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Weakness exposed in most common cancer gene

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NYU Langone Medical Center researchers have found a biological weakness in the workings of the most commonly mutated gene involved in human cancers, known as mutant K-Ras, which they say can be exploited by drug chemotherapies to thwart tumor growth.

Mutant K-Ras has long been suspected of being the driving force behind more than a third of all cancers, including colon, lung, and a majority of pancreatic cancers. Indeed, Ras cancers, which are unusually aggressive, are thought of as "undruggable" because every previous attempt to stall their growth has failed.

Reporting in the journal *Cancer Cell* online Feb. 10, researchers in the lab of NYU Langone's Dafna Bar-Sagi, PhD, led by Elda Grabocka, PhD, showed in experiments in human cancer cells that K-Ras tumor growth was highly dependent on the cells' constant need to check and mend their DNA.

Cell DNA is routinely damaged by several factors, including stress or ultraviolet light radiation, and must be repaired in order for cells to grow by cell division. In cancer cells, such "wear and tear" is accelerated.

In the study, researchers discovered how a commonly used chemotherapy drug could be much more effective in killing K-Ras cancer cells when their ability to check their DNA for any damage was blocked, by cutting off the activity of two related genes, H-Ras and N-Ras.

"Our finding suggests that K-Ras cancers can be made more susceptible to existing therapies by interfering with their DNA repair mechanisms," says Dr. Bar-Sagi, senior study investigator and biochemist. "What some researchers have described as therapeutic 'mission impossible' may now become a 'mission doable'," adds Dr. Bar-Sagi, senior vice president and vice dean for science, and chief scientific officer of NYU Langone Medical Center.

Lead study investigator and cancer biologist Dr. Grabocka, a postdoctoral fellow at NYU Langone, says the latest findings are believed to be the first to show that Ras mutations are part of a network of different forms of Ras acting in concert to determine how cancer cells respond to drug chemotherapies.

The team's investigation began with experiments to unravel how Ras signaling leads to the uncontrolled growth of cancer cells. They found that blocking the production of H-Ras and N-Ras in mutant K-Ras cells caused the buildup of damaged DNA and slowed down cell growth.

Specifically, Grabocka points out, the team found that K-Ras cancer cells, in the absence of H-Ras and N-Ras, failed to stop and repair their DNA at a key phase in cell division, controlled by an enzyme called checkpoint kinase 1, or Chk1.

Using K-Ras cancer cells developed at NYU Langone, Bar-Sagi and her team then set out to test the effects of the chemotherapy drug irinotecan on tumor growth.

Only when the drug was delivered in combination with the inactivation of H-Ras and N-Ras did tumor shrinkage and cell death occur.

"Discovering more about how these different forms of Ras act on one another—including how they control DNA damage repair at Chk1 in

combination with chemotherapy—could help us design drugs that greatly stall disease progression," says Dr. Grabocka.

Researchers plan further experiments on the biological interdependency of Ras proteins and what other chemotherapies might be involved in slowing cancer growth. Their goal, Dr. Grabocka says, is to "map out" the Ras signaling pathways and to identify as many therapeutic drug targets as possible. "Our research is focused on finding multiple targets in K-Ras cancers, all working against what is known as its 'tumor fitness,' and weakening it so that it is as vulnerable as possible to chemotherapy," says Dr. Grabocka.

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