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New view of tumors' evolution

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Cancer cells undergo extensive genetic alterations as they grow and spread through the body. Some of these mutations, known as "drivers," help spur cells to grow out of control, while others ("passengers") are merely along for the ride.

MIT cancer biologists at the Koch Institute for Integrative Cancer Research and geneticists from the Broad Institute have now performed the most comprehensive analysis to date of these changes in mice programmed to develop cancer. The team discovered mutations and other genetic disturbances that arise at certain stages of lung cancer development; the researchers were also able to identify tumor cells that broke free to spread to other organs.

The findings, described in the March 13 issue of *Cell*, suggest possible new targets for drugs for this aggressive form of cancer, known as small cell lung cancer. There are now very few targeted drugs for small cell lung cancer, a highly lethal form of lung cancer that is associated with tobacco use and is usually treated with chemotherapy drugs that have severe side effects.

"Right now, small cell lung cancer is really lagging behind with respect to therapies that target a specific mutation or genetic alteration in the tumors, because we don't know a lot about the drivers in these cancers," says David McFadden, a postdoc at MIT's Koch Institute for Integrative Cancer Research and one of the lead authors of the *Cell* paper.

Other lead authors of the paper are Koch Institute postdoc Thales

Papagiannakopoulos and Broad Institute researchers Amaro Taylor-Weiner, Chip Stewart, and Scott Carter. Senior authors are Tyler Jacks, the David H. Koch Professor of Biology and director of the Koch Institute, and Gad Getz, director of cancer genome computational analysis at the Broad Institute and director of the bioinformatics program at Massachusetts General Hospital.

Tracking cancer progression

The research team studied a strain of mice that lacks two key tumor-suppressor genes, p53 and Rb. These mice develop small cell lung cancer, but scientists don't know exactly how the cancer progresses or which subsequent genetic alterations drive tumor growth.

In studies of human small cell lung cancer, it has been difficult to identify these driver mutations because potent carcinogens in cigarette smoke produce many mutations, most of which don't affect tumor growth. In the mouse model of the disease, fewer mutations arise because the mice are not exposed to cigarette smoke, making it easier to identify the key drivers.

Mice lacking p53 and Rb, the two most commonly mutated tumor suppressors in human small cell lung cancer, develop lung tumors that closely mimic the progression of human small cell lung cancer. These tumors are highly metastatic and usually spread to the lymph nodes near the lungs and then to the liver. The researchers isolated DNA from these tumors and analyzed the genetic alterations that occurred, including genetic mutations as well as changes in the number of copies of a gene or chromosome.

First, the researchers compared genetic alterations that appeared early and late in cancer development. They found that early on, tumors accumulate many extra copies of a gene called Mycl1, a known

oncogene that helps cells ignore signals to stop growing. Because Mycl1 is mutated so early, it is found in nearly all of the tumor cells, making it a good drug target, McFadden says. There are currently no cancer treatments that specifically target Mycl1, but scientists are now working on drugs that target a closely related oncogene, MYC.

Later in tumor progression, the mouse cancer cells lose a gene called Pten, which has previously been found mutated in about 20 percent of small cell lung cancer patients. In normal cells, Pten regulates a critical signaling pathway called PI3K, which influences many aspects of cell growth and survival. When Pten is lost, the pathway becomes overactive, allowing tumor cells to grow very rapidly.

Drugs that target the PI3K pathway are now in the early stages of clinical testing in human patients.

Retracing metastasis

The researchers also compared the genomes of cells from the original lung tumors and from tumors that later appeared in other sites. This enabled them to retrace the tumor cells' paths and to determine which lung tumors were the sources of the metastases. They found that while multiple subsets of cells from the lung tumors could move to the lymph nodes, usually only a single subset from the lymph nodes spread to the liver.

"Our data really add to this emerging idea that metastatic spread is quite complicated, and that there may be different populations within a single cancer moving around to different sites, which may complicate treatments," McFadden says.

The researchers now hope to perform further genetic analysis to identify which mutations make certain cells more likely to metastasize. They also

plan to try treating small cell lung tumors with chemotherapy drugs and observing the genetic changes that occur as cancer cells become resistant to treatment.

Provided by Massachusetts Institute of Technology

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