Getting to the Bottom of Why KRAS Inhibitors Stop Working

The study helps explain how cancer cells adapt and tolerate treatment and identify combination therapies to improve outcomes in people.

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After decades of trying, scientists developed drugs that target one of the most elusive cancer-causing proteins, KRAS, which is activated in nearly a third of cancers, including difficult to treat lung and colorectal cancers. In 2016, Piro Lito, MD, PhD, (Damon Runyon Clinical Investigator '17-'20) and his colleagues at Memorial Sloan Kettering Cancer Center showed that a compound could shut down the most common form of the KRAS mutation in lung cancer without harming healthy cells. The protein cycles between an "on" and "off" form, creating subtle shape changes that enable drugs called KRAS G12C inhibitors to bind to and disable it.

Last year, these drugs showed promising but partial responses in phase I clinical trials—tumors shrank incompletely and in only a subset of patients. Now, a new study from Lito and his colleagues at Memorial Sloan Kettering have identified a mechanism responsible for this tumor resistance and suggested ways to circumvent it.

The researchers used a technique called single-cell RNA sequencing to measure the drug responses of thousands of individual cells simultaneously. They discovered that while some cancer cells remained inhibited by the drug, others rapidly adapted to treatment.

From this data, they were able to shed light on what was happening on the molecular level. The inhibitors caused cancer cells to produce a new form of KRAS G12C protein, which takes on a shape that is insensitive to the drug and enables some cancer cells to escape its effects. The cells that produce the KRAS protein in a drug-sensitive state continue to be inhibited by the treatment.

Lito and his colleagues found that this adaptive response could be minimized by adding a second drug that helps keep the new KRAS G12C protein in the druggable state. "Our study helps us better understand how cancer cells adapt and tolerate treatment and identify combination therapies that can improve outcomes in patients," Lito says. Clinical trials of such combinations are set to begin this year.

This research was published in Nature. Read Dr. Lito's one-on-one interview in Cancer Health magazine.

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