Cancer and metabolism have been linked since the 1920s, when German biochemist Otto Warburg, M.D., Ph.D., observed that tumor cells rapidly take up glucose and convert most of it to lactate, even in the presence of oxygen—the “Warburg effect.” But until very recently, there were no solid links between mutations in metabolic genes and common cancers, casting doubt on metabolism’s central role in the disease.

Then in 2008 researchers at Johns Hopkins and Duke universities, while sequencing 22 human glioblastomas, found that five of these tumors harbored mutations in the isocitrate dehydrogenase 1 (IDH1) gene. This was a major surprise, because IDH1, a metabolic enzyme, had never before been implicated in cancer. More than 70% of low- and medium-grade gliomas, and about 12% of glioblastomas, turned out to carry mutations in IDH1 or IDH2. (Researchers later found IDH1 and IDH2 mutations in 15%–20% of adult acute leukemias.)

The genetic connection has given a major boost to the field of cancer metabolism. Compared with normal cells, which primarily generate energy aerobically in mitochondria, most tumor cells rely more heavily on glycolysis (the anaerobic conversion of glucose to lactate) to generate energy. Tumors also display other unique metabolic features. But the discovery of a mutated metabolic enzyme was strong evidence that metabolic abnormalities play an important role in oncogenesis, and it set off a frantic effort to understand what the mutation was doing in such common and lethal cancers. Answers have proven just as surprising as the initial discovery.

Oncometabolite? IDH1 Discoveries Raise Possibility of New Metabolism Targets in Brain Cancers and Leukemia

By Ken Garber

Oncometabolite? IDH mutations in brain cancer and leukemia give rise to the metabolite 1-hydroxyglutarate (2-HG). 2-HG may block a variety of enzymes, thus promoting tumor growth.

Tumor Suppressor or Oncogene?

An explanation for the role of mutant IDH1 in cancer first appeared last year in the journal Science, where researchers from the University of North Carolina (UNC) at Chapel Hill reported that the mutation caused a loss of function of IDH1. They concluded that it was a tumor suppressor gene. Normally, the IDH enzymes catalyze the conversion of isocitrate to α-ketoglutarate (α-KG), both metabolites ultimately derived from glucose in the course of generating energy for the cell. α-KG is also required for the activity of about 60 enzymes known as dioxygenases.

The UNC group inserted mutant IDH1 into cells and saw α-KG go down and levels of hypoxia-inducible factor (HIF) go up. HIF, a master regulator of cell response to hypoxia, is normally held in check by one of the α-KG–dependent
dioxigenases, so it made sense that IDH1 mutations, by reducing levels of α-KG, would lead to HIF upregulation, often seen in tumors. It was a neat and coherent explanation, and cancer researchers assumed that IDH1 was a tumor suppressor gene. End of story.

But other researchers were just getting started. Noting that the IDH1 mutations were monoallelic and confined to a single residue in the enzyme’s active site—unusual features for tumor suppressor genes, where mutations are typically dispersed and affect both alleles—researchers from Agios Pharmaceuticals, a startup biotech company in Cambridge, Mass., investigated further. “When we looked at these [Science] papers, and we looked at the genetics of the IDH mutations, the two did not fit together,” said Agios CEO David Schenkein, M.D.

So they inserted mutant IDH1 into cells and profiled them, looking for abnormalities. They found high levels of a single metabolite, 2-hydroxyglutarate (2HG). 2HG was a known biomolecule normally found at trace levels, but its role was obscure. Agios researchers determined that mutant IDH1, instead of performing its normal function (generating α-KG), acted on existing α-KG, catalyzing its transformation to 2HG. Indeed, they found high levels of 2HG in IDH1-mutant tumors. At a cancer conference last November they announced that IDH1 was an oncogene, not a tumor suppressor. Schenkein called 2HG an “oncometabolite”—a small-molecule breakdown product that promotes tumors. (Traditional oncoproteins are protein macromolecules.) “All the signs would point to [2HG as] a very important factor in initiating and/or driving these tumors,” Schenkein said. Nature published the Agios 2HG results in December.

But the case for mutant IDH1 as onco gene and 2HG as oncometabolite is not yet sealed. “It has to be formally shown,” said Gottlieb. “We really don’t know what [2HG] is doing.” (For a comprehensive review of normal and mutant IDH, including possible 2HG effects, see the article by Reitman and Yan in this issue of the Journal.)

Conflicting Data
Gottlieb and Yue Xiong, Ph.D., leader of the UNC group, accept the oncogene hypothesis. But Xiong argues that IDH1 is both an oncogene and a tumor suppressor gene. The mutant gene, in his model, causes a loss of enzyme function and lowers α-KG levels. At the same time, mutant IDH1 catalyzes the production of 2HG. Both effects converge downstream of α-KG to promote tumor growth. “We think, with some evidence now, that both the reduction of α-KG [levels] and the accumulation of 2HG contribute to tumorigenesis,” he said.

