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Featured Article

Lung Cancer Genome Surveys Find Many Potential Drug Targets

Five new studies have identified genetic and epigenetic alterations in hundreds of lung tumors, including many changes that could be targeted by drugs that are already available or in clinical testing.

New information about genetic changes in lung tumors could help doctors match patients with existing targeted drugs.

The reports, all published this month, included genomic information on more than 400 lung tumors. In addition to confirming genetic alterations previously tied to lung cancer, the studies identified other changes that may play a role in the disease. (Links to the study abstracts appear in the sidebar below.)

"These five papers are the first major salvo of genome-wide studies using all of the newest technologies to analyze a large number of lung cancers," said Dr. John Minna, a clinician and lung cancer researcher at the University of Texas Southwestern Medical Center, who co-authored one of the studies.

Collectively, the studies covered the main forms of the disease—lung adenocarcinomas, squamous cell cancers of the lung, and small cell lung cancers.

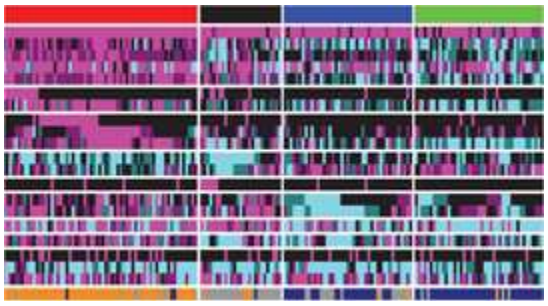
Although preliminary, the findings could be used to develop molecular markers for identifying patients who are candidates for certain targeted drugs. At the same time, researchers in the lab can now evaluate the newly discovered changes to identify novel potential therapeutic targets.

"All of these studies say that lung cancers are genomically complex and genomically diverse," said Dr. Matthew Meyerson of Harvard Medical School and the Dana-Farber Cancer Institute, who co-led several of the studies, including a large-scale analysis of squamous cell lung cancer by The Cancer Genome Atlas (TCGA) Research Network.

Some genes, Dr. Meyerson noted, were inactivated through different mechanisms in different tumors. He cautioned that little is known about alterations in DNA sequences that do not encode genes, which is most of the human genome.

Squamous Cell Tumors

The TCGA investigators sequenced the genomes or exomes (the protein-coding regions of DNA) of tumor samples from 178 patients with squamous cell lung cancer. In more than half of the tumors examined, the researchers found a change to a gene or a signaling pathway that is targeted by a drug that exists or is in development. The findings were reported in *Nature* on September 9.



Detail of a figure showing gene-expression differences in subtypes of squamous cell lung cancer

"This gives us an enormous opportunity for progress in this disease," said Dr. Meyerson.

The TCGA model integrates genomic data for squamous cell lung cancers with clinical information, when available, and with other tumor characteristics, such as gene expression, epigenetic changes to cells, and alterations in the number of gene copies.

"The framework for these five studies was built on a convergence of new technologies and the need to better understand the biology of lung cancers as it relates to new therapies for our patients," said Dr. Paul Paik, who treats patients with lung cancer at Memorial Sloan-Kettering Cancer Center and was part of the clinical team involved in TCGA.

Small studies (for example, here and here) have provided hints that certain signaling pathways are important in squamous cell lung cancers, leading to new trials of targeted drugs. "Now, with the publication of the TCGA study, we know that squamous cell lung cancers have a myriad of potentially targetable changes," Dr. Paik noted.

An unexpected finding was the presence of mutations in the *EGFR* gene in about 1 percent of squamous cell tumors. These tumors might respond to available drugs that block signals through the EGFR pathway.

The researchers also found evidence of genetic changes that may help lung cancer cells evade surveillance by the immune system.

Testing Lung Tumors

Any therapeutic targets to emerge from the new reports would need to be incorporated into molecular tests that can identify candidates for certain drugs. A leader in this work is the Lung Cancer Mutation Consortium , which has been building knowledge of the mutations associated with the disease and testing for these changes.

Many patients with lung adenocarcinomas have benefited from targeted drugs. Crizotinib (Xalkori), for instance, has elicited some dramatic responses in patients whose tumors harbor a particular gene fusion. Some medical centers now routinely test tumors before selecting treatment for patients with lung adenocarcinomas.

