Published in final edited form as:

N Engl J Med. 2009 February 19; 360(8): 813–815. doi:10.1056/NEJMe0810213.

Metabolic Enzymes as Oncogenes or Tumor Suppressors

Craig B. Thompson, M.D

University of Pennsylvania School of Medicine, Philadelphia

Whether mutations in metabolic pathways contribute to the pathogenesis of cancer is controversial.^{1,2} Cancer cells have long been noted to preferentially metabolize glucose through glycolysis, a discovery that has been translated to the clinic through positron-emission-tomography imaging of ¹⁸F-deoxyglucose uptake in tumors. Moreover, recent studies have uncovered recurrent somatic mutations in four genes involved in the metabolism of mitochondrial citrate that either cause or predispose cells to become malignant.

In this issue of the *Journal*, Yan and colleagues³ report that 70% or more of low-grade gliomas bear mutations in one of two NADP⁺-dependent isocitrate dehydrogenase enzymes (IDH1 and IDH2). A similar result has been reported by Balss et al.⁴ These studies follow the discoveries that mutations in succinate dehydrogenase are linked to paraganglioma and that mutations in fumarate hydratase (fumarase) lead to leiomyoma and leiomyosarcoma.⁵ Recurrent mutations in the metabolic regulatory genes of these types of cancer constitute the best evidence to date that alterations in cellular metabolism contribute to the pathogenesis of human cancer.

Mutations in *IDH1* were found in 12% of glioblastomas as part of a genomewide mutational analysis of glioblastoma multiforme.⁶ The mutation was associated with a relatively good prognosis and was also found in secondary glioblastomas, which probably arise from the transformation of lower-grade gliomas. Moreover, in stage II or III astrocytomas or oligodendrogliomas, more than 70% of tumors had mutations in either *IDH1*, the gene for the form of NADP⁺-dependent isocitrate dehydrogenase associated with cytosol or peroxisomes, or *IDH2*, the mitochondria-associated form of the enzyme. On the basis of the analysis of the mutational status of other genes implicated in the pathogenesis of gliomas, these studies provide compelling evidence that *IDH1* mutations occur at an early stage in the development of gliomas.

These mutations of enzymes that are involved in the metabolism of citrate might share a mechanism that promotes tumorigenesis (Fig. 1). Mutations of fumarate hydratase and succinate dehydrogenase in certain cancers are recessive and lead to a reduction in or elimination of enzyme function,⁵ which increases the accumulation of fumarate and succinate, respectively. The excess of these metabolites inhibits the proline hydroxylases that suppress the expression of hypoxia-inducible factor 1 (HIF-1), a transcription factor implicated in tumor angiogenesis and tumor-cell glycolysis. This accounts for the highly vascular nature of the tumors associated with fumarase or succinate dehydrogenase deficiency.

Deficiencies in IDH1, IDH2, or both might also stabilize HIF-1. In addition to oxygen, the proline hydroxylases that suppress HIF-1 require α -ketoglutarate as a substrate. Recent genetic evidence from patients with deficiency in mitochondrial NAD⁺-dependent isocitrate dehydrogenase (IDH3) suggests that IDH1, IDH2, or both may be the primary enzyme that produces α -ketoglutarate in tissues other than the retina.⁷ Thus, inactivation of IDH could promote the accumulation of HIF-1 as a result of lower levels of cytosolic α -ketoglutarate.

Such a mechanism could explain why most glioma mutations are in *IDH1*, the cytosolic form of the enzyme. Nevertheless, this explanation may not account for the role of *IDH* mutations in gliomas. First, low-grade and intermediate-grade gliomas rarely have a notable vascular component. Second, the *IDH* mutations were always monoallelic (i.e., the second allele of the gene was unaffected). Finally, all the 391 somatic mutations reportedly involved the codon of a single amino acid in *IDH1* or the analogous codon in the *IDH2* gene.^{3,4} The frequency of somatic mutations affecting this single codon in the absence of any other mutation that would cause gene inactivation suggests that the mutations in *IDH1* and *IDH2* do not result in a simple loss of function. Furthermore, the affected residue in mutated *IDH1*, arginine 132, appears to contribute to the regulation of IDH1 activity.⁸ The activity of IDH1 is regulated by its transition between an open and closed configuration. In the active configuration, arginine 132 stabilizes the α -carboxyl of the substrate, isocitrate, and the product, α -ketoglutarate. Since α -ketoglutarate exerts end-product inhibition of IDH1, mutation of arginine 132 could interfere with the ability of α -ketoglutarate to regulate the enzymatic activity of IDH1. Thus, the mutant enzyme might have a gain of function under certain metabolic conditions.

This hypothesis may seem at odds with the conclusions of Yan et al., who provide evidence that *IDH1* and *IDH2* mutations do not enhance enzymatic activity when measured under optimal substrate availability in vitro. However, the data do not preclude an alteration in the regulation of enzymatic activity under physiologic conditions. Glial cells may have a higher-than-normal level of α -ketoglutarate because of their participation in glutamate–glutamine cycling with their neuronal neighbors. The avidity with which glial cells take up glutamate and the ability of intracellular aminotransferases to equilibrate glutamate with α -ketoglutarate suggest that glial cells have a high level of feedback inhibition of their IDH activity. Therefore, mutations that affect end-product inhibition might facilitate increased production of NADPH in glial cells.

