

Unexpected finding reveals new target for aggressive form of lung cancer

December 2 2020



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Targeted therapies are currently available for about one-third of people with lung adenocarcinoma, the most common kind of lung cancer. These drugs inhibit cancer cells by thwarting the molecular changes that drive them to grow while largely sparing healthy tissues. But for the other two-thirds of people with this type of cancer, there are fewer treatment

options.

A team from Memorial Sloan Kettering is reporting new findings about a particularly aggressive subset of lung adenocarcinomas that are driven by two mutations that frequently occur together, in genes called KEAP1 and STK11. The [molecular changes](#) characteristic of these tumors were surprising to the investigators who discovered them: they block a type of cell death called ferroptosis. Cancers with these changes require this blockade to stay alive and grow. The study was published December 1, 2020, in *Cell Reports*.

Ferroptosis is a type of programmed cell death that is dependent on iron. Ferroptosis was discovered less than a decade ago, but it has already emerged as an important target for cancer therapies as well as drug treatments for other diseases. When ferroptosis fails to occur when it should, [cells](#) can grow uncontrollably.

"We really didn't know what particular vulnerabilities we would find in these cancer cells," says MSK physician-scientist Charles Rudin, Chief of the Thoracic Oncology Service, Co-Director of the Fiona and Stanley Druckenmiller Center for Lung Cancer Research, and the paper's senior author. "But all of the work we report in this study pointed toward ferroptosis as a key player."

Two Mutations Working Together

The genetic change that allows the cancer cells to block ferroptosis is called a co-mutation: alterations in two genes called STK11 and KEAP1 work together to create an environment in which tumor cells are able to grow even when they are receiving signals that would otherwise induce [cell death](#). The combination of mutations in these two genes is found in more than 10% of lung adenocarcinomas, so a drug that could successfully target this alteration would have a meaningful impact.

MSK biostatistician Ronglai Shen was the first to discover that the STK11/KEAP1 co-mutation is often found in lung adenocarcinomas that are very aggressive and hard to treat. She made the discovery when doing an analysis of [lung](#) cancer using data from MSK-IMPACT™, a test that looks for hundreds of mutations in tumors at the same time. Dr. Shen is a co-author on the new study.

The connection to ferroptosis was unexpected. "Our findings suggest that targeting certain proteins that play a role in the regulation of ferroptosis could lead to new treatments for this [cancer](#)," Dr. Rudin says.

CRISPR Helps Create Useful Lab Models

In the current study, first author Corrin Wohlhieter, a graduate student in the lab that's co-led by Dr. Rudin and Triparna Sen, used the gene editing tool CRISPR—which allows researchers to make very specific changes to the genetic code—to create three types of cells: some of these cells had the gene STK11 knocked out, some had KEAP1 knocked out, and some had both genes knocked out. She then isolated each of the three cell types and studied them in the lab, including in mouse models. By analyzing the cells' behaviors, she was able to figure out which other genes were activated when STK11 and KEAP1 were lost.

"Lung cancers tend to be very heterogeneous, so if you don't do these kinds of controlled experiments it's hard to isolate changes attributable to a particular gene or set of [genes](#)," Dr. Rudin says. "By creating these knockouts, it allows us to really focus on cells with these mutations and to link any behaviors we observe to the presence or absence of these factors."

The team's observations helped them make the connection to ferroptosis. They found that cells with both the STK11 and KEAP1 mutations also had high levels of proteins already known to make cells resistant to

ferroptosis. Dr. Rudin and his colleagues pinpointed one of these proteins, called SCD1, as a particularly good target for these tumors.

"Although the current SCD1 inhibitors that we have are not likely to make good drugs," he explains, "there are many labs at MSK that are actively investigating strategies for targeting ferroptosis in [cancer cells](#)."

Dr. Rudin says he plans to work with other researchers to learn more about these interactions and to look for compounds that could be developed into drugs. "We hope to find drugs that inhibit the pathways in these tumor cells, ultimately developing a targeted therapy strategy for these particularly difficult cancers," he concludes.

More information: Corrin A. Wohlieter et al, Concurrent Mutations in STK11 and KEAP1 Promote Ferroptosis Protection and SCD1 Dependence in Lung Cancer, *Cell Reports* (2020). [DOI: 10.1016/j.celrep.2020.108444](#)

Provided by Memorial Sloan Kettering Cancer Center

Citation: Unexpected finding reveals new target for aggressive form of lung cancer (2020, December 2) retrieved 7 July 2024 from <https://medicalxpress.com/news/2020-12-unexpected-reveals-aggressive-lung-cancer.html>

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