

Nutrients Turn on Key Tumor Signaling Molecule, Fueling Resistance to Cancer Therapy

Research provides new insights into glioblastoma's ability to overcome chemotherapy

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Tumors can leverage glucose and other nutrients to resist targeted therapies directed at specific cellular molecules, according to researchers at University of California, San Diego School of Medicine and Ludwig Cancer Research. In the study, published this week in *Proceedings of the National Academy of Sciences*, the team used human tissue and mouse models to demonstrate that nutrients can strongly affect the signaling molecules that drive tumors in glioblastoma, a deadly brain cancer.



Paul Mischel, MD, professor of pathology at UC San Diego School of Medicine and Ludwig San Diego member.

"This study shows that metabolic and nutritional factors might be quite important in cancer development and treatment," said co-senior author Paul Mischel, MD, professor of pathology at UC San Diego School of Medicine and Ludwig San Diego member. Mischel led

the study with Webster Cavenee, PhD, Distinguished Professor of Medicine at UC San Diego School of Medicine and Ludwig San Diego member.

The study also highlights one way tumors can evade targeted drugs such as erlotinib and gefitinib. These drugs work by inhibiting a mutant form of EGFR (epidermal growth factor receptor), a molecule that drives the growth of many glioblastomas and other tumor types.

Cancer researchers have known for years that tumors have unusual metabolisms — their rapid use of glucose is used as a diagnostic tool for tumors in PET scans. But only recently have scientists begun to flesh out the details of this metabolic shift. Mischel and other researchers have previously shown that this shift can occur through the activation of a central cellular signal, mTORC2. mTORC2 is involved in switching cancer cells to a hyperactive metabolic state, for instance prompting the increased influx of glucose and another nutrient, acetate, into cancer cells. Glucose and acetate provide fuel and cellular building blocks to perpetuate the rapid growth of tumors.

In the new study, Mischel and colleagues found that glucose and acetate in turn regulate mTORC2, propelling tumor growth and fending off targeted drugs.

"This is a two-way street," Mischel said. "Signaling molecules like mTORC2 can change metabolism, and metabolites can change mTORC2."

The findings first emerged from experiments in glioblastoma cells cultivated in the lab. In one experiment, the researchers treated the cells with either glucose or acetate and found that at least one of these nutrients was required in order to turn on mTORC2 in response. The researchers also tested glioblastoma cells with a mutant form of EGFR that turns on mTORC2 and propels tumor growth. In the absence of glucose and acetate, EGFR inhibitors can switch off mTORC2 signaling. But when the researchers added glucose and acetate, the drugs did not work — mTORC2 stayed on and the cells thrived. The researchers delved further, showing how acetate and glucose activate mTORC2 through a molecule formed from these metabolites, acetyl-coA, which is critical for activating a key component of mTORC2.

Together, the experiments show that glucose or acetate can activate mTORC2 through the production of acetyl-coA, enabling tumors to resist targeted therapies such as EGFR inhibitors. Activated mTORC2 in turn propels tumor growth by regulating metabolism and other cellular processes. The researchers provide evidence that a similar mechanism operates in cells taken directly from glioblastoma patients and in human glioblastoma cells implanted into mice.

The findings provide a window into the treatment of glioblastoma, which leaves most newly diagnosed patients with less than two years to live. To reduce deadly brain swelling, many glioblastoma patients require treatment with steroids, which are known to raise blood glucose levels. The new study suggests that the drugs, which may be necessary to control brain swelling, could also have the paradoxical effect of propelling tumor growth through activation of mTORC2. Findings in the study also suggest that developing drugs to effectively target mTORC2 may be one avenue to shutting down glioblastoma and possibly other types of tumors.

"We think this may be a general mechanism in cancer," said Mischel, who plans to investigate the role of glucose and acetate in other types of tumors.

While Mischel and his team are also beginning to think about how to modify the diets of mouse models to affect the production of these and other metabolites, he notes that this latest study does not point to the value of any particular diet for counteracting cancer.

"How do you turn these findings into something you do for patients? It is going to take diligent and careful work to determine how lifestyle changes, including diet, can alter tumor cell metabolism," he said. "We are actively studying this process and hope that this information can be used to develop more effective prevention and treatment strategies for cancer patients."

From a broader perspective, Mischel is also intrigued by long-standing arguments among scientists about how much of cancer can be ascribed to environment and how much is random and uncontrollable. The new study suggests that there may be more interplay between genes involved in cancer and the environment than previously thought.

Co-authors of this study also include Kenta Masui, Ludwig Cancer Research and Tokyo Metropolitan Institute of Medical Science; Kazuhiro Tanaka, Kobe University; Shiro Ikegami, Genaro R. Villa, and Huijun Yang, Ludwig Cancer Research; William H. Yong, and Timothy F. Cloughesy, David Geffen UCLA School of Medicine; Kanato Yamagata, and Nobutaka Arai, Tokyo Metropolitan Institute of Medical Science.

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