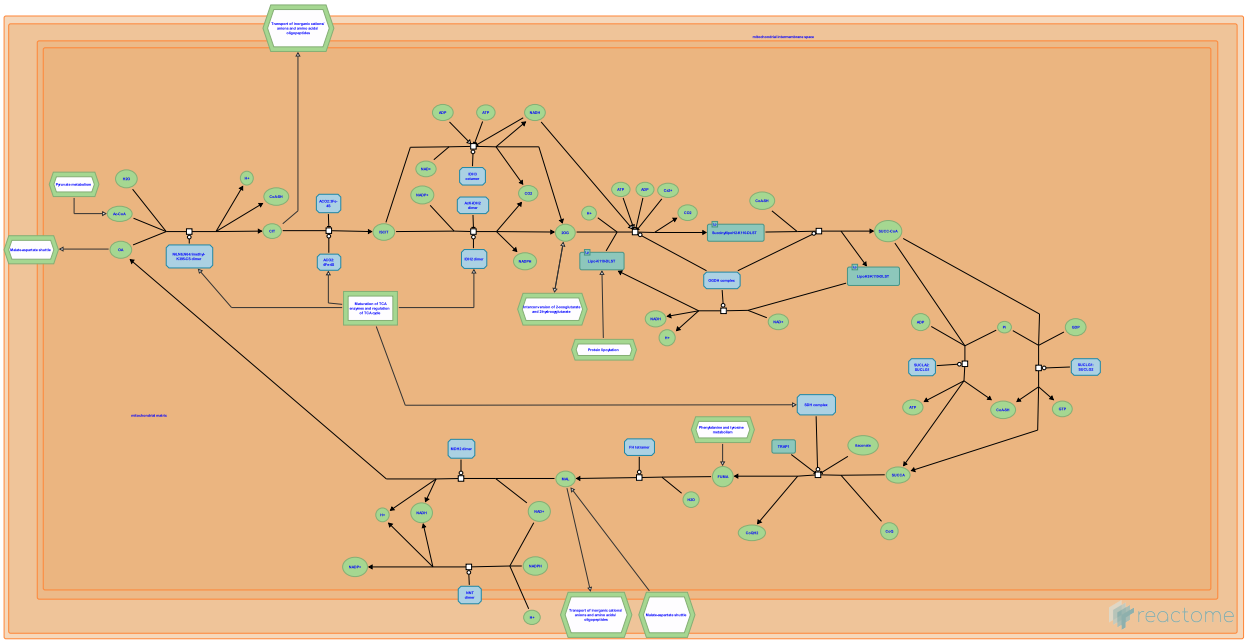
Citric acid cycle (TCA cycle)



Birney, E., D'Eustachio, P., Hill, DP., Stephan, R.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

07/10/2024

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).