"If you look at lung cancer as a whole, the big therapeutic targets were first identified in adenocarcinomas," Dr. Minna explained. "Now there are new targeted therapies that could make an impact on squamous

The Five Studies

- Comprehensive Genomic Analysis Identifies SOX2 as a Frequently Amplified Gene in Small Cell Lung Cancer (*Nature Genetics*)
- Integrative Genome Analyses Identify Key Somatic Driver Mutations of Small Cell Lung Cancer (*Nature Genetics*)

cell lung cancer."

At Memorial Sloan-Kettering, all patients with squamous cell lung cancer have their tumors tested for drug targets using various techniques, including DNA sequencing. Among 28 of these patients evaluated recently, more than 60 percent had tumors that contained a potential target.

Dr. Paik noted that his group will use the TCGA results to expand their testing. "In a sense, the future potential of this new work is being realized now," he said. "That's pretty exciting."

- Comprehensive Genomic Characterization of Squamous Cell Lung Cancers (*Nature*)
- Genomic Landscape of Non-Small Cell Lung Cancer in Smokers and Never-Smokers (*Cell*)
- Mapping the Hallmarks of Lung Adenocarcinoma with Massively Parallel Sequencing (*Cell*)

Small Cell Lung Cancer

Two new reports describe genetic changes in small cell lung cancers, which tend to be aggressive and about which little has been known. The research teams conducted exome or whole-genome sequencing on a total of 82 samples of such tumors.

"This study gave us a host of new targets to explore," said Dr. Charles Rudin of the Johns Hopkins Kimmel Cancer Center, who led one study. The next steps will be to validate which targets are driving the growth of tumors and are "druggable," he added.

The researchers found that a gene called *SOX2*, which plays a role in normal development, may contribute to some small cell lung cancers, as well as other cancers, and could be targeted.

Small cell lung cancers have been challenging to study because most are not treated surgically, so tumor samples are rare. What's more, these tumors have high rates of genetic mutations due to tobacco smoke, yet only some mutations are driving the disease, noted Dr. Roman Thomas of the University of Cologne in Germany, who led the other study.

Using statistical "filters," his group found that genes involved in modifying histone proteins, which help package DNA within a cell, were frequently mutated in the disease.

"These cancers are extraordinarily complex, so as researchers our steps forward are incremental—but, still, they are steps," Dr. Thomas noted. "No one would have imagined that lung cancer would be the prototypical disease for targeted medicine."

Comparing Tumors in Smokers and Nonsmokers

Non-small cell lung cancers were the focus of two additional studies, which appeared in *Cell*. One group sequenced the exomes or genomes of 183 tumor samples, and the other conducted whole-genome sequencing of tumor tissues from 17 smokers and nonsmokers.

"We found a substantially lower number of mutations in the genomes of tumors from nonsmokers compared to the smokers," said Dr. Ramaswamy Govindan of the Washington University School of Medicine in St. Louis, MO, who led the study. Five study participants who had never smoked had a mutation that could be targeted by an existing drug.

In all, the study authors found 54 genes with potentially targetable alterations in the 17 patients.

> All these studies show how diverse and how complicated the cancer genome is. But we now have a panoramic view of the genomic landscape, and this is important for moving forward in this disease.
>
> *—Dr. Ramaswamy Govindan*

"The days of large clinical trials for lung cancer are over," Dr. Govindan said, noting that patients need to be selected for specific treatments based on the characteristics of their tumors. "We also need to develop clinical trials that move targeted therapies to earlier stages of lung cancer, where we have a better chance of a cure."

Future clinical trials, he predicted, would look for relatively large effects of drugs in selected patients. Dr. Minna agreed, saying, "If the effects are not there, we will move on to the next target and the next drug."

The new results are really a teaser for what's coming. TCGA plans to sequence a total of 500 adenocarcinomas and 500 squamous cells tumors. These results could help shed light on issues such as epigenetic changes in lung cancer, mechanisms of drug resistance, and how tumors are influenced by the surrounding tumor microenvironment.

"All these studies published back to back show how diverse and how complicated the cancer genome is," Dr. Govindan said. "But we now have a panoramic view of the genomic landscape, and this is important for moving forward in this disease."

Dr. Minna added, "After treating thousands of patients with lung cancer and not doing too well, I am very excited about the new results."

—Edward R. Winstead

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