Genetic 'balance' may influence response to cancer treatment

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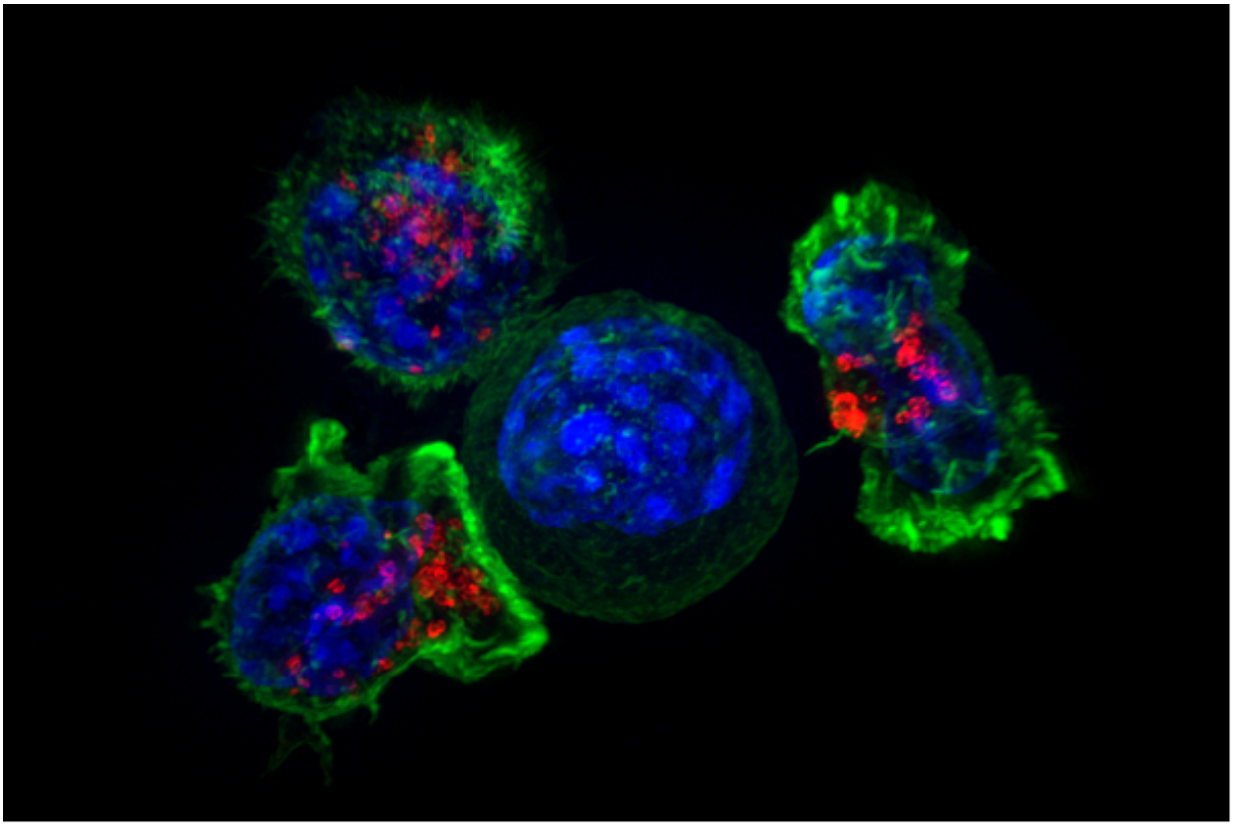

Killer T cells surround a cancer cell. Credit: NIH

Choosing among cancer treatments increasingly involves determining whether tumor cells harbor specific, mutated "oncogenes" that drive abnormal growth and that may also be especially vulnerable or resistant

to particular drugs. But according to a new study led by UCSF researchers, in the case of the most commonly mutated cancer-driving oncogene, called KRAS (pronounced "kay-rass"), response to treatment can change as tumors evolve, either when a normal copy of the gene from the other member of the matched chromosome pair is lost, or when the cancers cells evolve to produce additional copies of the mutated form of the gene.

