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Review

IDH1, lipid metabolism and cancer: Shedding new light on old ideas

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ABSTRACT

Background: Since the initial discovery of mutations in the isocitrate dehydrogenase 1 (IDH1) gene in a large subset of human low-grade gliomas and acute myelogenous leukemia (AML), much interest focused on the function of IDH1 and on the relationship between mutations in IDH1 and tumor progression. To date, mutations in the IDH1 gene have been found in numerous cancers with the highest frequencies occurring in gliomas, chondrosarcomas/enchondromas and cholangiocarcinomas.
Scope of review: IDH1 was first described in the scientific literature as early as 1950. Early researchers proposed that the enzyme likely functions in cellular lipid metabolism based on the observation that the enzymatic reaction produces NADPH and partially localizes to peroxisomes. This article highlights the studies implicating IDH1 in cytoplasmic and peroxisomal lipid metabolism from the early researchers to the recent studies examining mutant IDH1^{R132}, the most common IDH1 mutation found in cancer.
Major conclusions: While a role for IDH1 in lipid biosynthesis in the liver and adipose tissue is now established, a role in lipid metabolism in the brain and tumors is beginning to be examined. The recent discoveries that IDH1^{R132H} interferes with the metabolism of phospholipids in gliomas and that IDH1 activity could participate in the synthesis of acetyl-CoA from glutamine in hypoxic tumors highlight roles for IDH1 in lipid metabolism in a broad spectrum of tissues.
General significance: Interferences in cytoplasmic and peroxisomal lipid metabolism by IDH1^{R132} may contribute to the more favorable clinical outcome in patients whose tumors express mutations in the *IDH1* gene.

1. Introduction

With the discovery of heterozygous mutations in the *IDH1* gene in a large subset of human low-grade gliomas and in AML [1–3], much interest focused on the function of IDH1 and on the role of mutant IDH1 in the development of cancer. Mutations in *IDH1* have now been reported in numerous cancers, most notably in gliomas (>70%), chondrosarcomas (~50%), cholangiocarcinomas (~20%) and AML (~10%) [1–5]. In gliomas and cholangiocarcinomas mutations in the *IDH1* gene predict longer survival and a favorable prognosis [1,2,6].

IDH1 belongs to the family of isocitrate dehydrogenase enzymes which is comprised of 3 members: IDH1, IDH2 and IDH3 [7]. IDH1 is localized within the cytoplasm and peroxisomes [8,9]. IDH2 and IDH3 are located exclusively within the mitochondria [10]. All IDH enzymes catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate with the reduction of either $NADP^+$ or NAD^+ to generate NADPH or NADH respectively [7,11]. IDH1 and IDH2 utilize $NADP^+$ as a cofactor and IDH3 utilizes NAD^+ and functions in the tricarboxylic acid (TCA) cycle [7,10]. IDH1 and IDH2 can also catalyze the reverse reaction where α-ketoglutarate (in the presence of NADPH and CO_2) is converted to isocitrate and $NADP^+$ via reductive carboxylation [10,11]. The most frequent mutation in IDH1 found in cancer occurs at the substrate binding site at arginine 132 (R132) where R132 is replaced by either histidine (R132H), cysteine (R132C), serine (R132S), glycine (R132G), leucine (R132L) or glutamine (R132Q) [2,12]. The frequency with which each amino acid substitution at R132 occurs varies and depends on the type of cancer; the IDH1^{R132H} mutation is the most frequent IDH1 mutation found in gliomas, whereas IDH1^{R132C} is more often observed in cholangiocarcinomas and chondrosarcomas/enchondromas [1,2,4,5]. Mutation of R132 at the substrate binding site abolishes the wild-type activity of the enzyme [1,2] and induces a novel enzymatic activity which catalyzes the conversion of α-ketoglutarate to 2-hydroxyglutarate (2-HG) utilizing NADPH as a cofactor [13]. The accumulation of 2-HG produced by mutant IDH1^{R132} may contribute to the development of cancer by inhibiting collagen maturation, upregulating HIF1α and inhibiting histone demethylases leading to increased histone methylation and altered gene expression [14–18].

