Combination therapies could help treat fatal lung cancers

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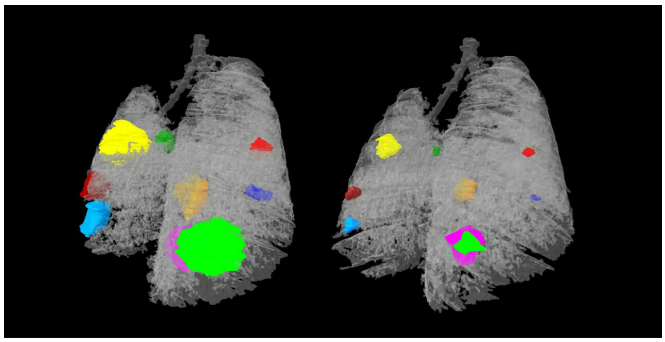

A mouse lung before and after treatment with a new three-drug treatment strategy, with each colour representing a distinct tumour. The tumours shrank significantly after a combination therapy with inhibitors for G12C KRAS, MTOR and IGF1R. Credit: Dr Miriam Molina-Arcas, Francis Crick Institute

Combining a new class of drug with two other compounds can significantly shrink lung tumours in mice and human cancer cells, finds a new study led by the Francis Crick Institute and The Institute of Cancer Research, London.

The study, published in *Science Translational Medicine*, looked at G12C KRAS inhibitors. This new type of drug targets a specific mutation in the KRAS gene that can cause cells to multiply uncontrollably and lead to fast-growing cancers.

These mutations are found in 14% of lung adenocarcinomas, the most common form of lung cancer. There are still no effective treatments for most patients, and more than eight in ten will die within five years of diagnosis. Every year, around 2,800 people in the UK will develop lung cancers with the deadly G12C KRAS mutation.

Drugs targeting G12C KRAS mutations are showing promising anti-tumour activity and few adverse effects in US clinical trials, but it is unclear how long any response will last before the cancer becomes resistant.

"It's likely that tumours will develop resistance to the new drugs, so we need to stay one step ahead," explains senior author Professor Julian Downward, who led the research at the Crick and ICR. "We found a three-drug combination that significantly shrank lung tumours in mice and human cancer cells. Tumours treated with the combination shrank and stayed small, whereas those treated with the G12C KRAS inhibitor alone tended to shrink at first but then start growing again after a couple of weeks. Our results suggest that it would be worth trying this combination in human trials in the coming years, to prevent or at least delay drug resistance."

The other compounds in the combination block the mTOR and IGF1R pathways, both of which have been previously tested in cancer patients. There are already licensed mTOR inhibitors on the market, while IGF1R inhibitors are still at the trial stage.

To develop this combination, the team used tumour cells derived from patients with the G12C KRAS mutation. They edited these cells to block the activity of 16,019 different genes and treated them with compounds that KRAS mutant cancers are known to be susceptible to.

"We found that cell lines without the MTOR gene were significantly more vulnerable to both KRAS and IGF1R inhibitors," explains first author Dr. Miriam Molina-Arcas, Senior Laboratory Research Scientist at the Crick. "When we blocked all three pathways, the mutant cancer cells were simply unable to survive. This makes it a promising avenue for human trials in the coming years, although this is still early research. Promising results in mice and cells can tell us what's worth trying, but it's impossible to predict how patients will respond until we actually try."

More information: M. Molina-Arcas el al., "Development of combination therapies to maximize the impact of KRAS-G12C inhibitors in lung cancer," *Science Translational Medicine* (2019). stm.sciencemag.org/lookup/doi/ … scitranslmed.aaw7999

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