

Experimental drugs that change energy supply in cells could slow brain tumor growth

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Experimental drugs that alter cell metabolism also halted tumor growth and extended survival in mice with cancers linked to changes in the same gene, according to a new study led by researchers at NYU Langone Medical Center, its Laura and Isaac Perlmutter Cancer Center and Massachusetts General Hospital.

The study results, publishing in the Dec. 14 edition of the journal *Cancer Cell*, focus on brain tumors linked by previous research to changes in the code making up the gene for the enzyme isocitrate dehydrogenase 1, or IDH1. Such changes or mutations occur in a third of gliomas in the brain, as well as in some blood, skin, soft tissue, and cartilage cancers.

The research team found evidence that [cells](#) in tumors with IDH1 mutations have lower levels of a critical metabolic chemical, nicotinamide adenine dinucleotide (NAD). Cells require this chemical to help turn sugars and other nutrients into energy and to repair DNA.

For the study, the research team examined human cancer cells carrying IDH1 mutations. Cells from these tumors were studied in the laboratory and also implanted into mice. By surveying a large number of metabolic components, they noticed that NAD levels were abnormally low in IDH1 mutant tumors. They then tested the theory that such cells would not survive if NAD levels dropped further.

Indeed, the research team found that an IDH1 mutant soft tissue tumor, or fibrosarcoma, was halted by administration of drugs called NAMPT

inhibitors, which are known to lower NAD. The study drugs also helped mice with IDH1 glioma brain cancers to live longer. Furthermore, no significant side effects were seen in mice treated with these inhibitors.

Using cells from patients with IDH1 brain tumors, the researchers found that treatment with NAMPT inhibitors decreased NAD levels and caused these cells to run out of energy and die. By contrast, cancer cells without IDH1 mutations had higher, more normal, NAD levels and were not harmed by the drugs.

"Our study marks the first evidence tying IDH1 cancers, which involve a mutation that affects metabolism, with lower levels of a key cell metabolite NAD," says study co-senior investigator Andrew Chi, MD, PhD. "Our findings raise the possibility that NAMPT inhibitors, might be effective against such tumors, which are impervious to current anti-cancer drugs," says Chi, an assistant professor at NYU Langone. He also serves as chief of neuro-oncology for its Laura and Isaac Perlmutter Cancer Center and co-director of the NYU Langone Brain Tumor Center.

Chi says the work is urgent because no curative treatment exists for IDH1 mutant gliomas, a specific type of brain tumor which often strike people in their 20s and 30s. "Nearly all patients die from their [brain cancer](#)," says Chi, noting that half of all Americans diagnosed each year with IDH1 gliomas live for less than eight years. "Our findings provide yet another example of the need to personalize cancer therapy, as based on our results, we would only expect NAMPT inhibitors to be effective against IDH1-mutated cancers," he says.

Chi says that his team will next seek to determine why NAD levels drop specifically in IDH1-mutant cancers. He and his colleagues have a patent pending on their use of NAMPT inhibitors to treat IDH1 cancer. In the future, should further animal and human tissue testing prove successful,

the team hopes to launch clinical trials in select [cancer](#) patients with IDH1 mutations within three years.

Provided by New York University School of Medicine

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