Abbreviations: IDH1, isocitrate dehydrogenase 1; AML, acute myelogenous leukemia; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; PI, phosphatidylinositol; 2-HG, 2 hydroxyglutarate; RCDP, rhizomelic chondrodysplasia punctata; NADP, nicotinamide adenine dinucleotide phosphate; NAD, nicotinamide adenine dinucleotide; TCA, tricarboxylic acid; DHAP, dihydroxyacetone phosphate

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2. Lipid metabolism in the liver and adipose tissue

One of the earliest functions ascribed to wild-type IDH1 was a role in lipid metabolism based on the observation that the enzymatic reaction of IDH1 produces NADPH [19]. IDH1 was discovered as early as 1950 when Hogeboom and Schneider [20] identified isocitrate dehydrogenase activity in the cytoplasm of liver tissue obtained from adult mice. These investigators noted the increased production of NADPH following the addition of isocitrate to rat liver cytosolic preparations. Early investigators hypothesized that the function of IDH1 may be to provide high levels of NADPH for lipid biosynthesis since NADPH is an obligatory reducing equivalent for the synthesis of fatty acids and lipids [7,19]. It was also hypothesized that IDH1 participates in a biochemical pathway in the rat liver where carbons derived from glutamate become incorporated into fatty acids [11]. Further suggestion that IDH1 plays a role in lipid metabolism came from the observation that a small (≤25%) pool of IDH1 is localized within rat liver peroxisomes [8]. Peroxisomes are organelles found in all mammalian cells with the exception of erythrocytes [21]. Their size (0.1–1.0 μm) and number varies depending on the tissue being examined [22]. Tissues that are highly active in the metabolism of lipids such as the liver have large and more numerous peroxisomes [22,23]. Peroxisomes contain over 50 enzymes; half of which participate in functions related to lipid metabolism such as β-oxidation of very long chain fatty acids, α-oxidation of branched-chain fatty acids and the synthesis of ether-linked (plasmalogen) phospholipids [21,23,24]. Other functions of peroxisomes include purine and polyamine catabolism, amino acid metabolism and the synthesis of bile [21,23]. The name *peroxisome* was derived from the observation that hydrogen peroxide is produced and degraded within this organelle [25]. Hydrogen peroxide is formed during the first reaction in the β-oxidation pathway and is then reduced to water by catalase [21,25]. For the early researchers, the hypothesis that IDH1 participates in cellular lipid metabolism was primarily based on correlative data obtained from tissues with high lipogenic activity such as the liver, adipose tissue and mammary gland. The advent of techniques in molecular biology which allowed genetic manipulation provided a more direct link between IDH1 and cellular lipid metabolism. Koh et al. [26] generated transgenic mice overexpressing IDH1 in the liver and adipose tissue under the rat phosphoenolpyruvate carboxykinase promoter. These mice displayed a 35% increase in body weight, increased fat mass and adipocyte size, had fatty livers and increased serum cholesterol and triacylglycerols. The authors also showed that decreasing IDH1 mRNA in 3T3-L1 preadipocytes impaired adipocyte differentiation and reduced the lipid content of these cells. Conversely, mice transduced with IDH1 shRNA gained less weight when fed a high fat diet, had reduced fat mass and lower circulating triacylglycerols compared to control mice [27]. Consistent with these observations, Shechter et al. [28] showed that the *IDH1* promoter can be activated by the lipogenic transcription factors SREBP-1a and SREBP-2 in HepG2 cells.

