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Study finds new genetic error in some lung cancers

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A fine-grained scan of DNA in lung cancer cells has revealed a gene fusion – a forced merger of two normally separate genes – that spurs the cells to divide rapidly, scientists at Dana-Farber Cancer Institute and the University of Colorado Cancer Center report in a new paper in the journal *Nature Medicine*. Treating the cells with a compound that blocks a protein encoded by one of those genes – NTRK1 – caused the cells to die.

The finding suggests that the fusion of NTRK1 to other genes fuels the growth of some lung adenocarcinomas (a form of non-small cell lung cancer), and that drugs that target NTRK1's protein product could be effective in patients whose lung tumors harbor such fusions.

"Treatment with targeted therapies is now superior to standard chemotherapy for many patients with lung cancers that harbor genetic changes including those with fusions involving the gene ALK," says Pasi A. Jänne, MD, PhD, of Dana-Farber, the senior co-author of the paper with Robert C. Doebele, MD, PhD, of CU Cancer Center. "We know of several other genes that are fused in lung cancer and that offer attractive targets for new therapies. Our discovery places lung adenocarcinomas with NTRK1 fusions squarely within that group."

In the study, researchers performed next-generation DNA sequencing tests – which read the individual elements of the genetic code over long stretches of chromosomes – on tumor samples from 36 patients with lung adenocarcinomas whose tumors did not contain any previously

known genetic alterations that could be found with standard clinical tests. In two of those samples – both from women who had never smoked – investigators found that a key region of the NTRK1 gene had become fused to normally distant genes (to the gene MPRIP in one patient; and the gene CD74 in the other).

NTRK1 holds the blueprint for a protein called TRKA, which dangles from the surface of cells and receives growth signals from other cells. The binding of NTRK1 to other genes causes TRKA to issue cell-growth orders on its own, without being prompted by outside signals.

In the laboratory, investigators mixed NTRK1-inhibiting agents into lung adenocarcinoma cells harboring NTRK1 fusions. The result was a dampening of TRKA's activity and the death of the cancer cells.

Investigators then designed a new test using fluorescence in situ hybridization (FISH) to detect NTRK1 fusions and tested an additional 56 tumor samples. In total, three of 91 tumor samples which had no other sign of cancer-causing genetic abnormalities, had fusions involving NTRK1.

"These findings suggest that in a few percent of lung adenocarcinoma patients – people in whose cancer cells we had previously been able to find no genetic abnormality – tumor growth is driven by a fusion involving NTRK1," Jänne says. "Given that lung cancer is a common cancer, even a few percent is significant and translates into a large number of patients. Our findings suggest that targeted therapies may be effective for this subset of lung cancer patients."

"This is still preclinical work," Doebele says, "but it's the first – and maybe even second and third – important steps toward picking off another subset of lung cancer with a treatment targeted to the disease's specific genetic weaknesses."

More information: Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer, DOI: 10.1038/nm.3352