

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Metabolism, Gliomas, and *IDH1*

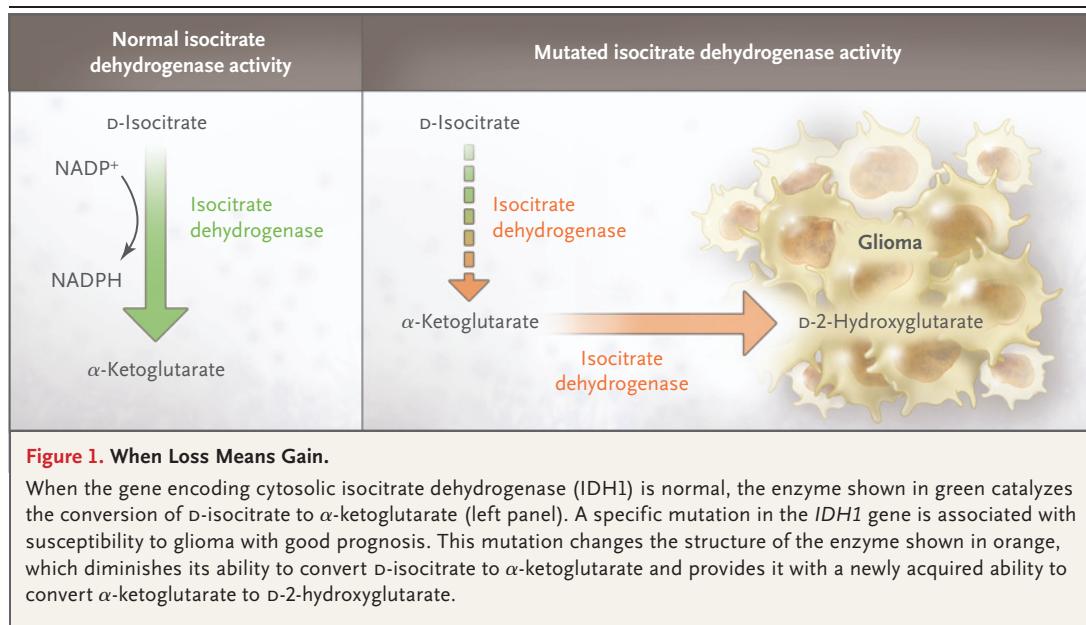
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Since the first description of a patient with an inborn error of metabolism was provided by Sir Archibald Edward Garrod more than 100 years ago, the study of rare disorders has received increasing attention. What started with the description of a single patient has evolved into a medical discipline — the study of metabolic disease — that pertains to common conditions, such as the process of aging, and common diseases, such as diabetes and cancer. On this note, Dang and coworkers¹ recently elucidated the effect of a mutant gene encoding cytosolic isocitrate dehydrogenase 1 (*IDH1*) on tumorigenesis, taking advantage of studies of persons with metabolic disease who excrete excessive amounts of 2-hydroxyglutaric acid in urine. The investigators found that a mutation observed in the *IDH1* gene, which occurs in the majority of grade II and grade III gliomas and secondary glioblastomas, effects both a gain of function and a loss of function.

The isocitrate dehydrogenases catalyze the oxidative decarboxylation of isocitrate to alpha-ketoglutarate, generating NADPH from NADP⁺. Sev-

eral isocitrate dehydrogenases exist, each with a different cellular localization. *IDH1*, the focus of the work of Dang and colleagues, is localized in the cytoplasm and the peroxisomes.

Their work showed that the mutant *IDH1* acquires the ability to convert alpha-ketoglutarate to 2-hydroxyglutarate (Fig. 1),¹ which is known to accumulate in the inborn errors of metabolism that occur in the disorder 2-hydroxyglutaric aciduria.^{2,3} The accumulating metabolite, 2-hydroxyglutarate, exists in the form of two enantiomers, L-2-hydroxyglutarate and D-2-hydroxyglutarate (each the mirror image of the other), both of which accumulate whenever the relevant converting enzyme is defective. Dang and colleagues reported several findings, showing that cells expressing mutant *IDH1* have elevated concentrations of 2-hydroxyglutarate, that the crystal structure of the mutant *IDH1* enzyme reveals a distinct and novel active site, that the mutant consequently converts α -ketoglutarate to 2-hydroxyglutarate and has diminished ability to convert isocitrate to α -ketoglutarate, that levels of 2-hydroxyglu-



tarate are elevated in samples of human glioma, and that the accumulating 2-hydroxyglutarate is the D-2 enantiomer.

The finding that cancer-associated *IDH1* mutations result in the accumulation of 2-hydroxyglutarate provides an explanation for the pathophysiology of these particular tumors. That said, these findings would seem to be at odds with findings on the different forms of inborn errors of metabolism in which 2-hydroxyglutarate is produced — L-2-hydroxyglutaric aciduria and D-2-hydroxyglutaric aciduria. Specifically, L-2-hydroxyglutaric aciduria is associated with brain tumors and D-2-hydroxyglutaric aciduria is not (Jakobs C: personal communication).^{4,5} Thus, the conclusion that D-2-hydroxyglutarate is the “causative” oncometabolite in gliomas and secondary glioblastomas warrants further investigation. Because *IDH1* mutations occur predominantly in younger patients and are associated with a better prognosis than is the case with tumors that do not carry the *IDH1* mutation, D-2-hydroxyglutarate may become a biomarker, serving diagnostic, prognostic, and therapeutic purposes. One wonders whether D-2-

hydroxyglutarate is also increased in patients with mutations in the *IDH2* gene, which encodes a mitochondrial isocitrate dehydrogenase.

The research by Dang and colleagues illustrates how the study of inborn errors of metabolism facilitates an understanding of the pathophysiology of more common disorders. Archibald Garrod would be impressed.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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1. Dang L, White DW, Gross S, et al. Cancer-associated *IDH1* mutations produce 2-hydroxyglutarate. *Nature* 2009;462:739-44.
2. Duran M, Kamerling P, Bakker HD, van Gennip AH, Wadman SK. L-2-hydroxyglutaric aciduria: an inborn error of metabolism? *J Inher Metab Dis* 1980;3:109-12.
3. Chalmers RA, Lawson AM, Watts RWE, et al. D-2-hydroxyglutaric aciduria: case report and biochemical studies. *J Inher Metab Dis* 1980;3:11-5.
4. Van Schaftingen E, Rzem R, Veiga-da-Cunha M. L-2-hydroxyglutaric aciduria, a disorder of metabolite repair. *J Inher Metab Dis* 2009;32:135-42.
5. Knaap MS, Jakobs C, Hoffmann GF, et al. D-2-hydroxyglutaric aciduria: further clinical delineation. *J Inher Metab Dis* 1999;22:404-13.

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CLINICAL TRIAL REGISTRATION

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