Many Cancer Drugs May Be Going After Unintended Targets

This mix-up may help explain why cancer drugs aren't always as effective as hoped.

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One reason many cancer drugs have not proved as effective as researchers have expected could be that these drugs are not attacking the targets they were designed to go after, The New York Times reports. In fact, the crux of this problem may be that the intended targets were never the cancer's weak spot in the first place and that attacking those unintended targets results in only a modest effect.

Publishing their findings in Science Translational Medicine, a research team led by Jason Sheltzer, PhD, a cancer biologist at Cold Spring Harbor Laboratory in New York state, arrived at this conclusion while searching for a new test for breast cancer.

Focusing on a protein called MELK that is seen in high levels in certain forms of breast cancers and that previous studies had suggested was essential to the growth of the cancer, the investigators used the CRISPR gene-editing technology to edit out the gene for MELK in cancer cells.

Although conventional wisdom suggested that the excision of this gene would have stopped the cancer cells from growing, this did not occur. However, exposing the cancer cells to a drug that targeted MELK did stop their growth—despite the cells' lack of the gene this drug was supposed to target.

The team proceeded to run this experiment with 10 other drugs currently in clinical trials that target proteins thought to be involved in cancer growth. The results were identical in all cases. It turned out that although the proteins these drugs targeted were not crucial to cancer growth, the drugs nevertheless stopped cancer cell growth.

The reason for such confusion, the team came to theorize, was that prior to the advent of CRISPR, the RNAi interference technology used to impede the production of specific cancer proteins was simply not as precise as once believed. RNAi may have had off-target effects on proteins that cancer investigators were unaware of. This led to the development of cancer therapies that targeted one protein that affects cancer growth while the scientists thought the drug went after a different protein, one that actually was of little or no consequence to the spread of the malignancy.

To test this theory, Sheltzer's team looked at OTS964, one of the 10 drugs included in the larger investigation. They gave the drug to laboratory cancer cell colonies and found that it killed off most cells. DNA sequencing revealed that the few cells that did survive all had mutations in a gene that gives rise to a protein known as CDK11B. This protein, it turned out, was the true target of the drug, so cells with a mutated form of the protein evaded the treatment.

Next, the investigators used CRISPR to snip the CDK11B gene out of cancer cells; sure enough, the cells died.

"We suggest that stringent genetic validation of the mechanism of action of cancer drugs in the preclinical setting may decrease the number of therapies tested in human patients that fail to provide any clinical benefit," the study authors concluded.

To read the New York Times article, click here.

To read a press release about the study, click here.

To read the study abstract, click here.

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