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

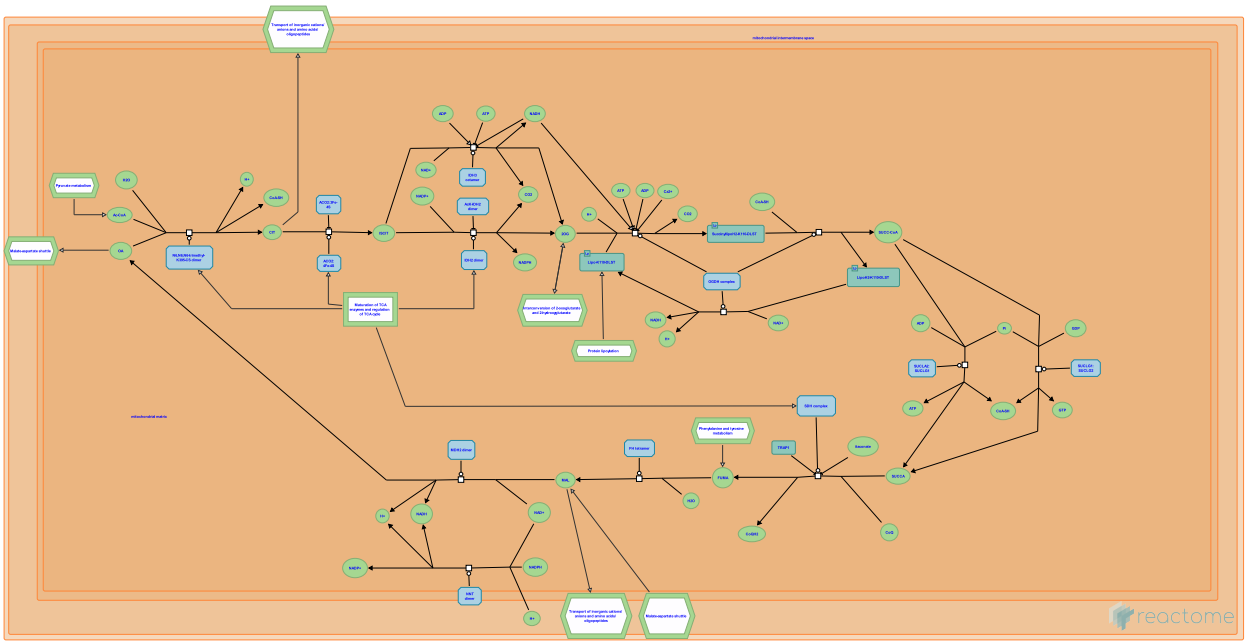
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Citric acid cycle (TCA cycle) ↗

Stable identifier: R-HSA-71403

Compartments: mitochondrion



In the citric acid or tricarboxylic acid (TCA) cycle, the acetyl group of acetyl CoA (derived primarily from oxidative decarboxylation of pyruvate, beta-oxidation of long-chain fatty acids, and catabolism of ketone bodies and several amino acids) can be completely oxidized to CO2 in reactions that also yield one high-energy phosphate bond (as GTP or ATP) and four reducing equivalents (three NADH + H+, and one FADH2). Then, the electron transport chain oxidizes NADH and FADH2 to yield nine more high-energy phosphate bonds (as ATP). All reactions of the citric acid cycle take place in the mitochondrion.

Eight canonical reactions mediate the synthesis of citrate from acetyl-CoA and oxaloacetate and the metabolism of citrate to re-form oxaloacetate. Three reactions are reversible: the interconversions of citrate and isocitrate, of fumarate and malate, and of malate and oxaloacetate. The reverse reactions are irrelevant under normal physiological conditions but appear to have a role in glucose- and glutamine-stimulated insulin secretion (Zhang et al., 2020) and cancer metabolism (e.g., Jiang et al., 2016). Succinate synthesis from succinyl-CoA can be coupled to the phosphorylation of either GDP (the canonical reaction) or ADP; we annotate both reactions. Two mitochondrial isocitrate dehydrogenase isozymes catalyze the oxidative decarboxylation of isocitrate to form alpha-ketoglutarate (2-oxoglutarate): IDH3 catalyzes the canonical reaction coupled to the reduction of NAD+, while IDH2 catalyzes the same reaction coupled to the reduction of NADP+, a reaction whose normal physiological function is unclear. Both reactions are annotated.

The cyclical nature of the reactions responsible for the oxidation of acetate was first suggested by Hans Krebs from biochemical studies of pigeon breast muscle (Krebs et al., 1938; Krebs and Eggleston, 1940). Ochoa and colleagues studied many molecular details of individual reactions, mainly by studying enzymes purified from pig hearts (Ochoa, 1980). While the human homologs of these enzymes have all been identified, their biochemical characterization has, in general, been limited, and many molecular details of the human reactions are inferred from those worked out in studies of the model systems. Studies examining the impact of elevated citric acid cycle intermediates such as succinate and fumarate led to the recognition of the role of metabolites in driving cancer progression ('oncometabolites') (Pollard et al., 2005; reviewed in Hayashi et al., 2018). The role of TCA enzymes in disease was reviewed by Kang et al., 2021.