IDH1 is one of three enzymes that contribute to cytosolic NADPH production in cells.¹ The production of NADPH has been linked to the suppression of apoptosis and to enhanced cell survival and growth.^{9–11} NADPH is required for the synthesis of glutathione, which protects cells from redox stress and promotes resistance to apoptosis.⁹ Moreover, cytosolic NADPH is the substrate for the membrane-associated NADPH oxidases, whose production of hydrogen peroxide inhibits protein tyrosine phosphatases, thereby promoting sustained activation of kinases that promote cell survival and mitogenic signaling.¹⁰ Recent evidence suggests that IDH1 and, to a lesser extent, IDH2 provide a significant fraction of cellular NADPH for these processes, all of which promote cell-autonomous survival and growth.¹¹

Despite the high preponderance of mutations of *IDH* genes in gliomas, Yan et al. did not find mutations in either gene in samples from 494 patients with tumors not involving the central nervous system. This suggests that mutations in *IDH1* play a unique role in the pathogenesis of gliomas. If it turns out that the mutations result in the activation of IDH1 under physiologic conditions, then this work will have identified a potential molecular target for the treatment of cancers of the central nervous system. The identification of succinate dehydrogenase and fumarate mutations has already led to the investigation of cell-permeant α -ketoglutarate derivatives with the potential to suppress the transforming effects of these mutations.¹² A potential benefit of identifying metabolic-enzyme mutations that are pathogenic in specific cancers is that such cancers may be susceptible to pharmacologic manipulations that are more effective and less toxic than existing therapies.

References

1. DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab* 2008;7:11–20. [PubMed: 18177721]

2. Gasparre G, Porcelli AM, Bonora E, et al. Disruptive mitochondrial DNA mutations in complex I subunits are markers of oncocytic phenotype in thyroid tumors. *Proc Natl Acad Sci U S A* 2007;104:9001–6. [PubMed: 17517629]
3. Yan H, Parsons DW, Jin G, et al. *IDH1* and *IDH2* mutations in gliomas. *N Engl J Med* 2009;360:765–73. [PubMed: 19228619]
4. Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, von Deimling A. Analysis of the *IDH1* codon 132 mutation in brain tumors. *Acta Neuropathol* 2008;116:597–602. [PubMed: 18985363]
5. King A, Selak MA, Gottlieb E. Succinate dehydrogenase and fumarate hydratase: linking mitochondrial dysfunction and cancer. *Oncogene* 2006;25:4675–82. [PubMed: 16892081]
6. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science* 2008;321:1807–12. [PubMed: 18772396]
7. Hartong DT, Dange M, McGee TL, Berson EL, Dryja TP, Colman RF. Insights from retinitis pigmentosa into the roles of isocitrate dehydrogenases in the Krebs cycle. *Nat Genet* 2008;40:1230–4. [PubMed: 18806796]
8. Xu X, Zhao J, Xu Z, et al. Structures of human cytosolic NADP-dependent isocitrate dehydrogenase reveal a novel self-regulatory mechanism of activity. *J Biol Chem* 2004;279:33946–57. [PubMed: 15173171]
9. Kil IS, Kim SY, Lee SJ, Park JW. Small interfering RNA-mediated silencing of mitochondrial NADP⁺-dependent isocitrate dehydrogenase enhances the sensitivity of HeLa cells toward tumor necrosis factor- α and anticancer drugs. *Free Radic Biol Med* 2007;43:1197–207. [PubMed: 17854715]
10. Lee JK, Edderkaoui M, Truong P, et al. NADPH oxidase promotes pancreatic cancer cell survival via inhibiting JAK2 dephosphorylation by tyrosine phosphatases. *Gastroenterology* 2007;133:1637–48. [PubMed: 17983808]
11. Kil IS, Huh TL, Lee YS, Lee YM, Park JW. Regulation of replicative senescence by NADP⁺-dependent isocitrate dehydrogenase. *Free Radic Biol Med* 2006;40:110–9. [PubMed: 16337884]
12. MacKenzie ED, Selak MA, Tennant DA, et al. Cell-permeating α -ketoglutarate derivatives alleviate pseudohypoxia in succinate dehydrogenase-deficient cells. *Mol Cell Biol* 2007;27:3282–9. [PubMed: 17325041]

Figure 1. The Roles of IDH1, IDH2, Succinate Dehydrogenase, and Fumarase in Cellular Metabolism

CytoOx denotes mitochondrial cytochrome oxidase, HIF-1 hypoxia-inducible factor 1, HIF-1-OH hydroxylated HIF-1, IDH isocitrate dehydrogenase, SDH succinate dehydrogenase, VEGF vascular endothelial growth factor, and VHL von Hippel–Lindau tumor-suppressor protein.