- which could have implications for future drug development;
- The most common neuroendocrine SCLC subtypes showed high expression of the enzyme ARG2, a possible suppressor of immune responses; and
- Support for the known association between the Wnt pathway and chemoresistance in advanced SCLC.

"Our results need to be validated by larger studies," says Roychowdhury, "but they suggest that subtyping SCLC patients before systemic therapy could someday play a role in drug development and therapy selection."

More information: Hui-Zi Chen et al. Genomic and Transcriptomic Characterization of Relapsed SCLC Through Rapid Research Autopsy, *JTO Clinical and Research Reports* (2021). DOI: 10.1016/j.jtocrr.2021.100164

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