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Targeting brain cancer cell metabolism may provide new treatment

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Inhibiting fatty acid synthesis in brain cancer cells may offer a new option to treat about 50 percent of deadly glioblastomas that are driven by amplified signaling of the epidermal growth factor receptor (EGFR), according to a first-of-its-kind study by researchers at UCLA's Jonsson Comprehensive Cancer Center.

Rapidly dividing cancer cells require fatty acids for the formation of new membranes. The fatty acids also provide an alternative energy source for the cancer cells, and may be important for regulating cell signaling, said Dr. Paul Mischel, a professor of pathology and laboratory medicine and senior author of the study, which appears in the Dec. 15 issue of the journal *Science Signaling*.

While healthy cells take up the fat they need to function through the blood stream, the cancer cells prefer to be autonomous of the body and convert glucose for the fatty acids they need to multiply out of control.

"This suggests an important link between cancer progression and fatty acid synthesis and has raised the idea that targeting fatty acid synthesis could be an effective way to block cancer growth," said Mischel, a Jonsson Cancer Center researcher. "Understanding the molecular links between oncogenes such as EGFR and the process by which simple sugars such as glucose are converted to fatty acids could lead to new treatments. It could also potentially be used to identify the subsets of patients most likely to benefit from treatment targeting fatty acid biosynthesis."

Although about half of glioblastomas involve amplified and mutated EGFR, which is clearly playing a role in the development and progression of the disease, clinical trials testing EGFR inhibitors have not been successful, with only about 10 to 15 percent of patients responding, Mischel said. The cancer, it appeared, finds a way to work around the inhibitor. Something more had to be going on. Previous studies have suggested that EGFR signaling needs to "team up" with other cellular processes for tumor development and progression.

As part of a Phase II clinical trial for EGFR inhibitor Tykerb, Mischel and his team at UCLA performed an analysis of brain tumor tissue before and after the drug was given to see what it did to cell signaling. They also decided to examine the tissue to determine whether EGFR was activating a master regulator in the cell called SREBP-1 that governs fatty acid synthesis. They also studied these processes in glioblastoma cell lines and in an animal model.

Mischel used genetic and pharmacologic approaches to identify the signaling pathways the EGFR uses to activate SREBP-1 and looked for targets for therapeutics. In addition, the team explored whether amplified or mutated EGFR signaling makes glioblastomas more dependent on fatty acid synthesis. If so, they asked, would inhibiting that synthesis, either by blocking activation of SREBP-1 or blocking a downstream fatty acid synthase enzyme, kill the EGFR-bearing tumors?

"We found that EGFR signaling does activate the master regulator SREBP-1 to increase the amount of fatty acids in the cells," Mischel said. "We also were able to uncover the molecular circuitry linking EGFR with increased fatty acid synthesis."

Most importantly, Mischel said, the team found that amplified EGFR signaling does make glioblastoma cells more dependent on fatty acid synthesis and interrupting that synthesis results in massive cell death in

EGFR-bearing tumors, but not in tumors with little EGFR signaling.

"This is exciting because it identified a previously undescribed EGFR-controlled metabolic pathway and suggests new treatment approaches for EGFR-activated glioblastomas and perhaps other cancers with amplified signaling," Mischel said. "We hope that interrupting fatty acid synthesis will kill tumor cells and spare the normal cells, decreasing treatment side effects."

There are drugs in development that block fatty acid synthesis, mostly targeted at weight loss, but they also disrupt other important enzymes and may cause toxicity in cancer patients. Mischel hopes this study will prompt drug companies to develop new therapies that target key points in the molecular circuitry linking EGFR with increased fatty acid synthesis.

"The current treatments we have now only modestly extend lives and are far from long-term disease suppression," Mischel said. "New strategies are absolutely essential. A drug that prevents tumors from making their own fatty acids could potentially provide a more effective way to treat the 50 percent of patients with EGFR-bearing glioblastoma."

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