Cancer metabolism discovery uncovers new role of IDH1 gene mutation in brain cancer

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Agios Pharmaceuticals today announced that its scientists have established, for the first time, that the mutated IDH1 gene has a novel enzyme activity consistent with a cancer-causing gene, or oncogene. This breakthrough discovery shows that the mutated form of IDH1 produces a metabolite, 2-hydroxyglutarate (2HG), which may contribute to the formation and malignant progression of gliomas, the most common type of brain cancers. This discovery appears to reverse the previously held belief that IDH1 was non functional for cancer-causing activity. It is also one of the first reported instances where a metabolic enzyme such as IDH1 is shown to play a role in cancer formation, in this case through altered metabolic activity.

This finding creates opportunities for therapeutic intervention in brain cancer and other cancers where IDH1 mutations are present using new drugs that can target the IDH1 metabolic pathway.. The Agios research also identified an exciting new biomarker, 2HG, that could be used to develop an important diagnostic. The research was published on November 22 by the journal *Nature*, in a paper entitled "Cancer-associated IDH1 mutations produce 2-hydroxyglutarate (2HG)".

"This groundbreaking work is profound for the field," said Professor Lew Cantley, Ph.D., Director of the Cancer Center at the Beth Israel Deaconess Medical Center, a founder of Agios and a supporting author. "The team at Agios has demonstrated that what was previously considered an inactive enzyme is in reality an active oncogene and a potential therapeutic target. This has fundamentally changed our

understanding of the field. Additionally, there is an easily measured metabolic biomarker, 2HG, that will help in the diagnosis and treatment of any related therapeutics that arise from this work."

Agios scientists uncovered the function of the IDH1 mutation by employing novel techniques in a new area of cancer biology called cancer metabolism, which focuses on studying profound changes in metabolic activity in cancer cells. Through a mix of large-scale profiling of hundreds of cellular metabolites, x-ray crystallography, and innovative enzymology, the Agios team demonstrated that a single amino-acid substitution in the IDH1 active site allows the enzyme to acquire an entirely new activity to produce the metabolite 2HG. Analysis of tumor samples of brain cancer patients with the IDH1 mutation revealed up to hundred-fold elevations in concentrations of 2HG, a metabolite that has been previously linked to the formation of brain cancer.

"Agios' founding principles included the belief that targeting important metabolic pathways of cancers could make a fundamental difference in the treatment of the disease. Our IDH1 discovery is a great example of the power of the team and of our approach in targeting cancer metabolic pathways. In just four months, scientists at Agios unraveled very complex biology to advance a new understanding of gliomas and the role of IDH1 and corresponding biomarkers," said David Schenkein, M.D., Chief Executive Officer, Agios. "We are able to do this by utilizing a unique approach of integrating deep biology and leveraging our proprietary platform for cancer metabolism research.

"We are looking forward to developing potential therapeutics specifically targeting IDH1 for patients with these devastating diseases, and to leveraging our unique cross functional approach to cancer metabolism research in order to discover insights into other targets and pathways," added Schenkein.

Recent research has linked mutations in the metabolic enzyme IDH1 to glioma and other cancers.[2] Approximately 70 percent of gliomas are known to have the IDH1 mutation. Recently, the IDH1 mutation was also shown to be present in a significant percentage of patients with Acute Myeloid Leukemia, another devastating disease.

The insight from this new research at Agios is the first to reveal the function of the mutated IDH1 gene and provides critical insight into the mechanism by which this mutation leads to the development of brain cancer. Reports to date about the role of IDH1 have suggested that the gene functions as a tumor suppressor that, when mutationally inactivated, may contribute to brain tumor growth. The most recent research from Agios scientists published in Nature [1] suggests that it is activation of a metabolic pathway - rather than inactivation of a tumor suppression function - that is the likely process for oncogene function of IDH1.

A glioma is a type of cancer that starts in the brain or spine. It is called a glioma because it arises from glial cells. The most common site of gliomas is the brain, but gliomas can also affect the spinal cord or any other part of the CNS, such as the optic nerves. High grade gliomas currently cannot be cured and the prognosis for patients is generally poor; of the 20,000 Americans affected each year, more than half die within eighteen months of diagnosis. Gliomas are the most common type of brain cancer and approximately 70 percent of lower grade gliomas are known to have the IDH1 gene mutation.

Cancer metabolism is a new and exciting field of biology that provides a novel approach to treating cancer. Cancer cell metabolism is marked by profound changes in nutrient requirements and usage to ensure cell proliferation and survival. Research in the field has demonstrated that cancer cells become addicted to certain fuel sources and metabolic pathways. In cancer, this metabolic reprogramming is coordinated with

proliferative signaling and regulated by the same oncogenes and tumor suppressor genes to ensure efficient proliferation. Glycolysis (sugar metabolism), fatty acid metabolism and autophagy (self metabolism) are three pathways shown to play a critical role in cancer metabolism. Identifying and disrupting certain enzymes in these, and perhaps other, metabolic pathways provides a powerful intervention point for discovery and development of cancer therapeutics.

Source: Agios Pharmaceuticals