Scientists identify the mechanisms leading to resistance to lung cancer treatment with Sotorasib

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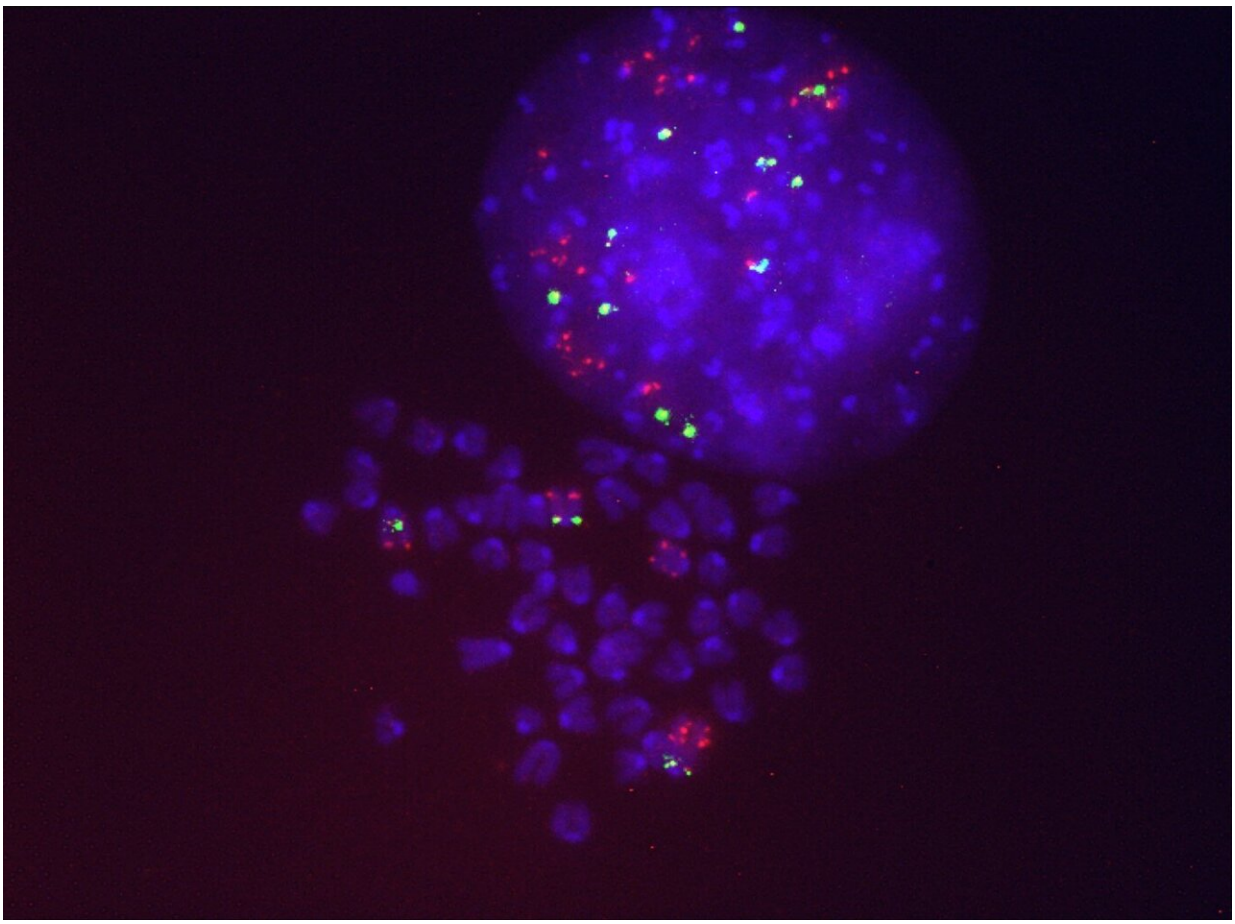

Sotorasib-resistant lung cancer cells displaying multiple copies of the mutated KRAS gene (in red) / CICANCER. Credit: CICANCER

According to recent figures published by the Spanish Society of Medical Oncology (SEOM), more than 30,000 new cases of lung cancer will be diagnosed in Spain in 2023, making it the second most frequent type of cancer in this country. In addition to its high prevalence, its 5-year survival rate is one of the lowest of all cancers. In fact, lung cancer is by far the deadliest cancer—it caused more than 22,000 deaths in 2021.

Personalized therapies, targeting the specific biology of each type of tumor, are one of the great advances in cancer research in recent decades, their success due to the fact that they act specifically on genes and proteins involved in the growth and survival of cancer cells. Given that the KRAS gene is mutated in a quarter of lung cancers, personalized therapies against this mutated gene would be a breakthrough in the treatment of lung cancer patients.

In fact, 2021 was a significant year in the approach to lung cancer because the first personalized drug (Sotorasib), targeting the most frequent KRAS mutation in lung cancer—which is a direct consequence of smoking—was approved in the US. Specifically, Sotorasib inhibits the mutant $KRASG^{12C}$ isoform. Each year approximately 3,000 newly diagnosed people could benefit from Sotorasib in Spain.

However, most patients quickly develop resistance to the drug and the treatment is no longer effective. The group led by Matthias Drosten, from the Cancer Research Center (CSIC-University), is studying how resistance to Sotorasib arises, to develop better prevention strategies.

The group uses genetically modified mouse models, whose mutations in KRAS and other mutated genes trigger the development of aggressive tumors similar to those in humans. "We have seenthat one of the best strategies to treat these tumors is to inhibit KRAS, because in a second mouse model we have found tumor regression and cure in all cases when the mutated KRAS gene is completely eliminated," says Matthias

Drosten.

Tumors adapt to the drug

It has been shown that resistance occurs because tumors can quickly adapt to the presence of the inhibitor. The treatment loses efficacy because the lung tumor cells, in response to the treatment, increase the copies of the KRAS gene.

In addition, a second cause explaining drug resistance and decreased drug activity has been detected in this study: transcriptional programs are activated (which allow the conversion of DNA into RNA) that increase the chemical modification of the drugs.

"These mechanisms studied in the mouse," says Marina Salmón, "researcher in the Experimental Oncology group at the CNIO and first author of the study, are also present in some human tumors. Therefore, the results of this research may help to identify new forms of treatment adapted to each patient."

Towards new personalized treatments

This research opens the door to the design of new personalized treatments based on the following evidence. On the one hand, it has been found that tumor cells with gene amplifications lose their fitness when they are no longer exposed to the inhibitor, which could help to define new treatment guidelines. On the other hand, other drugs can be targeted to other molecules, such as NF-kB and STAT3 proteins, also identified in this study as possible mediators of resistance in lung tumor cells.

In the event that resistance is detected through NF-kB and STAT3, inhibitors against these molecules are likely to be effective in reversing resistance.

With a wide variety of resistance mechanisms identified, lung cancer patients with the KRAS mutation who do not respond to treatments will need to undergo a personal analysis to detect what type of resistance the cells have developed so that treatment can be tailored.

Another challenge arising from this research, which would help to increase survival in lung cancer, would be to develop a therapy similar to the complete elimination of the KRAS oncogene from cancer cells.

In short, Drosten points out, "this research should encourage other researchers and the pharmaceutical industry to continue developing new therapies directed against KRAS."

The study is published in the *Journal of Clinical Investigation*.

More information: Marina Salmón et al, Kras oncogene ablation prevents resistance in advanced lung adenocarcinoma, *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI164413

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