IDH2 dimer decarboxylates isocitrate

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06/05/2024

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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

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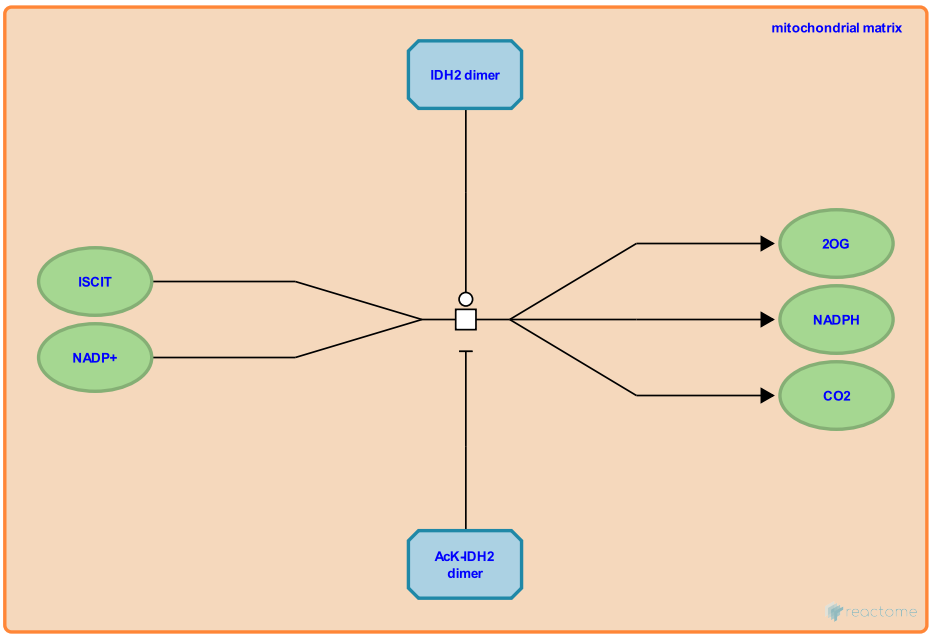
Stable identifier: R-HSA-450984

Type: transition

Compartments: mitochondrial matrix



Mitochondrial isocitrate dehydrogenase IDH2 catalyzes the irreversible reaction of isocitrate and NADP+ to form alpha-oxoglutarate (αOG, αKG), CO2, 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++ 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 αOG 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).

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Editions

2009-12-26	Authored	D'Eustachio, P.
2024-02-15	Reviewed	Hill, DP.