Literature references

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Eggleston, LV., Krebs, HA. (1940). The oxidation of pyruvate in pigeon breast muscle. *Biochem J, 34*, 442-459. ↗

Gray, SM., Lu, D., Wang, Y., Jensen, MV., Zhang, GF., El, K. et al. (2021). Reductive TCA cycle metabolism fuels glutamine- and glucose-stimulated insulin secretion. *Cell Metab, 33*, 804-817.e5. ↗

Wortham, NC., Griffiths, JR., Moat, SJ., Pollard, PJ., Barclay, E., Barwell, J. et al. (2005). Accumulation of Krebs cycle intermediates and over-expression of HIF1alpha in tumours which result from germline FH and SDH mutations. *Hum Mol Genet, 14*, 2231-9. ↗

Editions

2003-01-28	Authored	Birney, E.
2009-12-26	Revised	D'Eustachio, P.
2024-02-15	Reviewed	Hill, DP.
2024-08-27	Edited	D'Eustachio, P.

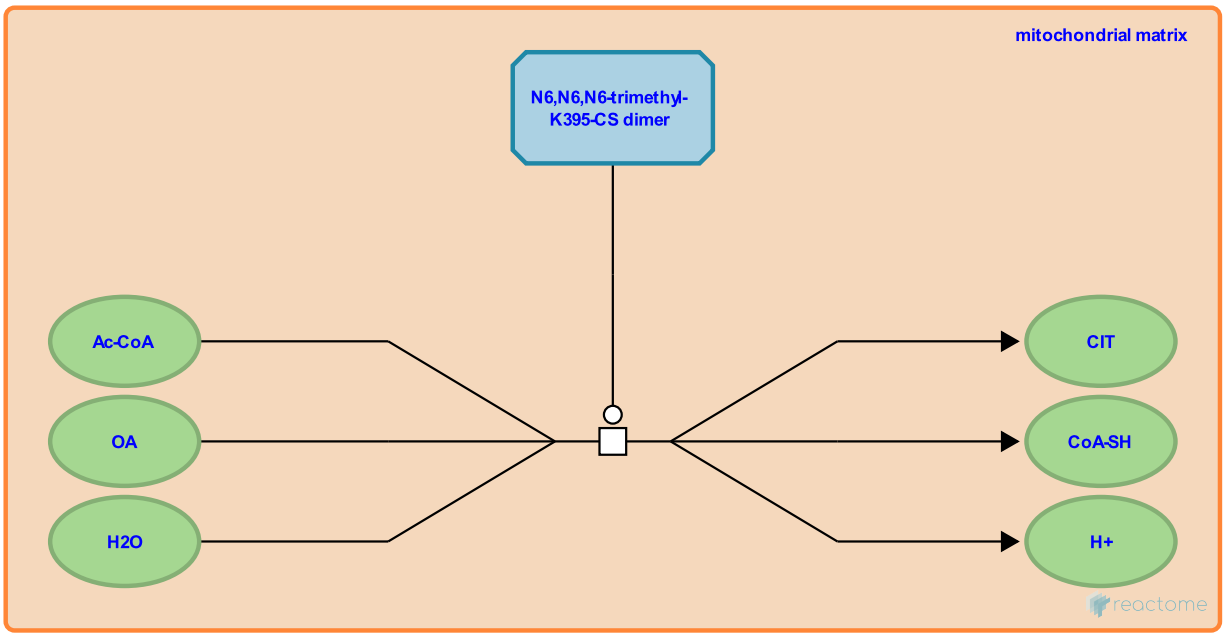
CS acetylates OA to citrate ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-70975

Type: transition

Compartments: mitochondrial matrix



Mitochondrial citrate synthase (CS) dimer catalyzes the irreversible reaction of acetyl-CoA, water, and oxaloacetate to form citrate and coenzyme A. This reaction is the entry point of two-carbon units into the citric acid cycle. The reaction is subject to allosteric regulation. Most of the time, CS is trimethylated on Lys-395 which attenuates its enzymatic activity (Malecki et al. 2017). The gene encoding the human enzyme has been cloned (Goldenthal et al. 1998), but the enzyme has not been characterized in detail. Its properties are inferred from those of the well-studied homologous pig enzyme (e.g., Morgunov and Srere 1998).

