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Study reports success in targeted therapy for common form of lung cancer

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The most common genetic subtype of lung cancer, which has long defied treatment with targeted therapies, has had its growth halted by a combination of two already-in-use drugs in laboratory and animal studies, setting the stage for clinical trials of the drugs in patients, researchers at Dana-Farber Cancer Institute and other scientists report in a new study.

The study, published in the journal *Cancer Discovery*, describes a new tack in the treatment of lung adenocarcinomas – which account for about 40 percent of all lung cancers – that carry mutations in the gene KRAS. While most efforts to target KRAS directly with drugs have not proven successful, the authors of the current study took a more circuitous approach – targeting KRAS's accomplices, the genes that carry out its instructions, rather than KRAS itself.

"About 30 percent of lung adenocarcinomas have mutations in KRAS, which amounts to nearly 30,000 of all patients diagnosed with lung cancer each year in the United States," says the study's senior author, David Barbie, MD, of the Lowe Center for Thoracic Oncology at Dana-Farber and the Broad Institute of Harvard and MIT. "That represents the single biggest subset of lung cancer patients, if grouped by the mutations within their tumor cells. Unfortunately, there hasn't been a reliable way at striking at the genetic mechanism that causes these cells to proliferate."

Mutations in KRAS cause cancer cells to grow and divide in a wildly

disordered way. The lack of drugs able to block KRAS safely has led investigators to look for ways of stifling its effects "downstream" – by interfering with the signals it sends to other genes.

Barbie was studying one of these signaling pathways, which involves TBK1, a protein active in the immune system. He conducted a search of scientific literature to see if there are any compounds capable of blocking this protein. One study stated, deep in the footnotes, that a drug known as CYT387 – already being tested as a treatment for the bone marrow disorder myelofibrosis – is also active against the TBK1 protein.

Barbie and his colleagues tested CYT387 in laboratory samples of lung adenocarcinoma cells and found it to be a potent inhibitor of TBK1 and, as a bonus, an effective suppressor of cytokines, proteins that congregate in the tissue around tumors and help cancer cells survive and spread to other parts of the body. Animal studies produced similarly encouraging results.

Barbie and study co-senior investigator Kwok-Kin Wong, MD, PhD, of the Lowe Center for Thoracic Oncology at Dana-Farber next ran tests in more aggressive lung adenocarcinomas, which, in addition to having mutations in KRAS, also had mutations in the key gene p53. The investigators tested two drugs in tandem against these tumor samples: CYT387 and AZD6244, which inhibits MEK, another downstream protein of KRAS. Neither drug had much of an effect by itself; together, they formed a potent combination against the tumors, both in laboratory cell samples and in animals with the disease.

"Cytokines play a key role in tumor survival and spread in cells with KRAS mutations," Barbie states, "so blocking cytokine signaling can deprive cancer cells of a critical survival strategy. Because the combination of a TBK1 and MEK inhibitor targets two pathways at once, it shuts off cytokine signaling very quickly." The shutdown of

cytokines contrasts with the effects of many other forms of targeted therapy, which impede cancer cells' ability to proliferate.

The drug combination didn't produce any notable side effects in the animal models," Barbie notes. He adds, however, that after about eight weeks of treatment, the cancer cells became resistant to the regimen, highlighting the potential need for additional drug combinations to produce lasting remissions.

"The next step will be to take these results to the clinic, where the combination can be tested in lung cancer patients," says Wong. "We're in the process of developing a clinical trial. Because KRAS mutations are also common in colon and pancreatic cancer, we're hopeful that trials will be organized for these patients as well."

Provided by Dana-Farber Cancer Institute