Additional challenges in KRAS-driven cancers identified

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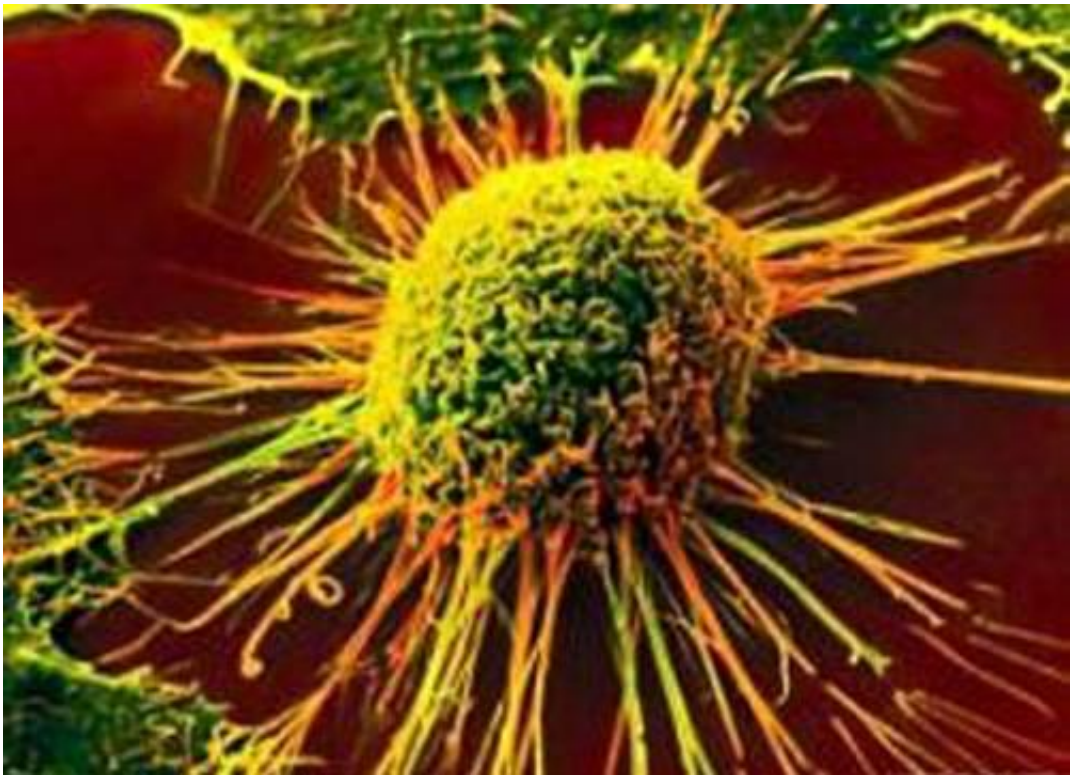

Cancers driven by – and dependent on – the potent mutated cancer gene KRAS have an especially poor prognosis, and three decades of scientific attempts have failed to produce drugs that can attack KRAS and halt the tumors' runaway growth.

A renewed assault on the problem is underway, but researchers report in the journal *Cell* they have identified a backup genetic pathway that can enable cancer cells to survive and thrive in the absence of KRAS. If and when it becomes possible to shut down the oncogene in human cancers, the findings suggest, this escape mechanism will have to be blocked as well to kill the tumor cells.

"It tells us that if we can turn off KRAS, the tumors are going to find a way of turning on this resistance program; it helps anticipate what molecules you need to target along with KRAS," said William Hahn, MD, PhD, of Dana-Farber Cancer Institute and the Broad Institute of MIT and Harvard. Hahn is co-senior author of the study along with Tyler Jacks, PhD, director of the Koch Institute for Integrative Cancer Research at MIT, the David H. Koch Professor of Biology, and senior associate member at the Broad Institute.

The newly identified mechanism is a biological partnership involving KRAS and YAP1, a gene that makes a regulatory protein. YAP1 is involved in regulating organ size during embryonic development, and extra copies of it have been found in liver cancers.

The investigators sifted through 16,000 different genes, searching for any that could "rescue" laboratory-maintained cancer cells in which KRAS was turned off. YAP1 stood out in that respect. The cells, which are "addicted" to KRAS signals for survival and growth, normally would die as a result. Instead, expression of the YAP1 gene replaced the need for KRAS. The experiments also revealed that YAP1 is necessary, along with KRAS, for the cells to become cancerous.

In addition, the notorious capability of KRAS-driven cancers to become invulnerable to treatments by developing drug resistance appears to stem from the interaction of KRAS and YAP1, the study revealed.

"This is a very important paper," commented Frank McCormick, PhD, of the Frederick National Laboratory for Cancer Research in Frederick, MD. "It highlights a pathway [YAP1 and related genes] involved in drug resistance that wasn't appreciated in this context before. This is something we will have to anticipate and get ahead of if we can find ways to target KRAS. It also focuses attention on how KRAS causes tumors in the first place."

McCormick leads the Solve RAS program, an effort launched by the National Cancer Institute in 2013 to find ways of targeting the RAS gene family to which KRAS belongs.

Discovered more than 30 years ago, mutant RAS oncogenes have been implicated in about 30 percent of human cancers, and KRAS is its most prominent and aggressive member. Mutant KRAS drives particularly hard-to-treat cancers, including many pancreatic, lung, and colon cancers. The RAS oncogenes have frequently been termed "undruggable;" their three-dimensional structure provides few if any footholds for drugs to bind with.

The launch of the RAS program reflects somewhat greater optimism that the problem may be solvable, thanks in part to more sophisticated tools for imaging the oncogene's structure and techniques, such as nanotechnology, that could provide a new avenue for drug delivery.

"There is reason to believe this won't be an unsolvable problem forever," said Hahn. He said he and his colleagues are continuing their research on the newly discovered KRAS "rescue" mechanism with the aim of finding methods to counteract it in KRAS –driven tumors.

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