CS dimer, malate dehydrogenase MDH2, and aconitase ACO2 form a multienzyme complex ("metabolon") that optimally channels the substrate flow between them (Fahien & Kmiotek, 1983; Wu & Minteer, 2014; Omini et al., 2021).

Preceded by: MDH2 dimer dehydrogenates MAL

Followed by: ACO2 isomerizes citrate

Literature references

Marin-Garcia, J., Ananthakrishnan, R., Goldenthal, MJ. (1998). Cloning and molecular analysis of the human citrate synthase gene. *Genome, 41*, 733-738. ↗

Kmiotek, E., Fahien, LA. (1983). Complexes between mitochondrial enzymes and either citrate synthase or glutamate dehydrogenase. *Arch Biochem Biophys, 220*, 386-97. ↗

Obata, T., Skirycz, A., Omini, J., Wojciechowska, I., Moriyama, H. (2021). Association of the malate dehydrogenase-citrate synthase metabolon is modulated by intermediates of the Krebs tricarboxylic acid cycle. *Sci Rep, 11*, 18770. ↗

Morgunov, I., Srere, PA. (1998). Interaction between citrate synthase and malate dehydrogenase. Substrate channeling of oxaloacetate. *J Biol Chem, 273*, 29540-29544. ↗

Jakobsson, ME., Falnes, PØ., Małecki, J., Rustan, AC., Moen, A., Ho, AYY. (2017). Uncovering human METTL12 as a mitochondrial methyltransferase that modulates citrate synthase activity through metabolite-sensitive lysine methylation. *J Biol Chem, 292*, 17950-17962. ↗

Editions

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

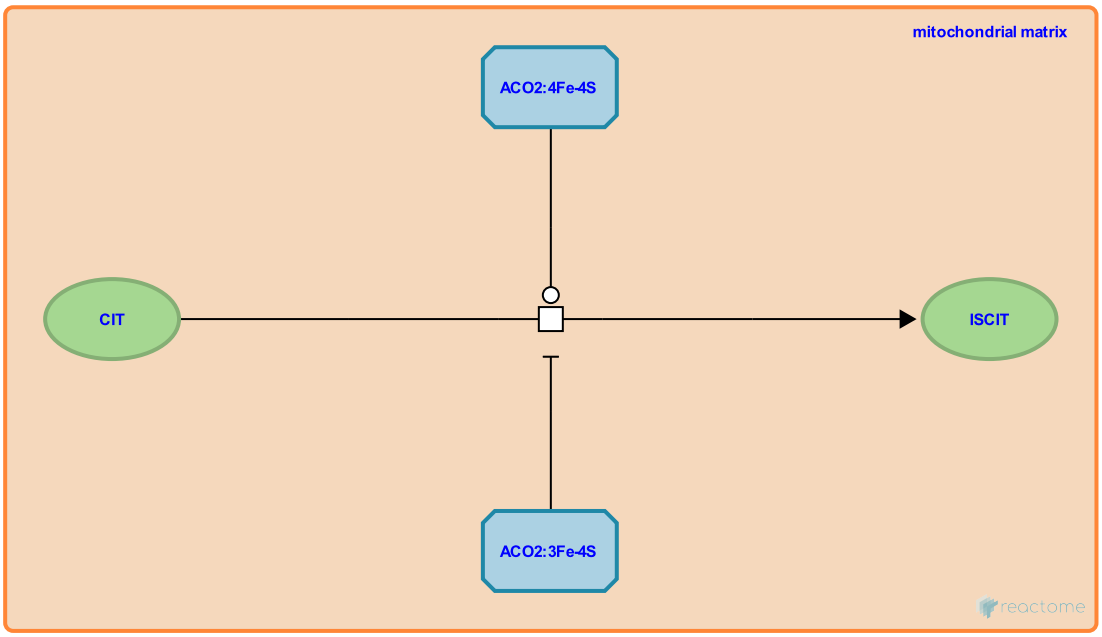
ACO2 isomerizes citrate ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-70971

