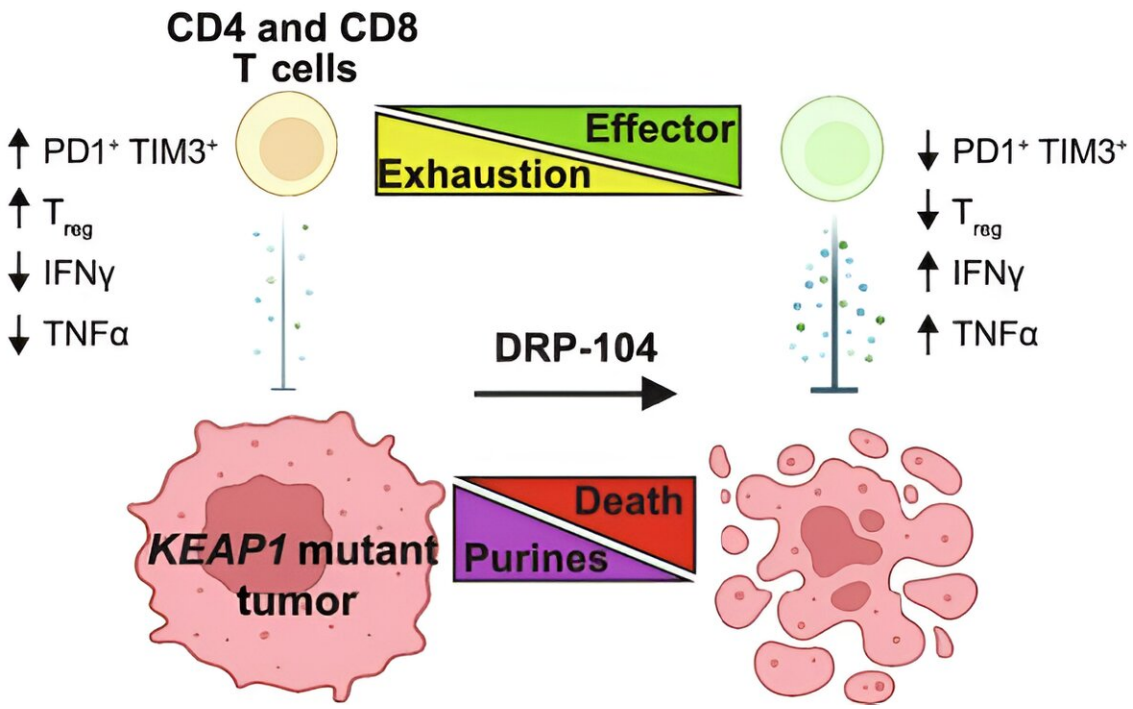
Drug shows promise for starving out cancer cells

May 6 2024, by Olivia Dimmer



Overview of effect of DRP-104 on KEAP1 mutant tumors and T cells. Credit: *Science Advances* (2024). DOI: 10.1126/sciadv.adm9859

Starving out tumor cells may be a promising therapy for treatment-resistant lung cancer, according to a new study published in *Science Advances*.

More than 230,000 new cases of lung cancer will be diagnosed this year in the U.S., according to the American Cancer Society, and roughly half of those diagnosed die from the disease. Lung adenocarcinoma, the most common lung cancer in the U.S., is one of the leading causes of cancer death nationwide.

A subset of treatment-resistant lung adenocarcinoma springs from a mutation in the gene KEAP1, and the lack of current therapies has led to poor prognoses for those diagnosed, said Shawn Davidson, Ph.D., assistant professor of Medicine in the Division of Pulmonary and Critical Care and a co-author of the study.

Davidson's previous research found that tumors arising from a KEAP1 mutation are extremely sensitive to deprivation of glutamine, an amino acid cells need for several essential processes.

"Cancer cells rely on certain nutrients, such as glutamine, to grow," Davidson said. "Glutamine can be used for energy, to make metabolic precursors for DNA synthesis and as a building block for proteins."

In the current study, Davidson and his collaborators administered DRP-104, a drug that blocks cancer cells from taking in glutamine, to patient-derived lung cancer cells. Investigators observed that DRP-104 was able to slow tumor growth, according to the study.

Using single-cell sequencing and functional assays to analyze the treated cells, investigators found that DRP-104 reversed T-cell exhaustion—a common feature of cancer proliferation in which immune cells can no longer defend against the tumor—and boosted anti-tumor immunity.

"In lung adenocarcinoma, DRP-104 targets glutamine metabolism but also other metabolic enzymes important for nucleotide synthesis and also worked to kill the cancer cells by starving them," Davidson said. "We

also found that DRP-104 reduces exhausted CD4 and CD8 T-cell populations, enhances T-cell cytokine production, and augments the response to anti-PD1 checkpoint inhibitor therapy in KEAP1 mutant tumors."

The findings suggest that DRP-104, which is currently in clinical trials, may be a potential therapeutic option for lung cancers caused by KEAP1 mutations, Davidson said.

"There are not many therapies that can simultaneously bolster immune cell responses and inhibit tumor cell growth, so this is exciting to us," Davidson said

Following up on the findings, Davidson and his laboratory will work to further test cancer responses to DRP-104 and better understand the mechanisms underlying it, he said.

"My lab has just received some funding to test the hypotheses generated in this study," Davidson said. "The goal is to determine the metabolic profiles of the immune cells and the metabolic profiles of the tumor cells and understand the cells' interactions. Doing this will allow us to specifically target immune and cancer cell populations further to potentially widen the therapeutic window."

More information: Ray Pillai et al, Glutamine antagonist DRP-104 suppresses tumor growth and enhances response to checkpoint blockade in KEAP1 mutant lung cancer, *Science Advances* (2024). DOI: 10.1126/sciadv.adm9859

Provided by Northwestern University