New combination therapy could help fight difficult-to-treat cancers with common mutations

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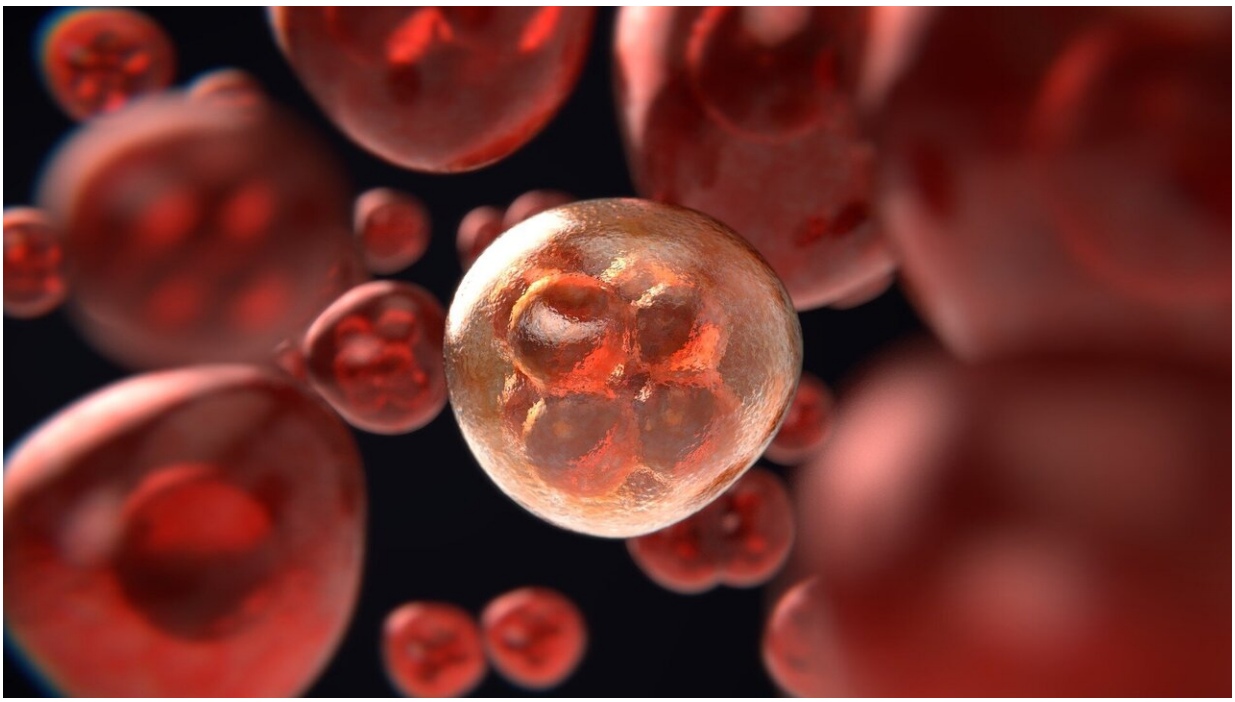

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Scientists have long known that therapies that target the cancer-driving MAPK pathway are only effective in a handful of cancers with specific mutations in a cancer gene called BRAF, and these cancers that initially respond to the therapy often end up developing resistance to the

treatment, resulting in relapse for many patients.

Now, scientists at the UCLA Jonsson Comprehensive Cancer Center describe a new combination therapy that suppresses the MAPK pathway by holding cancer-driving proteins in a death grip. This combination of two small molecules has the potential to treat not only BRAF mutated melanoma but also additional aggressive subtypes of cancers, including melanoma, lung, pancreatic and colon cancers that harbor common mutations in cancer genes called RAS or NF1.

The preclinical study, published today in *Cancer Discovery,* a journal of the American Association for Cancer Research, found that a second-generation RAF inhibitor (type II RAFi) in combination with a standard MEK inhibitor (MEKi) could be effective in treating cancers with these mutations and could also help overcome acquired resistance to the current standard-of-care treatment targeting specific BRAF mutations.

"The idea behind this study was to develop a combination treatment that helps people with common lethal cancers by eliciting durable anti-tumor responses," said senior author Roger Lo, MD, Ph.D., a professor of medicine at the David Geffen School of Medicine at UCLA and member of the UCLA Jonsson Comprehensive Cancer Center. "Right now, MEK inhibitors by themselves provide limited clinical benefits, and the current MAPK pathway-targeted, combination therapy can help only certain patients with cancers harboring specific BRAF mutations."

To test the effectiveness of the experimental combination, researchers used patient-derived models of melanoma, non-small cell lung cancer, pancreatic cancer and colon cancer as well as mouse tumors that mimic these human cancers. The team evaluated how the combination of type II RAFi plus MEKi impacts the MAPK pathway inside the cancer cells and the body's cancer-fighting immune or T-cells over time in order to achieve long-term response by suppressing drug-resistant clones.

The next-generation combination works by two unique mechanisms that can suppress drug-resistant clones. First, the two small molecules lock RAF and MEK proteins in the MAPK signaling pathway into a tight complex, which is unusual. Normally, molecules in this pathway touch and go in order to fire off growth-promoting signals. Keeping these molecules stuck together allows the drugs to effectively and durably block the MAPK pathway.

"It is quite remarkable that two drugs were able to bind to each of two proteins and sequester them from further propagating signals inside the cancer cells," said co-senior author Gatien Moriceau, Ph.D., assistant adjunct professor at the David Geffen School of Medicine at UCLA.

Second, the combination prevented an attrition of killer T-cells inside the tumor and promoted T-cell clonal expansion, which is an important immune mechanism that will allow immunotherapies, such as anti-PD-1/L1, to effectively attack the tumors when combined with a MAPK-targeted therapy.

"The combination unexpectedly preserves killer T-cells inside the tumors, which allows them to hunt down drug-resistant tumor clones," said Moriceau. "This favorable impact on T-cells paves the way to combine MAPK-targeted therapies with anti-PD-1/L1 immune checkpoint therapy."

The combination of type II RAFi plus MEKi is currently being tested in clinical trials in both melanoma and other solid cancers such as non-small cell lung cancer.

More information: Aayoung Hong et al, Durable Suppression of Acquired MEK Inhibitor Resistance in Cancer by Sequestering MEK from ERK and Promoting Anti-Tumor T-cell Immunity, *Cancer Discovery* (2020). DOI: 10.1158/2159-8290.CD-20-0873

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