Type: transition

Compartments: mitochondrial matrix



Mitochondrial aconitase (ACO2) reversibly converts citrate to isocitrate via a cis-aconitate intermediate. Mitochondrial aconitase activity has been demonstrated in diverse human tissue extracts (Slaughter et al., 1975), and a protein homologous to the well-characterized porcine enzyme has been purified from human tissues (Baldwin et al., 1991). Mutations in the ACO2 gene can lead to an infantile neurodegenerative disease (ICRD; MIM:614559) and optic atrophy (OPA9; MIM:616289) (see Guehlouz et al., 2021).

Preceded by: CS acetylates OA to citrate

Followed by: IDH3 complex decarboxylates isocitrate, IDH2 dimer decarboxylates isocitrate

Literature references

Desquiret-Dumas, V., Milea, D., Procaccio, V., den Dunnen, JT., Bris, C., Reynier, P. et al. (2021). ACO2 clinicobiological dataset with extensive phenotype ontology annotation. *Sci Data, 8*, 205. ↗

Baldwin, GS., Moritz, RL., Toh, BH., Simpson, R., Callaghan, J., Seet, KL. et al. (1991). Purification and partial amino acid sequence of human aconitase. *Protein Seq Data Anal, 4*, 63-67. ↗

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Editions

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

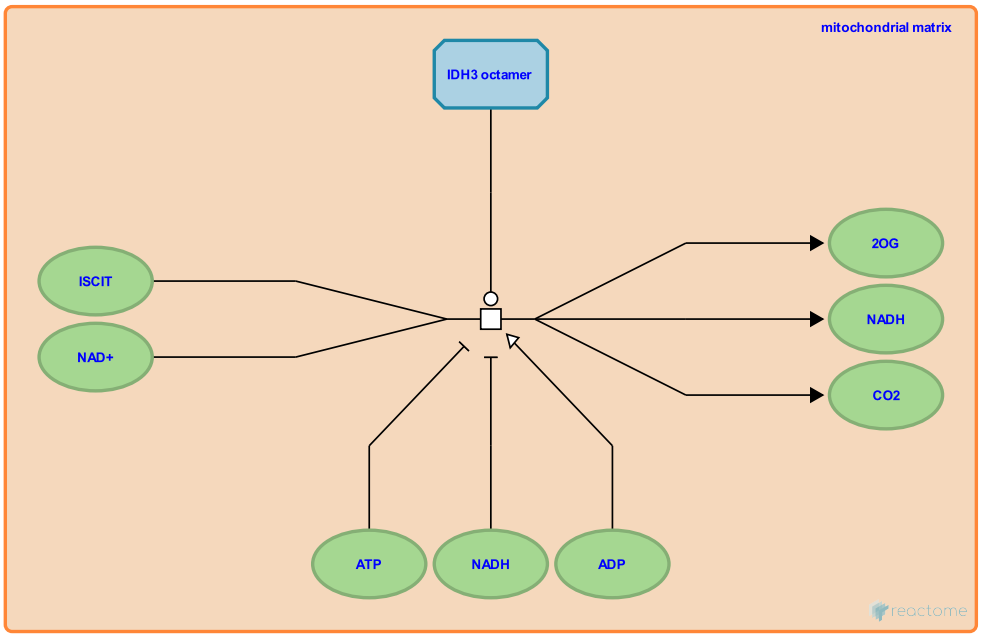
IDH3 complex decarboxylates isocitrate ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-70967

Type: transition

Compartments: mitochondrial matrix



Mitochondrial isocitrate dehydrogenase IDH3 catalyzes the irreversible reaction of isocitrate and NAD+ to form alpha-ketoglutarate, CO2, and NADH. The enzyme is a heterooctamer containing two copies of a heterotetramer of two IDH3A, one IDH3B, one IDH3G, and two Mn++ (PDB 7CE3; Sun et al., 2020; Dange and Colman, 2010). It is activated by ADP (Soundar et al., 2003, 2006; Bzymek and Colman, 2007) and inhibited by NADH and high concentrations of ATP (Cohen & Colman, 1972; Sun et al., 2020). This is the first of four oxidation reactions in the citric acid cycle and the first decarboxylation.

