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Insight offers new angle of attack on variety of brain tumors

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A newly published insight into the biology of many kinds of less-aggressive but still lethal brain tumors, or gliomas, opens up a wide array of possibilities for new therapies, according to scientists at Brown University and the University of California, San Francisco (UCSF). In paper published online Dec. 15 in the *Journal of the National Cancer Institute*, they describe how a genetic mutation leads to an abnormal metabolic process in the tumors that could be targeted by drug makers.

"What this tells you is that there are some forms of tumors with a fundamentally altered process," said Karl Kelsey, a professor of pathology and laboratory medicine and community health in the Warren Alpert Medical School of Brown and one of the paper's senior authors. "This is a really new way to look at potentially modifiable factors in brain tumors."

Scientists have known for a couple of years that a mutation in a gene called IDH is associated with glioma. They've also observed that people with gliomas carrying the mutation survive longer than those afflicted with tumors lacking the mutation. What the Brown and UCSF team show in the new paper is that the mutation is associated with a consistent pattern of an alteration known as "methylation" of the DNA which is associated with changes in gene expression. The pattern of methylation in tumors with the IDH mutation often occurred in metabolic genes, regardless of the tumor's specific type.

Margaret Wrensch, a professor of neurological surgery, epidemiology

and biostatistics at UCSF's Helen Diller Family Comprehensive Cancer Center, said what the team found surprising is that DNA from almost all tumors with IDH mutations had the same distinctive methylation pattern. The degree of methylation throughout the genome was unusually high, and the same specific DNA was methylated.

"This one mutation is common to a whole subset of brain tumors," she said. "It's quite unique. It seems to dominate other mutations in the tumor and the epigenetic changes are very uniform."

The researchers hope now that if a drug could inhibit this methylation process in any number of these affected genes, not necessarily just IDH, that might correct the errant metabolism of the tumors and control their growth.

"We know now that there are all these genes related to metabolism that have altered methylation," said Brock Christensen, a Brown postdoctoral scholar in pathology and laboratory medicine and a lead author of the paper, which also involved researchers from the University of Minnesota and Dartmouth Medical School. "In this suite of genes there might be a much easier target to try to design a therapy for."

The heart of the study was a tumor-by-tumor analysis of the methlylation, led by Christensen and Brown graduate student Ashley Smith, in scores of samples from the Brain Tumor Research Center at UCSF. Their analysis revealed an unusually iron clad correlation between the IDH mutation and methylation in metabolic genes in gliomas of many different names and classifications.

"The strength of the correlation was absolutely stunning," Christensen said. "It's not the kind of thing you see very often in cancer epidemiology, to have almost all of these mutant tumors having the same methylation profile."

The IDH gene has a role in glucose sensing, so the association of the mutation with altered metabolism genes (occurring through enhanced DNA methylation) is reasonable, Christensen said. The researchers are now looking into the role that mutation in IDH plays in perhaps altering other metabolism genes in the cells.

The research leaves many questions about brain tumors unanswered. Among them is what causes the IDH mutation, what causes the mutation to affect other genes in the cell, and most importantly, what is the best way take therapeutic advantage of these new observations.

But Kelsey said the fight against brain cancer has long had a dearth of hope, so he's encouraged to see some emerge.

"Gliomas are such a deadly disease, and so little is known about them, that people are pretty excited about this because it is a whole new way in," he said. "We have a new clue about what to study."

Provided by Brown University