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Researchers develop new strategy to target KRAS mutant cancer

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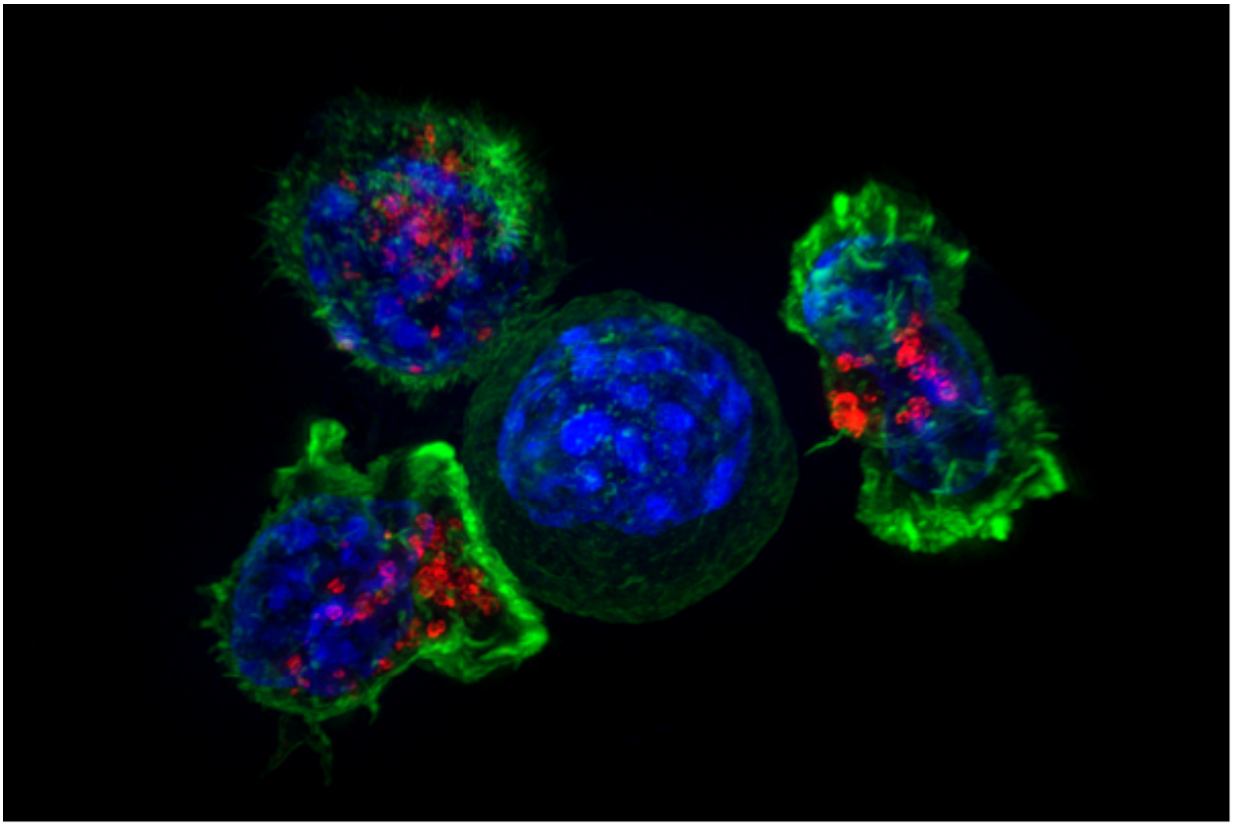

Killer T cells surround a cancer cell. Credit: NIH

Although KRAS is one of the major oncogenes associated with aggressive cancers, drugs designed to block KRAS function have not been able to halt cancer progression in a clinical setting. Until now,

KRAS has remained infamously "undruggable."

In a new study, published this month in *Cancer Discovery*, University of California San Diego School of Medicine researchers report that approximately half of lung and pancreatic cancers that originate with a KRAS mutation become addicted to the gene as they progress. By understanding the mechanism that causes these cancers to remain dependent on KRAS for survival, they were able to identify a drug capable of targeting it.

"Certain tumors use mutant KRAS to boost their survival by helping them take up nutrients and process toxins, causing them to become addicted to KRAS," said David Cheresh, PhD, UC San Diego School of Medicine Distinguished Professor of Pathology and senior author of the paper. "Other tumors that do not use KRAS in this way can do without it, even though it is needed to initiate cancer. Based on a biomarker we discovered, we now know which cancers will be addicted and which will not."

There are currently no effective treatments for the 95 percent of pancreatic cancers and up to 30 percent of non-small cell lung cancers with KRAS mutations. The team of researchers found that binding of the protein Galectin-3 to the cell surface receptor integrin avb3 amplifies the advantages driven by mutant KRAS, creating a unique vulnerability that could be targeted with an existing drug.

Cheresh and team found that a Galectin-3 inhibitor called GCS-100 was able to kill KRAS-addicted cells *in vitro* and halt progression of KRAS-addicted tumors in mouse models. Importantly, they discovered that a tumor would respond to the drug only if it was positive for integrin αvb3.

"This may be among the first approaches to successfully target KRAS

mutant cancers. Previously, we didn't understand why only certain KRAS-initiated cancers would remain addicted to the mutation," said Cheresh, associate director of innovation and industry alliances at UC San Diego Moores Cancer Center. "Now we understand that expression of integrin αvb3 creates the addiction to KRAS. And it's those addicted cancers that we feel will be most susceptible to targeting this pathway using Galectin-3 inhibitors."

Interrupting the origins of this pathway may be more promising than attempting to block individual KRAS-driven functions, wrote the researchers. Considering that KRAS-addicted cancers were found to be highly sensitive to Galectin-3 inhibitors in preclinical models, the next step would be to clinically test a currently available Galectin-3 inhibitor in patients whose tumors express both mutant KRAS and αvb3, a companion biomarker that predicts response.

"KRAS mutations impact a large number of patients with cancer. If a patient has a KRAS mutant cancer, and the cancer is also positive for αvb3, then the patient could be a candidate for a therapeutic that targets this pathway," said Cheresh. "Our work suggests a personalized medicine approach to identify and exploit KRAS addicted tumors, providing a new opportunity to halt the progression of tumors that currently have no viable targeted therapeutic options."

More information: Laetitia Seguin et al, Galectin-3, a druggable vulnerability for KRAS-addicted cancers, *Cancer Discovery* (2017). DOI: 10.1158/2159-8290.CD-17-0539

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