

Potential therapy found for incurable pediatric brain cancer

17 November 2014

Northwestern Medicine scientists have discovered a new potential drug therapy for a rare, incurable pediatric brain tumor by targeting a genetic mutation found in children with the cancer.

By inhibiting the tumor-forming consequences of the mutation using an experimental drug called GSKJ4, they delayed tumor growth and prolonged survival in mice with pediatric brainstem glioma.

Also known as diffuse intrinsic pontine glioma (DIPG), the disease occurs when tumors form in the brainstem, which controls essential body functions such as breathing, heartbeat and motor and sensory pathways. The tumors are inoperable because of their vital location, and radiation and chemotherapy are largely ineffective. Most patients do not survive more than a year after diagnosis.

"No significant advances in the survival of DIPG patients have been made over the last few decades, and new therapeutic approaches are desperately needed," said first author of the study Rintaro Hashizume, MD, assistant professor in neurological surgery at Northwestern University Feinberg School of Medicine.

Working with senior author C. David James, professor in neurological surgery, Hashizume focused on a mutation in the H3F3A gene that was recently discovered in the majority of patients with DIPG. The mutation encodes a type of protein called a histone that helps package DNA inside cells. The unexpected finding suggested the mutation had a role in DIPG development.

James and Hashizume also are members of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The mutation leads to reduced histone methylation, a process that influences gene expression. Hashizume hypothesized that pharmacologically restoring histone methylation

could prevent tumor formation. He suggested that GSKJ4, a small molecule inhibitor previously reported to increase methylation for immune disorder treatment, could also work for DIPG.

In the study, published in *Nature Medicine*, mice who received GSKJ4 treatment for 10 days survived significantly longer than those in a control group that did not receive GSKJ4.

"We are so excited by these findings, which for the first time provide evidence for pharmacologic treatment connected to a histone mutation," Hashizume said. "Furthermore, we've identified a compound that may be useful for treating DIPG patients with this mutation."

Now that the investigators know the inhibitor works against DIPG, they plan to conduct future research to see how long its effects can last with longer treatments. They also want to test the drug in combination with radiation in animal models. The ultimate goal is a clinical trial with human patients. Fast scientific developments made this work possible

Little progress toward understanding DIPG has been made in the past for several reasons: First, there are only about 200 cases of the disease in the United States each year. In addition, it was not possible until recently to collect DIPG tissue from living patients because of the tumor's location in the brain.

"For these reasons, there have been very few DIPG resources available to do any sort of investigation," James said.

A few years ago, Nalin Gupta, MD, PhD, a surgeon from the University of California, San Francisco, and a collaborator on this study, developed a procedure to safely biopsy [patients](#) with DIPG, accessing tumor tissue samples of the disease unmarred by radiation and drug therapy.

Hashizume modified two of these samples to establish sustainable cell lines, enabling scientists to examine the disease in this study and others.

"We're hopeful about what these findings might do for children with this disease," James said.

More information: *Nature Medicine*,
[dx.doi.org/10.1038/nm.3716](https://doi.org/10.1038/nm.3716)

Provided by Northwestern University

APA citation: Potential therapy found for incurable pediatric brain cancer (2014, November 17) retrieved 27 April 2021 from <https://medicalxpress.com/news/2014-11-potential-therapy-incurable-pediatric-brain.html>

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