Mutations in the IDH3A, IDH3B gene can cause retinitis pigmentosa (RP46; MIM:612572; RP90; MIM:619007) (Hartong et al., 2008).

Preceded by: ACO2 isomerizes citrate

Literature references

Berson, EL., McGee, TL., Dange, M., Dryja, TP., Hartong, DT., Colman, RF. (2008). Insights from retinitis pigmentosa into the roles of isocitrate dehydrogenases in the Krebs cycle. *Nat Genet, 40*, 1230-4. ↗

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Park, JH., Colman, RF., Soundar, S. (2003). Evaluation by mutagenesis of the importance of 3 arginines in alpha, beta, and gamma subunits of human NAD-dependent isocitrate dehydrogenase. *J Biol Chem, 278*, 52146-52153. ↗

Dange, M., Colman, RF. (2010). Each conserved active site tyr in the three subunits of human isocitrate dehydrogenase has a different function. *J Biol Chem, 285*, 20520-5. ↗

Bzymek, KP., Colman, RF. (2007). Role of alpha-Asp181, beta-Asp192, and gamma-Asp190 in the distinctive subunits of human NAD-specific isocitrate dehydrogenase. *Biochemistry, 46*, 5391-7. ↗

Editions

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

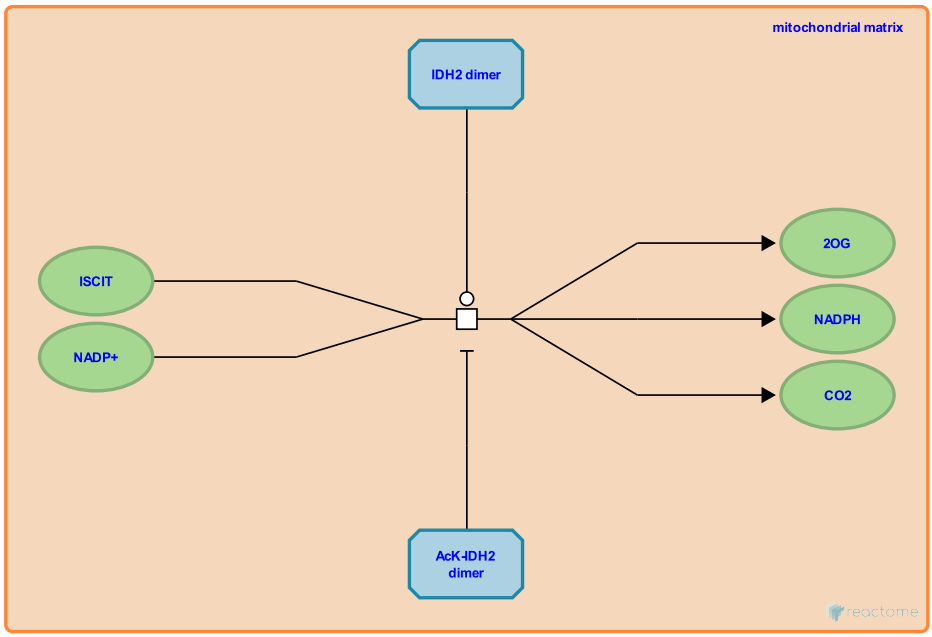
IDH2 dimer decarboxylates isocitrate ↗

Location: Citric acid cycle (TCA cycle)

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).

