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Isocitrate dehydrogenase (IDH) inhibition as treatment of myeloid malignancies: Progress and future directions

Vivek A. Upadhyay [a], Andrew M. Brunner [b], Amir T. Fathi [b,*]

[a] Department of Medicine, Massachusetts General Hospital, Boston, MA, United States
[b] Department of Hematology/Oncology, Massachusetts General Hospital, Boston, MA, United States

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ABSTRACT

Isocitrate dehydrogenase (IDH) is an essential metabolic enzyme. Over the last two decades, there has been a growing focus on the metabolic derangements that occur with *IDH1* and *IDH2* mutations. The altered IDH protein leads to accumulation of 2-hydroxyglutarate (2-HG), a metabolite with oncogenic activity via epigenetic mechanisms. The advent of IDH inhibitors has engendered hope in novel and targeted therapies in *IDH1/2* mutant myeloid malignancies. We here summarize the basic physiology of IDH, the metabolic and oncogenic consequences of mutant *IDH1/2*, and the clinical significance of IDH inhibition in hematologic malignancies. We also discuss completed and ongoing clinical trials focusing on the inhibition of IDH proteins, which have demonstrated preliminary indications of efficacy. The promise of IDH inhibition is now being further investigated as a novel therapeutic approach for AML and other myeloid malignancies.

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1. Introduction

Metabolism has long been suspected to play a role in carcinogenesis. Otto Warburg's eponymous observation that cancer cells generate energy by metabolizing glucose to lactate, even in the presence of oxygen, anticipated metabolic differences between cancer cells and non-cancer cells almost 100 years ago (Dang, 2012; Losman & Kaelin, 2013; Vander Heiden, Cantley, & Thompson, 2009; Warburg, 1956). This observation has identified metabolic pathways as potential therapeutic targets (Locasale et al., 2011; Sebastián et al., 2012; Son et al., 2013; Ying et al., 2012). In recent years, isocitrate dehydrogenase (IDH), one of the primary enzymes in the Krebs Cycle, has emerged as one such target. Recurrent mutations of the *IDH1* and *IDH2* genes have been identified in a number of malignancies, and appear to play a key role in oncogenesis. The recent development and study of targeted IDH inhibitors have generated promise, particularly in patients with acute myeloid leukemia (AML) and other myeloid neoplasms. This review will focus on alterations impacting IDH proteins and related pathophysiology,

* Corresponding author at: Harvard Medical School, Department of Hematology/Oncology, Zero Emerson Place, Suite 118, Boston, MA 012114, United States.
E-mail address: atfathi@partners.org (A.T. Fathi).

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their implicated roles in malignant transformation, and the therapeutic promise of IDH inhibition in AML.

2. The physiology of isocitrate dehydrogenase

The isocitrate dehydrogenase (IDH) protein family consists of three self-regulating enzymes (IDH1, IDH2, IDH3). IDH1 and IDH2 are both nicotinamide adenine dinucleotide phosphate (NADP)-dependent enzymes that catalyze the oxidative decarboxylation of isocitrate to alpha-ketoglutarate (α-KG), while producing NADPH either in peroxisomes and the cytosol (IDH1) or in mitochondria (IDH2) (Parker & Metallo, 2015; Xu et al., 2004). IDH3 catalyzes the same reaction in the mitochondria, but in an NAD-dependent fashion (Henderson, 1965). Structural analysis of human cytosolic IDH proteins suggests a mechanism whereby activation of the enzyme occurs via isocitrate binding to arginine residues, causing a conformational change that allows interaction with a serine residue. Given their sequence homology, this mechanism is suggested to apply to mitochondrial IDH2 as well (Xu et al., 2004). Under physiologic circumstances, isocitrate levels drive IDH1/2 to catalyze the formation of α-KG (Rendina et al., 2013) in an auto-regulated process, in which activation of the enzyme leads to an allosteric change, thereby attenuating its own activity (Parker & Metallo, 2015).

