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Disabling enzyme reduces tumor growth, cripples cancer cells

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Knocking out a single enzyme dramatically cripples the ability of aggressive cancer cells to spread and grow tumors, offering a promising new target in the development of cancer treatments, according to a new study by researchers at the University of California, Berkeley.

The paper, to be published Monday, Aug. 26, in the journal *Proceedings of the National Academy of Sciences*, sheds new light on the importance of lipids, a group of molecules that includes fatty acids and cholesterol, in the development of cancer.

Researchers have long known that cancer cells metabolize lipids differently than normal cells. Levels of ether lipids—a class of lipids that are harder to break down—are particularly elevated in highly malignant tumors, although the nature of that correlation has been unclear for decades.

"Cancer cells make and use a lot of fat and lipids, and that makes sense because cancer cells divide and proliferate at an accelerated rate, and to do that, they need lipids, which make up the membranes of the cell," said study principal investigator Daniel Nomura, assistant professor in UC Berkeley's Department of Nutritional Sciences and Toxicology. "Lipids have a variety of uses for cellular structure, but what we're showing with our study is that lipids can also send signals that fuel cancer growth."

In the study, Nomura and his team tested the effects of reducing ether

lipids on human skin cancer cells and primary breast tumors. They targeted an enzyme, alkylglycerone phosphate synthase, or AGPS, known to be critical to the formation of ether lipids.

The researchers first confirmed that AGPS expression increased when normal cells turned cancerous. They then found that inactivating AGPS substantially reduced the aggressiveness of the cancer cells.

"The cancer cells were less able to move and invade," said Nomura.

The researchers also compared the impact of disabling the AGPS enzyme in mice that had been injected with cancer cells.

"Among the mice that had the AGPS enzyme inactivated, the tumors were nonexistent," said Nomura. "The mice that did not have this enzyme disabled rapidly developed tumors."

The researchers determined that inhibiting AGPS expression depleted the cancer cells of ether lipids. They also found that AGPS altered levels of other types of lipids important to the ability of the cancer cells to survive and spread, including prostaglandins and acyl phospholipids.

"The effect on other lipids was unexpected and previously unknown," said study lead author Daniel Benjamin, doctoral student in the Nomura Research Group. "Other studies have investigated specific lipid signaling pathways, but what makes AGPS stand out as a treatment target is that the enzyme seems to simultaneously regulate multiple aspects of lipid metabolism important for tumor growth and malignancy."

Future steps include the development of AGPS inhibitors for use in cancer therapy, said Nomura.

More information: Ether lipid generating enzyme AGPS alters the

balance of structural and signaling lipids to fuel cancer pathogenicity , www.pnas.org/cgi/doi/10.1073/pnas.1310894110