Researchers discover new genetic anomalies in lung cancer

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Number of fusions in a tumor linked to more aggressive cancer

ANN ARBOR, Mich. — Developing effective treatments for lung cancer has been challenging, in part because so many genetic mutations play a role in the disease.

By analyzing the DNA and RNA of lung cancers, researchers at the University of Michigan Comprehensive Cancer Center found that patients whose tumors contained a large number of gene fusions had worse outcomes than patients with fewer gene fusions. Gene fusions are a type of genetic anomaly found in cancers that occurs when genes get rearranged and fuse together.

In addition, the researchers identified several new genetic anomalies that occur in lung cancer, including in patients with a history of smoking.

“Lung cancer is quite a complex disease with many causes. Our deep sequencing analysis found new gene fusions in lung cancers that were negative for the most commonly known fusions. These new anomalies could potentially be targets for developing new treatments,” says study author Arul Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology and S.P. Hicks Professor of Pathology at the University of Michigan Medical School.

The study looked at 753 lung cancer samples that represented both smokers and non-smokers. The first 153 samples came from the University of Michigan and were combined with 521 samples from a report published by The Cancer Genome Atlas.

The researchers found 6,348 unique fusions with an average of 13 fusions per tumor sample. Anomalies in two gene pathways were most prevalent: the Hippo pathway, which has previously been linked to some rare cancers, and NRG1, which has not previously been seen in cancer.

The study appears in *Nature Communications*.

Researchers know that three common gene fusions – involving ALK, RET and ROS – play a role in about 5 percent of lung cancers, but primarily in non-smokers. The new anomalies were found only in patients who did not have ALK, RET or ROS fusions.

“Our results indicate that in the more genomically complex smoking-related lung cancers, gene fusion events appear to be frequent,” says study author David G. Beer, Ph.D., John and Carla Klein Professor of Thoracic Surgery and professor of radiation oncology at the University of Michigan Medical School and co-director of cancer genetics at the U-M Comprehensive Cancer Center.

Drug companies are already investigating drugs that could target the Hippo pathway and NRG1. The research team suggests exploring these inhibitors as potential therapeutics in lung cancer.

In addition, the finding that the number of gene fusions was tied to prognosis suggests that a screen could be developed to help doctors determine how aggressive a patient’s tumor is likely to be – and to tailor treatment accordingly.

The study identified many different gene fusions that comprise the landscape of lung cancer, with most occurring in only a small number of individual tumor samples. The Hippo pathway fusions were present in 3 percent of patients and NRG1 fusions in 4 percent. The researchers suggest expanding lung cancer subtypes based on these molecular characteristics.

“We’ve previously had success in targeting therapies against low-recurrence gene fusions. Large-scale genome analyses like this allow us to identify more of the key drivers of each patient’s tumor so that we can match the most appropriate therapies,” Chinnaiyan says.

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