

# IDH2 dimer decarboxylates isocitrate

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## Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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## Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 88

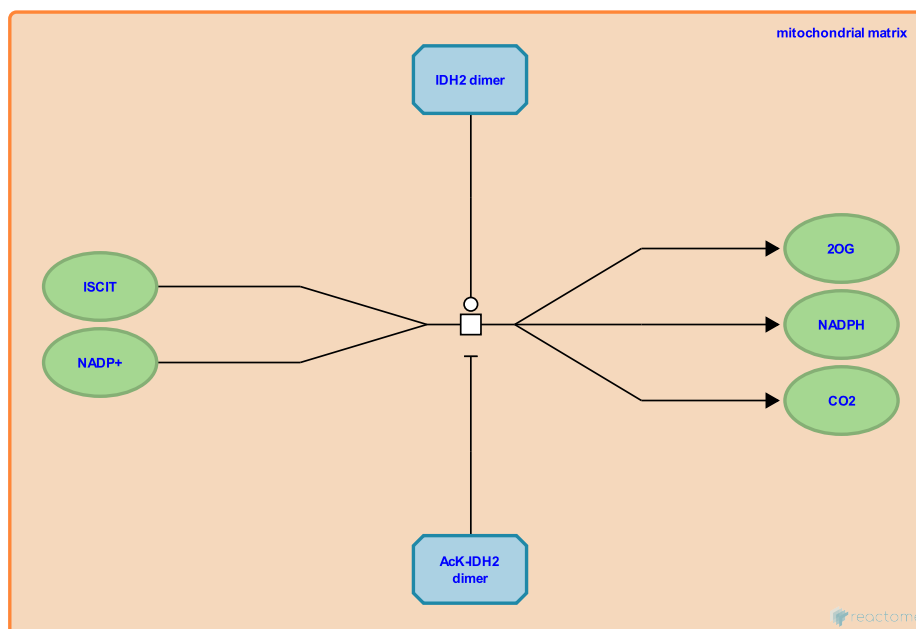
This document contains 1 reaction ([see Table of Contents](#))

## IDH2 dimer decarboxylates isocitrate ↗

**Stable identifier:** R-HSA-450984

**Type:** transition

**Compartments:** mitochondrial matrix



Mitochondrial isocitrate dehydrogenase IDH2 catalyzes the irreversible reaction of isocitrate and NADP<sup>+</sup> to form alpha-oxoglutarate ( $\alpha$ OG,  $\alpha$ KG), CO<sub>2</sub>, and NADPH (Hartong et al. 2008). The structure of the active human enzyme has not been determined experimentally but is inferred to be a homodimer with one Mn<sup>++</sup> bound to each subunit based on detailed studies of the homologous pig enzyme (Ceccarelli et al. 2002). NADP-specific IDH2 was the first isocitrate dehydrogenase isoenzyme to be characterized in biochemical studies of the mammalian TCA cycle (Ochoa 1948). Later work with yeast revealed the existence of both NADP-specific (IDH2-homologous) and NAD-specific (IDH3-homologous) enzymes and demonstrated the ADP-dependence of the latter (Kornberg and Pricer 1951), consistent with the now widely accepted view that IDH3 mediates the conversion of isocitrate to alpha-ketoglutarate in the TCA cycle. The recent observation that individuals homozygous for IDH3 mutations that sharply reduce its activity do not show symptoms of deficient energy metabolism in most tissues raises the possibility that the IDH2 reaction may play an accessory role in the TCA cycle (Hartong et al. 2008). Also, IDH2 is a major NADPH producer in the mitochondria and thus plays a crucial role in cellular defense against oxidative stress-induced damage (Jo et al., 2001).

Specific mutations in the IDH2, and also the IDH1 gene, lead to dysfunction of its normal catalytic activity, but also to a new ('neomorphic') function where  $\alpha$ OG is reduced to D-2-hydroxyglutarate (D2HG). D2HG is an oncometabolite, accumulating considerably in tumors with mutant IDH. While gliomas with mutant IDH1/2 have a better outcome than those with wild-type IDH, mutant IDH can also lead to the rare metabolic disorder D-2-hydroxyglutaric aciduria 2 (D2HGA2; MIM:613657; Kranendijk et al., 2010; reviewed in Alzial et al., 2021).

### Literature references

- Pricer, WE Jr., Kornberg, A. (1951). Di- and triphosphopyridine nucleotide isocitric dehydrogenases in yeast. *J Biol Chem*, 189, 123-36. ↗
- Bahnson, BJ., Ceccarelli, C., Ariyaratne, N., Grodsky, NB., Colman, RF. (2002). Crystal structure of porcine mitochondrial NADP<sup>+</sup>-dependent isocitrate dehydrogenase complexed with Mn<sup>2+</sup> and isocitrate. Insights into the enzyme mechanism. *J Biol Chem*, 277, 43454-62. ↗
- Kirk, EP., Hofstede, FC., Morris, A., Grange, DK., Morava, E., Vallance, H. et al. (2010). IDH2 mutations in patients with D-2-hydroxyglutaric aciduria. *Science*, 330, 336. ↗
- Ochoa, S. (1948). Biosynthesis of tricarboxylic acids by carbon dioxide fixation; enzymatic mechanisms. *J Biol Chem*, 174, 133-57. ↗

Son, MK., Lee, YS., Lee, SM., Koh, HJ., Kim, WB., Jo, SH. et al. (2001). Control of mitochondrial redox balance and cellular defense against oxidative damage by mitochondrial NADP+-dependent isocitrate dehydrogenase. *J Biol Chem*, 276, 16168-76. [↗](#)

Editions

2009-12-26	Authored	D'Eustachio, P.
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