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New target found to attack an incurable brain tumor in children

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A study published in *Molecular Cancer Research* reveals that a tumor suppressor gene p16 is turned off by a histone mutation (H3.3K27M), which is found in up to 70 percent of childhood brain tumors called diffuse intrinsic pontine glioma (DIPG). This insight suggests that restoring p16 is a promising therapeutic strategy. The authors have demonstrated that this can be accomplished in vitro using a drug that is approved for treatment of adult leukemia and other cancers.

Histone is a protein that acts like a spool for DNA, helping to package the six-foot long DNA strand into the tiny nucleus of every cell. Histones also help regulate which genes turn on and off, a process that goes awry when there is a histone mutation.

"Using a genetic mouse model of DIPG, we found that the histone mutation turns off p16, which is a gene that acts like a break on dividing cells," says senior author Oren J. Becher, MD, from Stanley Manne Children's Research Institute at Ann & Robert H. Lurie Children's Hospital of Chicago. "When p16 is repressed, cells can divide faster, which gives rise to a tumor. We also found that in DIPG, the histone mutation cooperates with overactive growth factor (called PDGF) signaling, which further accelerates brain stem tumor formation."

DIPG is the most deadly brain tumor in children and currently there are no approved drugs for treating it. The last advance in treatment was in the 1960s with the introduction of radiation therapy, which temporarily decreases symptoms but does not cure DIPG. The discovery of the

histone mutation in 2012 has opened up a new line of research and a search for new treatment targets.

Becher and colleagues discovered that in vitro the p16 gene can be turned back on using a drug that inhibits DNA methylation - a mechanism that typically acts as an off switch for the gene. The result was restored p16 function, which slowed down tumor growth.

"This was an unexpected finding," says Becher, the Rory David Deutsch Scholar and oncologist at Lurie Children's, as well as Associate Professor of Pediatrics at Northwestern University Feinberg School of Medicine. "We first tried a histone methylation inhibitor—a promising new class of cancer drugs—but that did not restore p16 or had any effect on tumor growth. But when we used a DNA methylation inhibitor, it worked. We now have early evidence that targeting DNA methylation may be useful in restoring p16, and thereby arresting tumor growth. We need more research to confirm this finding in animal models before studying this strategy in children with DIPG. This is incremental progress."

Provided by Ann & Robert H. Lurie Children's Hospital of Chicago

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