2HG on the brain (tumor)

By Michael J. Haas, Senior Writer

A **Harvard Medical School** team has shown that a specialized MRI technique can noninvasively diagnose patients with isocitrate dehydrogenase 1–mutant gliomas by detecting a key metabolite produced by the tumors.[1] Although few imaging centers have the resources needed to adopt the method for routine diagnostic applications, **Agios Pharmaceuticals Inc.** plans to use it to study the biology of the isocitrate dehydrogenase 1–mutant gliomas and monitor the response to glioma therapies the company has in preclinical development.

In normal tissues, isocitrate dehydrogenase 1 (IDH1) plays a role in glucose metabolism by catalyzing the conversion of isocitrate to α-ketoglutarate. IDH1 and a related enzyme, IDH2, are mutated in about 70% of brain cancers and 25% of adult leukemias.[2] The mutated enzymes also occur in a smaller percentage of other solid tumors. The current method of diagnosing IDH1-mutant glioma requires a biopsy.

In 2009, Agios showed that expression of the mutant IDH1 enzyme resulted in higher levels of the metabolite *R*(–)-2-hydroxyglutarate (2HG) than wild-type IDH1 expression in tumors and normal brain tissue.[3] The study did not elucidate the metabolite's role in tumor growth and progression but did suggest 2HG could be a marker for IDH1-mutant gliomas.[4]

In the new study, the team postulated that magnetic resonance spectroscopy (MRS) could detect 2HG in the brain to diagnose IDH1-mutant gliomas noninvasively. The problem was that standard 1D MRS techniques generated signals from other abundant brain metabolites—primarily glutamate and glutamine—that overlapped with signals from 2HG. Thus, it was difficult to detect and quantify 2HG *in vivo*.

To overcome the problem, the team turned to a 2D MRS technique that is more complex and time-consuming than standard 1D MRS. Indeed, the 2D technique produced 2HG signals that were readily distinguished from those of other metabolites.

2D MRS exposes a sample to two series of frequencies and then displays the results for each on a different axis to form a 2D plot. By examining how and where the two sets of results overlap, the spectroscopist can assign each signal to a particular proton—and thus the molecule to which it belongs—with greater confidence than when using 1D MRS.

The team used the 2D MRS technique on patient biopsies from gliomas expressing mutant or wild-type IDH1 to refine the method for the quantification of 2HG. Finally, the team used the method on six patients with glioma and four healthy controls and correctly diagnosed each as having a mutant IDH1 glioma, wild-type IDH1 glioma or no glioma.

The group included researchers from **Massachusetts General Hospital**, **Dana-Farber Cancer Institute**, **Massachusetts Institute of Technology** and Agios. Data were reported in *Science Translational Medicine*.[1]

"The key advantage of the team's method is that it is noninvasive," Agios CSO Scott Biller told *SciBX*. "2HG has not been detected in the blood plasma of patients with IDH1-mutant gliomas, and the question of whether it appears in urine or cerebrospinal fluid has not been thoroughly explored. Currently, there is no other noninvasive way to use 2HG as a marker to diagnose those gliomas."

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>
> ***—Patrick Wen, Dana-Farber Cancer Institute***

Noninvasive diagnosis could be useful when a standard biopsy is not feasible, he said. Additionally, Biller said the method "could be used over time to follow the effects of drug treatment on IDH1-mutant gliomas when surgery isn't possible or to watch for tumor recurrence" after surgery.

Patrick Wen added that the method might obviate the need for an invasive biopsy in cases in which "the patient presents with a lesion in the brain that is not necessarily a glioma but could be brain inflammation or scarring that results from another cause." If the lesion is relatively small or the physician suspects that it is not a tumor, a negative result from the team's method could help confirm a noncancer diagnosis, he said.

Wen is director of neuro-oncology at Dana-Farber and professor of neurology at Harvard Medical School. He was not involved in the study.

New dimensions in imaging

Wen cautioned that the method is unlikely to find routine clinical use in the near term, given the complexity of the 2D MRS technique and the need to validate the findings in a larger patient population.

Because MRS diagnostics are usually not reimbursed by healthcare payers, "most imaging facilities do not have the equipment, expertise and time necessary to conduct the lengthy experiments" described in the study, said Wen.

"If future studies validate the method and 2HG as a marker, then people might pay more attention to 2D MRS and put more resources into it," added Wen. Until then, he said, clinical use of the method would probably be confined to large, specialized imaging centers.

In the meantime, Wen said the method could be used to test whether therapies targeting IDH1-mutant tumors decrease 2HG levels in animal models. "This could provide preclinical proof of

concept that the method could monitor tumor response in patients," he said.

Indeed, Agios plans to incorporate the method into the preclinical development of therapies to treat IDH1-mutant gliomas. Agios has compounds targeting IDH1 and IDH2 in preclinical development to treat brain cancer, acute myelogenous leukemia (AML) and other cancers in which mutant IDH1 or IDH2 occurs.

"We have already made great progress in understanding the connection between mutant IDH1, 2HG and gliomal tumors," said Biller. "As we learn more about the role of 2HG in gliomal biology, we will apply the method to our studies in animal models."

He added that Agios plans to validate 2D MRS detection of 2HG as a marker of response to treatment in IDH1-mutant glioma in animal models—particularly in cases where there may be residual disease. The company also is running studies to determine whether 2HG appears in urine, cerebrospinal fluid and/or tissues besides the brain in patients with IDH1-mutant gliomas.

The authors have applied for a patent covering the method described in the *Science Translational Medicine* study.

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