3. Lipid biosynthesis in tumors

Studies examining the metabolism of glutamine in various cultured tumor cells have shown that IDH1 and IDH2 participate in the synthesis of acetyl-CoA from glutamine to support lipid biosynthesis in normoxia, hypoxia and when mitochondrial function is impaired [29–31]. Tumor cells avidly take up glutamine to sustain their growth and survival [32]. In both the cytoplasmic (IDH1) and mitochondrial (IDH2) pathways, glutamine is converted to glutamate and subsequently to α-ketoglutarate (Fig. 1) [29–31]. IDH1 and IDH2 convert α-ketoglutarate to isocitrate via reductive carboxylation. Isocitrate undergoes further conversion to citrate and subsequently to acetyl-CoA and oxaloacetate. Acetyl-CoA is then used as a building block for the synthesis of fatty acids (Fig. 1). In the mitochondria, this metabolic pathway is induced by the reversal of the TCA cycle (Fig. 1) [29–31]. Although acetyl-CoA derived from glutamine can be used for de novo synthesis of fatty acids and lipids, this may not be the only mechanism to increase lipid biosynthesis in tumors. Instead, tumor cells may increase the uptake of fatty acids [33]. Mutant $IDH1^{R132H}$ lacks the ability to convert α-ketoglutarate to isocitrate via reductive carboxylation [34].

3.1. Phospholipid and peroxisomal metabolism in the brain and gliomas

The brain is an organ rich with lipids where lipids comprise up to 50% of the brain's dry weight [35]. The most abundant lipids in the brain are the phospholipids, sphingolipids and sterols (cholesterol) with each lipid class containing numerous lipid species. The phospholipids are structural components of the plasma membrane and membranes of

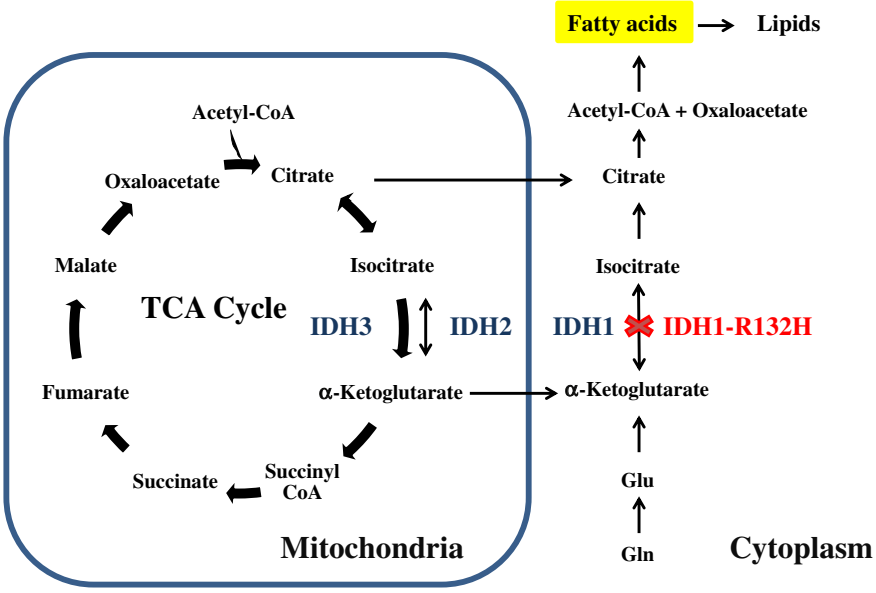

Fig. 1. IDH1 and IDH2 mediate reductive carboxylation of α-ketoglutarate to isocitrate in the mitochondria and cytoplasm for the synthesis of lipids [29–31]. Carbons derived from glutamine (Gln) are incorporated into acetyl-CoA for fatty acid synthesis. In the TCA cycle, IDH3 catalyzes the conversion of isocitrate to α-ketoglutarate. IDH2 reverses the metabolite flux of the TCA cycle for the production of citrate from α-ketoglutarate. Citrate and α-ketoglutarate may exit the mitochondria and enter the cytoplasmic pathway. Due to the loss of wild-type IDH1 activity, mutant $IDH1^{R132H}$ (indicated in red) lacks the ability to interconvert isocitrate to α-ketoglutarate [34]. Glu = glutamate.