It’s not clear who is right, UNC or Agios. Their experimental data don’t agree: Xiong’s group observed a decrease in α-KG in cells with mutant IDH1, but Agios didn’t. “We do not see changes in the [α-KG] pool” in primary tumors and in transfected cells, said Valeria Fantin, Ph.D., associate director of the molecular oncology group at Agios. Until a third party repeats these experiments and determines who’s right, the question of whether IDH is a tumor suppressor gene will remain unresolved.

Because all agree that mutations in IDH1 impair its ability to produce α-KG, why would α-KG levels stay the same, as Agios found? “The molecular mechanism behind it is definitely something that we and others are trying to chase,” Fantin said. She speculated that α-KG generated by the remaining wild-type IDH1 replenishes the pool or that α-KG arrives from another source. (The amino acid glutamine, for example, can be converted to α-KG in a separate metabolic pathway.)

The disagreement matters because if UNC is right that IDH1 is a tumor suppressor gene as well as an oncogene, then efforts to target mutant IDH1 with a drug—Agios’ strategy—will fall short. Such a drug would not restore the depleted pool of α-KG. Xiong argues for combining an IDH1 inhibitor with a drug that restores α-KG levels, an approach that works for him in cell lines. Gottlieb’s group has developed a cell-permeable form of α-KG that shows antitumor activity in cell lines and mouse models.

The 2HG Mystery
The paramount question is, What is 2HG doing to promote tumors? Research under way may yield answers. “We’re actively working on it; it’s just not ready for prime time yet,” said Schenkein.

Xiong is more forthcoming. Besides reducing HIF levels, he said, 2HG also acts on the family of dioxigenases known as histone demethylases. “We now have evidence that the reduction of α-KG also reduces the activity of those enzymes,” he said. Histone demethylases, by removing methyl groups from histones (proteins around which DNA is coiled), regulate gene expression, among other processes. Thus, 2HG might be epigenetically reprogramming cells for malignant transformation or growth (see diagram).

2HG may be doing other things in tumors. Fantin points out that because cells secrete 2HG, it may be also acting on the tumor microenvironment. And 2HG was already known to affect mitochondria—organelles that generate much of the cell’s energy. 2HG in tumors, Fantin speculated, could be disabling mitochondria. “This could . . . potentially lead to the reprogramming of the cells and basically push the cells toward anaerobic glycolysis, so basically promote the so-called Warburg effect,” she said. Agios is exploring all these possible 2HG protumor mechanisms, including mitochondrial dysfunction.

Diagnostics and Drugs
Warburg claimed that mitochondrial dysfunction, by shifting tumor cells to relying on glycolysis for energy production, causes...
cancer. Some researchers continue to hold that view. If 2HG is disabling mitochondria and causing a shift to glycolysis, would that constitute genetic evidence for a causative role of the Warburg effect in tumors?

Not yet, said Fantin. 2HG “has the possibility of affecting so many events,” she said. “It’s very hard to dissect that component and be able to place it as a primary versus a cooperative event. So it could be really the sum of all things that are really driving the malignant transformation.”

Vindicating Warburg [who died in 1970] is, for now, secondary. For oncologists, the bigger implication of the 2HG story is the hope of identifying brain cancer and leukemia patients with driver mutations in IDH1 and IDH2 and treating them with a drug that targets their genetic abnormality. Such patient selection should be feasible, said Schenkein. “As we move closer to the clinic, we will be able to identify patients with a very appropriate biomarker, so that we can do patient stratification early on in clinical trials, based on either the [IDH] mutation or the production of [2HG],” he said.

Agios plans to develop drugs targeting mutant or wild-type IDH, said Schenkein. “We’ve been in full [drug] discovery mode” for quite a while, he said. In April, Celgene Corp. in Summit, N.J., announced an up-front payment of $130 million to Agios (plus future milestone payments) in exchange for the option to develop any drugs from the Agios cancer metabolism research platform. Meanwhile, several labs are competing with Agios to settle the question of 2HG function in cancer. In barely more than a year, an obscure metabolite has triggered a scientific explosion. “It’s a gold mine,” said Gottlieb. “It might be a short-lived gold mine, but [it’s] no wonder people are jumping into this area.”

Drs. Schenkein and Fantin are employees of Agios Pharmaceuticals. Dr. Gottlieb receives grant support from Cancer Research UK, which has allied with AstraZeneca to commercialize cancer metabolism drugs.

© Oxford University Press 2010. DOI: 10.1093/jnci/djq262