Cancer-Associated Isocitrate Dehydrogenase Mutations

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The Warburg effect, which describes the remarkable dependence of tumors on nonoxidative fermentation of sugar into lactic acid (glycolysis), was first described in 1926, but only recently, with the discovery of cancer-specific mutations in intermediary metabolism, has interest focused on this field as a source of new targets for treating cancer. Metabolic targets derived from this field are likely to fall into three broad classes: mutations in normal metabolic enzymes, re-expression of fetal isoforms of metabolic enzymes, and dysregulated metabolic pathways within cancers. In the first of these classes, recently discovered somatic mutations in the gene encoding isocitrate dehydrogenase (*IDH*) have become the most prominent examples of a mutated metabolic enzyme associated with human cancer, and offer clear potential as a therapeutic target.

The biochemistry underlying the oncogenicity of *IDH* mutations is particularly instructive. Heterozygous point mutations, which map to arginine residues involved in substrate binding (Table 1), impair the ability of *IDH1* and *IDH2* to catalyze the normal conversion of isocitrate to α -ketoglutarate (α -KG). Initially, these mutations were thought to totally abolish the catalytic activity of the enzyme. However, further work revealed that the mutations actually confer a novel gain of enzymatic function, leading to the reduction of α -KG to the metabolite 2-hydroxyglutarate (2-HG), (Fig. 1). This observation was supported when extraordinarily high levels of 2-HG (50- to 100-fold higher than in normal tissues) were also found in malignant glioma samples from patients harboring either *IDH1* or *IDH2* mutations [1].

Following the initial discovery of *IDH1* and *IDH2* muta-

tions in low-grade gliomas and secondary glioblastomas, additional sequencing efforts identified alterations in these two genes in subsets of acute myeloid leukemia (AML), prostate cancer, acute lymphoblastic B-cell leukemia, and other cancer types (Table 1) [2]. In gliomas and AML, mutations in *IDH1* and *IDH2* are mutually exclusive of one another and occur at very early stages of tumor development, suggesting that the generation of 2-HG may be the initial oncogenic event. Recently, the identification of *IDH1* and *IDH2* mutations in central and periosteal chondrosarcomas [3] as well as intrahepatic cholangiocarcinomas [4] further expanded the role of *IDH1* and *IDH2* mutations in human cancer and implied that the functional consequence of these mutations (i.e., high levels of 2-HG) may confer similar biological effects across multiple tissue types.

The potential mechanism by which *IDH* mutations and their product, 2-HG, cause cancer has been elucidated by the discovery that 2-HG acts as a competitive inhibitor of α -KG-dependent dioxygenases. Dioxygenases play a pivotal role in demethylation reactions involving histones, nucleic acids, and, potentially, a diverse group of cytosolic proteins. More than 30 dioxygenases have been identified in mammalian cells. This class of enzyme includes histone demethylases, responsible for modulating histone regulation of gene expression, and the *TET* family of 5-methylcytosine hydroxylases, responsible for demethylation of DNA cytosine residues and therefore controlling broad patterns of gene expression (Fig. 1) [5]. It is widely believed that inhibition of these dioxygenases can lead to genomewide alterations in histone and DNA methylation and, in fact, hypermethylation phenotypes are seen in both glioma and

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Table 1. Somatic <i>IDH1</i> and <i>IDH2</i> mutations identified in a variety of cancers			
Cancers	<i>IDH1</i>	<i>IDH2</i>	References
CNS cancers (gliomas, sPNET)	R132H R132C R132S R132G R132L R132V	R172K R172M R172S R172G R172W	Parsons et al. (2008) [9], Yan et al. (2009) [2], Dang et al. (2009) [1], Balss et al. (2008) [10], Hayden et al. (2009) [11], Hartmann et al. (2009) [12]
AML, MDS, and MPN	R132H R132G R132C R132S R132L V71I	R140Q R172K R140W R172G R140L	Mardis (2009) [13], Green and Beer (2010) [14], Chou et al. (2010) [15], Gross et al. (2010) [16], Ward et al. (2010) [17], Kosmider et al. (2010) [18], Marcucci et al. (2010) [19], Ho et al. (2010) [20]
Prostate cancer	R132H R132C		Kang et al. (2009) [21]
B-ALL	R132H		Kang et al. (2009) [21]
Paragangliomas	R132C R132H		Gaal et al. (2009) [22]
Colon cancer	R132C		Sjöblom et al. (2006) [23], Kang et al. (2009) [21], Bleeker et al. (2009) [24],
Follicular and anaplastic thyroid cancer	V71I* G123R*		Murugan et al. (2010) [25]
Chondrosarcomas	R132C R132H R132G	R172S	Amary et al. (2011) [3]
Cholangiocarcinoma (intrahepatic)	R132C R132L R132G	R172W	Borger et al. (2011) [4]
Abbreviations: AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CNS, central nervous system; IDH, isocitrate dehydrogenase; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; sPNET, supratentorial primitive neuroectodermal tumor.			

AML patient samples [6, 7]. Inhibition of two other α -KG-dependent dioxygenases, prolyl hydroxylases, and collagen prolyl-4-hydroxylase has been shown to activate hypoxia-inducible factor 1 α and endostatin expression [5]. Although the precise biological impact of dioxygenase inhibition has yet to be determined, it is highly likely that their inhibition may confer many of the features of malignant transformation and maintenance (angiogenesis, dedifferentiation, resistance to apoptosis) in tumors harboring *IDH* mutations (Fig. 1).

Finally, *IDH* mutations have attracted the interest of a number of biotechnology and large pharmaceutical companies, and compounds that inhibit *IDH* are likely to enter clinical trials in the near future. The clinical evaluation of such agents will require the development of companion mo-

lecular assays capable of detecting the mutations as well as downstream biomarkers (such as 2-HG) useful for following drug action in the clinic. *IDH* mutations are readily detected via gene sequencing as well as by immunohistochemistry with mutant-specific antibodies. Furthermore, because mutant *IDH* produces high levels of 2-HG, this metabolite may become a biomarker for pharmacodynamic endpoints, response, and detection of minimal residual disease. Measurement of 2-HG as a biomarker in tumor and in plasma samples may be useful in guiding clinical trial design with inhibitors of mutant *IDH*. Noninvasive detection of 2-HG through magnetic resonance spectroscopy imaging also offers an attractive alternative to tumor biopsy to aid in the diagnosis and to gauge the effectiveness of *IDH* inhibitors in patients with glioma and other tumor types

Figure 1. Hypotheses linking 2-HG with cancer-relevant processes.

Abbreviations: 2-HG, 2-hydroxyglutarate; 5-ALA, 5-aminolevulinic acid; 5mC, 5-methylcytosine; α -KG, α -ketoglutarate; CoA, co-enzyme A; IDH, isocitrate dehydrogenase; OAA, oxaloacetate.

not amenable to repeat tumor biopsy [8]. To date, although *IDH* mutations are found in very specific tumor types, it is quite conceivable that, as more genetic sequencing data become available, other subgroups of tumors harboring these mutations will be identified. Selective inhibitors of mutant *IDH* enzymes will provide the initial

foray into the exciting new field of disorders of metabolism underlying cancer.

AUTHOR CONTRIBUTIONS

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