The identification of distinctive abnormalities in DNA sequences within the genomes of tumor cells from biopsy specimens is becoming a more common aid to help guide cancer treatment decisions, and the authors of the new study, published in the February 23 edition of *Cell*, said their discovery of KRAS "imbalances" that emerge over time could be added to a growing list of genetic characteristics that may be clinically valuable.

"It's an unexpected result and a new idea for the field of cancer genetics," said the study's principal investigator, Kevin Shannon, MD, the Roma and Marvin Auerback Distinguished Professor in Pediatric Molecular Oncology at UCSF. "Those who enter the field are taught that oncogenes represent a dominant-acting mutation that is able to help drive abnormal growth within the tumor, and that a normal copy that is not mutated doesn't matter much. These new data show that the status of the normal copy of the gene can in fact matter in some cancers when it comes to determining whether tumor cells are sensitive to drug treatment."

Working with mice to generate multiple different leukemias that had a variety of easily traced genetic abnormalities and that could be easily transplanted and treated in additional mice, the scientists identified an especially interesting "outlier"—a cancer that was exceptional for its robust growth before treatment, for the duration of its responsiveness to a specific type of targeted therapy called a MEK inhibitor, and for the

way that it became resistant to that drug over time. These factors allowed the researchers to home in on the association between specific genetic changes and differences in treatment response.

This leukemia had a mutated KRAS gene on each chromosome, which enabled the cancer to grow aggressively, but also made it vulnerable to treatment with the MEK inhibitor. After treatment, the leukemia relapsed, and a third chromosome had emerged that carried a normal copy of KRAS, rendering the disease resistant to the drug.

First author Michael Burgess, MD, PhD, now a director in Translational Development at Celgene Corporation, led many of the mouse experiments while working in the Shannon lab with Eugene Hwang, a staff research associate at UCSF. "Starting with this mouse model of cancer we can more easily gain insight into mechanisms of drug response and resistance in cancer," Burgess said. "In human cancer, tissue is in very short supply and typically available at only one time point in the evolution of the tumor."

As part of the Cell study, Genentech researchers led by senior scientist Marie Evangelista, PhD, determined that a KRAS genetic profile similar to the outlier mouse cancer was also associated with vulnerability to MEK inhibitor treatment in human colon cancer cell lines grown in the lab, but not in human pancreatic or lung cancer cell lines.

Computational biologist Barry Taylor, PhD, associate director of the Marie-Josée & Henry R. Kravis Center for Molecular Oncology at the Memorial Sloan Kettering Cancer Center, led the genetic analysis of advanced human cancers for the study. Taylor developed mathematical algorithms and software to analyze relative dosage of mutant KRAS and normal KRAS in tumor cells from biopsy samples, which contain many normal cells as well as cancerous cells.

In the new study, loss of the normal copy of KRAS or duplication of the mutated copy, or both, was found in 55 percent of more than 1,100 biopsy samples from advanced, KRAS-driven human cancers originating in a variety of tissues.

To help optimize cancer treatment, it would be possible for clinical laboratories with additional skilled staff to use methods similar to those developed by Taylor to report results on duplicated oncogene mutations and loss of normal gene copies, according to Shannon and Burgess, but they said this approach is more likely to first be applied in clinical trials to test new experimental drugs.

"We had known that there were cancer cell lines that acquired more than one copy of mutant KRAS and lost the normal copy, but nobody had any idea that this also was so highly prevalent in primary human tumors." said Shannon, a member of the UCSF Helen Diller Family Comprehensive Cancer Center.

Major funders of the study included the National Institutes for Health, the Department of Defense and the American Cancer Society's Hillcrest Committee.

"In evaluating treatment response in clinical trials going forward, it will be important to understand not only whether a KRAS mutation is present, but also how much mutant KRAS is present, and whether there is a loss of the normal copy of the KRAS gene," Burgess said.

More information: Michael R. Burgess et al. KRAS Allelic Imbalance Enhances Fitness and Modulates MAP Kinase Dependence in Cancer, *Cell* (2017). DOI: 10.1016/j.cell.2017.01.020

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