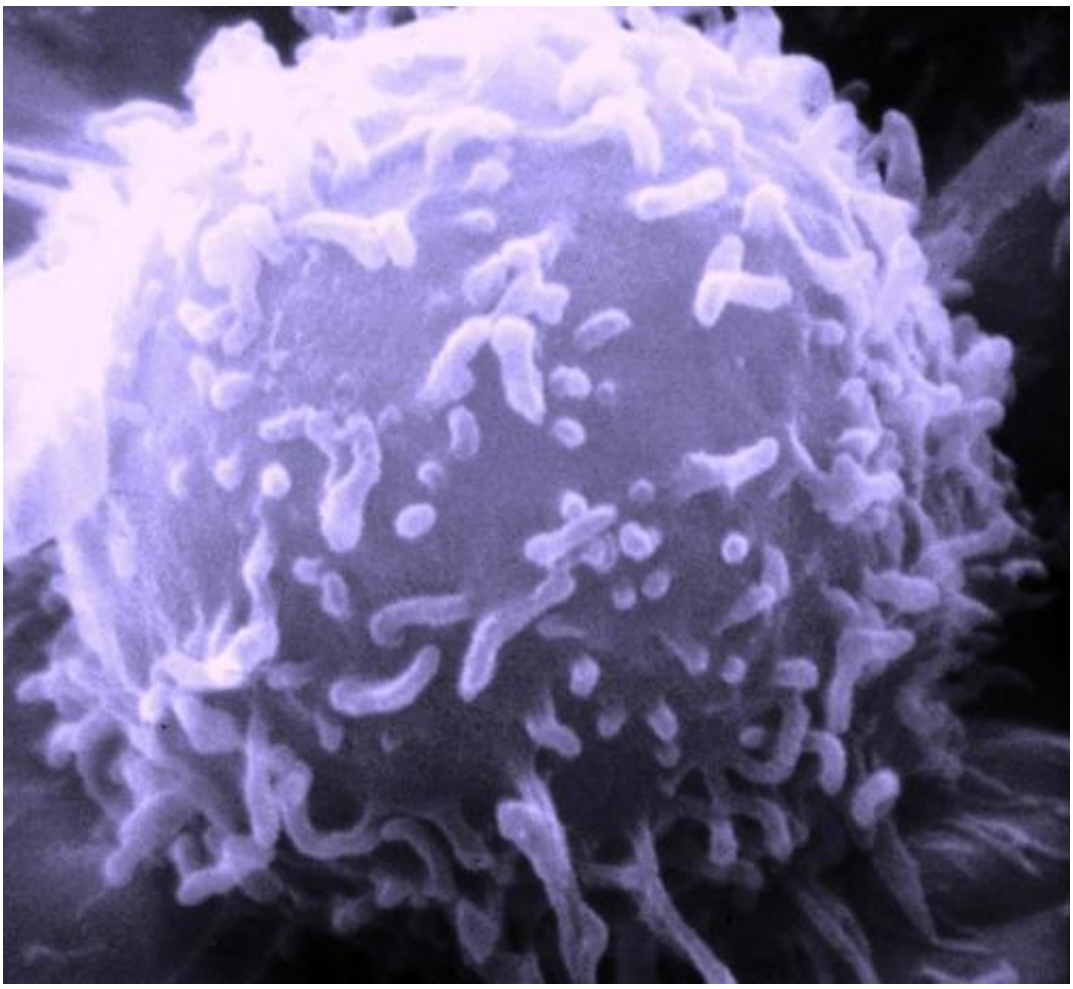
Coping mechanism suggests new way to make cancer cells more vulnerable to chemotherapies

December 15 2016



Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

The same signal that drives aggressive growth in a deadly cancer cell type also triggers coping mechanisms that make it "notoriously" hard to kill, according to a study published online December 15 in *Cell*. When stressed, this cell type - far more than most cancer cells - encases its genetic messages in protein globs called "stress granules" that lessen the effect of chemotherapies.

Led by two researchers from NYU Langone Medical Center and Thomas Jefferson University, the study revolves around the gene KRAS, which when changed, or mutated, drives abnormal growth in 90 percent of pancreatic cancers, as well as in many lung and colorectal tumors. As a second consequence of overactive KRAS, say the study authors, cells harboring this mutation form many more stress-coping granules.

"Our results explain why KRAS mutant cells are so good at resisting treatments, and suggest a way to make them many times more vulnerable to existing chemotherapies," says senior study author Dafna Bar-Sagi, PhD, Vice Dean for Science and Chief Scientific Officer at NYU Langone.

"Given the lack of good treatments for these patients, the ability to interfere with this coping mechanism would be revolutionary," says Bar-Sagi, also a professor in the Department of Biochemistry and Molecular Pharmacology at NYU Langone, and associated with its Perlmutter Cancer Center.

Constant Stress

All cells are continually exposed to stresses and rely on stress-coping mechanisms to survive. A growing body of evidence suggests that such resilience is especially vital for cancer cells, with the most resistant soon coming to dominate a growing tumor.

In a long-recognized stress response, cells halt the reading of DNA instructions in the middle - at the point when genetic messages are surrounded by proteins - to form protective granules. While the role of such granules in normal cellular life is established, their contribution to the stubborn survival of KRAS mutant cancer cells had not been clear.

In experiments, the research team showed that cells with KRAS mutations made six times more stress granules than cells without the mutations when exposed to either radiation or oxaliplatin, a chemotherapy that damages cancer cell DNA. Researchers were also able to capture and count the first images of stress granules in cancer cells resected from human pancreatic tumors, finding a marked increase.

The study found further that stressed cancer cells with KRAS mutations increase granule formation by making more of a hormone-like molecule called 15-deoxy-delta 12,14 prostaglandin J2 (15-d-PGJ2). Importantly, increases in levels of 15-d-PGJ2 triggered more stress granule formation, not only in mutated cells, but also in nearby cells without KRAS mutations (a 13-fold increase), which then became more resistant to oxaliplatin. This is because 15-d-PGJ2 is a signaling molecule secreted by cells.

"Mounting evidence suggests that the cancer cells making up even a single tumor are genetically diverse, so no treatment targeting just one genetic difference can kill them all," says study author Elda Grabocka, PhD, assistant professor of Cancer Biology at Sidney Kimmel Cancer Center at Jefferson. Grabocka designed the study while a post-doctoral scholar in Bar-Sagi's lab at NYU Langone. "If we could block the action of 15-d-PGJ2, we might make many more cancer cells in a tumor sensitive to a single therapy by removing a shared coping mechanism."

Moving forward, the authors plan to study whether, as hinted in past studies, adding a cyclooxygenase 2 (COX 2) inhibitor - a popular type of

anti-inflammatory painkiller - to chemotherapy can improve outcomes in patients with mutant KRAS cancers. Mutant KRAS cells are known to make extra COX 2, which increases 15-d-PGJ2 levels. At the same time, the researchers will seek to identify compounds that can directly counter 15-d-PGJ2 buildup, perhaps by using HPGD, an enzyme discovered in the current study to lower levels of 15-d-PGJ2.

Provided by New York University School of Medicine

Citation: Coping mechanism suggests new way to make cancer cells more vulnerable to chemotherapies (2016, December 15) retrieved 13 March 2024 from https://medicalxpress.com/news/2016-12-coping-mechanism-cancer-cells-vulnerable.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.