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Compound that blocks sugar pathway slows cancer cell growth

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Scientists at Johns Hopkins have identified a compound that could be used to starve cancers of their sugar-based building blocks. The compound, called a glutaminase inhibitor, has been tested on laboratory-cultured, sugar-hungry brain cancer cells and, the scientists say, may have the potential to be used for many types of primary brain tumors.

The Johns Hopkins scientists, are inventors on patent applications related to the discovery, caution that glutaminase inhibitors have not been tested in animals or humans, but their findings may spark new interest in the glutaminase pathway as a target for new therapies.

Glutaminase is an enzyme that controls how glucose-based nutrients are converted into the carbon skeleton of a cell. Additional enzymes that help construct the so-called "bricks" of the carbon skeleton are controlled by a gene called IDH1. In some brain cancer cells, IDH1 is mutated and the resulting enzyme grinds up the bricks into nutrients that feed cancer cells.

"Cancer cells with mutated IDH1 become addicted to the glutaminase pathway, and this pathway may represent an Achilles' heel of cancer cells," says Chi Dang, M.D., Ph.D., The Johns Hopkins Family Professor in Oncology Research and Vice Dean for Research at the Johns Hopkins University School of Medicine. "To combat cancer, we might block the flow of materials that help create the bricks, starting with glutaminase."

To establish proof of the principle, the Johns Hopkins scientists and a

team of chemists and geneticists at Princeton University used a glutaminase-blocking agent on cells engineered to have IDH1 mutations. The compound, called BPTES, reduced growth of the cancer cells by 30 percent. Their findings were published online November 2 in *Cancer Research*.

"The glutaminase inhibitor we tested does not completely stop cancer cell growth, but slows it down," says Gregory Riggins, M.D., Ph.D., the Irving J. Sherman, M.D. Professor of Neurosurgery Research and Ludwig Collaborative Laboratory Director at Johns Hopkins.

Riggins identified BPTES' anticancer potential after screening many compounds for their glutaminase-blocking activity. BPTES was developed at Hopkins' Brain Science Institute as a potential treatment for neurological disorders and injuries that damage brain cells.

Although BPTES itself may not be useful as a therapy because of solubility problems, says Riggins, scientists at Johns Hopkins' Brain Science Institute are creating new versions of it that may overcome the problem.

"We can envision a day when patients who have IDH1 mutations are given a glutaminase inhibitor in addition to therapies that target other genomic aspects specific to their cancer," says Dang.

The mutation in IDH1, which stands for isocitrate dehydrogenase 1, was first spotted in 2008 in results from a genomewide scan of brain cancers led by Johns Hopkins scientists. It is now linked to more than 70 percent of three common types of gliomas: low-grade astrocytomas, oligodendrogliomas, and secondary glioblastomas. Researchers also have found mutations in acute myelogenous leukemias.

The mutation occurs within a single spot along a string of thousands of

genetic coding letters. Among previous findings led by Johns Hopkins, patients with IDH1 mutations appear to survive at least twice as long as those without them. The researchers estimate that some 6,000 adults and children with brain cancer per year in the United States could have IDH1 mutations.

Dang and Riggins plan to test glutaminase inhibitors in cell cultures of other cancers and eventually combine the inhibitors with other gene "targeted" therapies in animal and human tests.

Both investigators also are co-inventors on a patent application on using glutaminase inhibitors for cancers with IDH1 mutations. Dang and researcher Joshua D. Rabinowitz from Princeton University are consultants for Agios Pharmaceuticals Inc. The terms of these arrangements are being managed by Johns Hopkins University in accordance with its conflict of interest policies.

Provided by Johns Hopkins Medical Institutions

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