3. Isocitrate dehydrogenase mutations in cancer

Mutations in *IDH1* and *IDH2* have been demonstrated in a variety of malignancies. An *IDH1* mutation was initially identified in a colonic tumor sample (Sjöblom et al., 2006), but subsequently, *IDH* mutations have been identified at higher prevalences in a number of other malignancies including glioblastoma multiforme (Parsons et al., 2008), low grade gliomas (Yan et al., 2009), acute myeloid leukemia (Mardis et al., 2009), chondrosarcoma (Amary et al., 2011), and cholangiocarcinoma (Borger et al., 2012). *IDH* mutations are somatically acquired and appear to be mutually exclusive of one another in the majority of cases (Rakheja, Konoplev, Medeiros, & Chen, 2012), with rare exception (Platt et al., 2015). While *IDH1* mutations are more common than *IDH2* mutations in low-grade gliomas, chondrosarcoma, and cholangiocarcinoma, *IDH2* mutations are more frequently seen in AML and other myeloid malignancies (Molenaar, Radivoyevitch, Maciejewski, van Noorden, & Bleeker, 2014; Ward et al., 2010). Mutant *IDH1* (*mIDH1*) typically impacts an arginine residue (R132), resulting in either R132H, R132C, R132G, or R132S variants (Dang et al., 2009). Mutation of this arginine residue conveys significant structural and functional impact on IDH function, as the side chain of R132 is pivotal in binding isocitrate (Xu et al., 2004). Mutations in *IDH2* (*mIDH2*) typically affect one of two arginine residues (R140 and R172) with similar functional impact (Ward et al., 2010). *IDH* mutations are generally monoallelic, and rarely result in loss of heterozygosity (Jin et al., 2013; Mullen & DeBerardinis, 2012). Rather, the mutations are neomorphic alterations in the case of both *mIDH1* (Dang et al., 2009) and *mIDH2* (Ward et al., 2010), enabling novel oncogenic activity of the enzyme.

4. Mutant IDH activity

The altered IDH enzyme (mIDH) resulting from these *IDH1/2* hotspot mutations fails to catalyze the oxidation of isocitrate to α-KG; instead, it reduces α-KG to 2-hydroxyglutarate (2-HG) in a NADPH-dependent fashion (Fig. 1). 2-HG (particularly the (*R*)-2-HG enantiomer), is typically only present at very low levels in healthy individuals. With mutated IDH, 2-HG accumulates in the cell and serum, and appears to act as an "oncometabolite" via multiple different pathways (Xu et al., 2011). Specifically, 2-HG is a competitive inhibitor of α-KG dependent histone demethylases, prolyl hydroxylases, and TET hydroxylases (Im et al., 2014; Kernytsky et al., 2015). *IDH1/2* mutations, and subsequent 2-HG accumulation, thus initiate important epigenetic alterations, including decreased hydroxylation of methyl groups on DNA cytosines (He et al., 2011; Ito et al., 2011), aberrant hypermethylation, decreased expression of key differentiating enzymes, and inhibition of normal cellular differentiation (Fathi, Wander, Faramand, & Emadi, 2015).

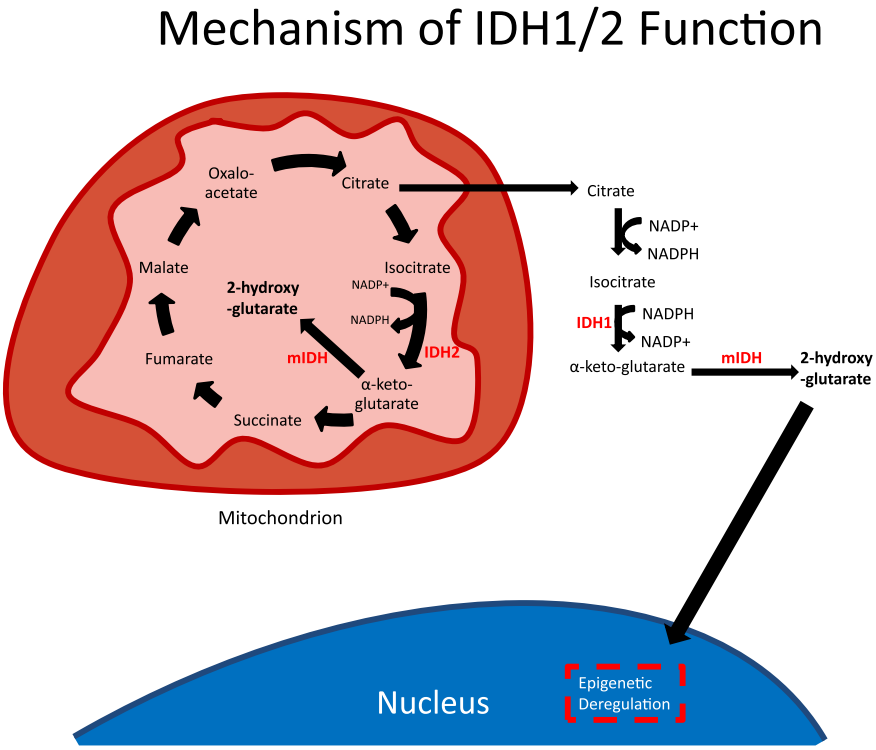

Fig. 1.