New lung cancer gene found

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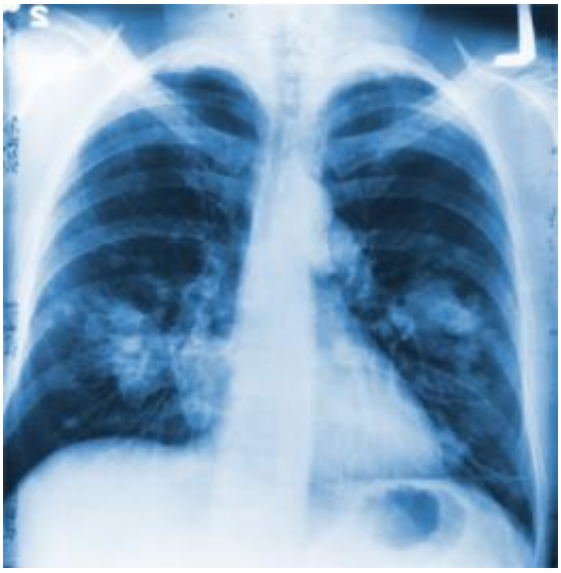

Image: National Cancer Institute

A major challenge for cancer biologists is figuring out which among the hundreds of genetic mutations found in a cancer cell are most important for driving the cancer's spread.

Using a new technique called whole-genome profiling, MIT scientists have now pinpointed a gene that appears to drive progression of small cell lung cancer, an aggressive form of lung cancer accounting for about 15 percent of lung cancer cases.

The gene, which the researchers found overexpressed in both mouse and human lung tumors, could lead to new drug targets, says Alison Dooley,

a recent PhD recipient in the lab of Tyler Jacks, director of MIT's David H. Koch Institute for Integrative Cancer Research. Dooley is the lead author of a paper describing the finding in the July 15 issue of *Genes and Development*.

Small cell lung cancer kills about 95 percent of patients within five years of diagnosis; scientists do not yet have a good understanding of which genes control it. Dooley and her colleagues studied the disease's progression using a strain of mice, developed in the laboratory of Anton Berns at the Netherlands Cancer Institute, that deletes two key tumor-suppressor genes, p53 and Rb.

"The mouse model recapitulates what is seen in human disease. It develops very aggressive lung tumors, which metastasize to sites where metastases are often seen in humans," such as the liver and adrenal glands, Dooley says.

This kind of model allows scientists to follow the disease progression from beginning to end, which can't normally be done with humans because the fast-spreading disease is often diagnosed very late. Using whole-genome profiling, the researchers were able to identify sections of chromosomes that had been duplicated or deleted in mice with cancer.

They found extra copies of a few short stretches of DNA, including a segment of chromosome 4 that turned out to include a single gene called Nuclear Factor I/B (NFIB). This is the first time NFIB has been implicated in small cell lung cancer, though it has been seen in a mouse study of prostate cancer. The gene's exact function is not known, but it is involved in the development of lung cells.

Researchers in Jacks' lab collaborated with scientists in Matthew Meyerson's lab at the Dana-Farber Cancer Institute and the Broad Institute to analyze human cancer cells, and found that NFIB is also

amplified in human small cell lung tumors.

That makes a convincing case that the gene truly is playing an important role in human small cell lung cancer, says Barry Nelkin, a professor of oncology at Johns Hopkins University School of Medicine, who was not involved in this research.

“The question, always, with mouse models is whether they can tell you anything about a human disease,” Nelkin says. “Some tell you something, but in others, there may be only a similarity in behavior, and the genetic changes are nothing like what is seen in humans.”

The NFIB gene codes for a transcription factor, meaning it controls the expression of other genes, so researchers in Jacks’ lab are now looking for the genes controlled by NFIB. “If we find what genes NFIB is regulating, that could provide new targets for small cell lung cancer therapy,” Dooley says.

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