Preceded by: ACO2 isomerizes citrate, NNT dimer transfers proton from NADPH to NAD+

Followed by: NNT dimer transfers proton from NADPH to NAD+

Literature references

Berson, EL., McGee, TL., Dange, M., Dryja, TP., Hartong, DT., Colman, RF. (2008). Insights from retinitis pigmentosa into the roles of isocitrate dehydrogenases in the Krebs cycle. *Nat Genet, 40*, 1230-4. ↗

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. ↗

Ochoa, S. (1948). Biosynthesis of tricarboxylic acids by carbon dioxide fixation; enzymatic mechanisms. *J Biol Chem, 174*, 133-57. ↗

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. ↗

Bahnson, BJ., Ceccarelli, C., Ariyaratne, N., Grodsky, NB., Colman, RF. (2002). Crystal structure of porcine mitochondrial NADP+-dependent isocitrate dehydrogenase complexed with Mn2+ and isocitrate. Insights into the enzyme mechanism. *J Biol Chem, 277*, 43454-62. ↗

Editions

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

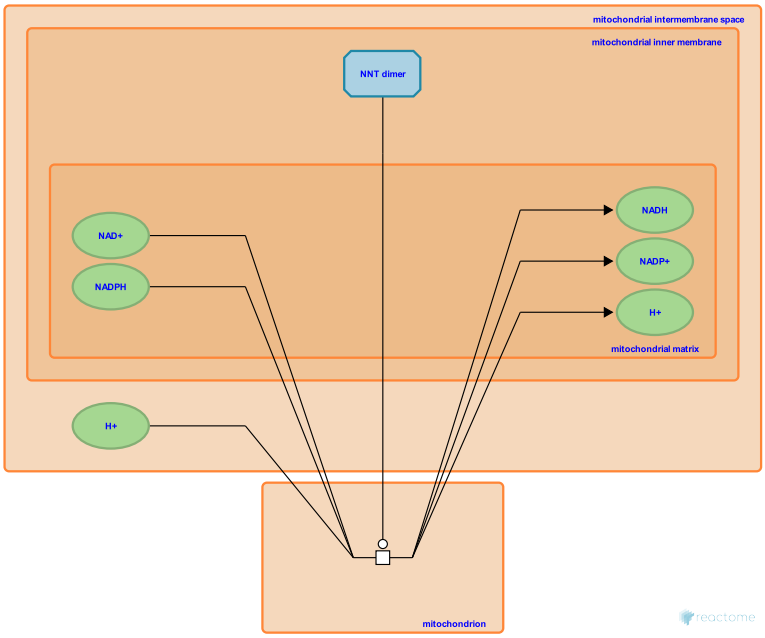
NNT dimer transfers proton from NADPH to NAD+ ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-450971

Type: transition

Compartments: mitochondrion



NNT (nicotinamide nucleotide transhydrogenase) associated with the inner mitochondrial membrane catalyzes the reaction of mitochondrial NADPH and NAD+ to form NADP+ and NADH. The reaction is coupled to the translocation of a proton across the inner mitochondrial membrane into the mitochondrial matrix (Arkblad et al., 1996; White et al., 2000). The active form of NNT is inferred to be a homodimer based on the known structure of its bovine homolog (Yamaguchi & Hatefi, 1991) and the structure of the ovine homolog (Kampjut & Sazanow, 2019). Mutations in NNT can lead to glucocorticoid deficiency (GCCD4; MIM:614736; reviewed in Francisco et al., 2021).

Preceded by: IDH2 dimer decarboxylates isocitrate

Followed by: IDH2 dimer decarboxylates isocitrate

Literature references

Arkblad, EL., Rydström, J., Betsholtz, C. (1996). The cDNA sequence of proton-pumping nicotinamide nucleotide transhydrogenase from man and mouse. *Biochim Biophys Acta, 1273*, 203-5. ↗

Yamaguchi, M., Hatefi, Y. (1991). Mitochondrial energy-linked nicotinamide nucleotide transhydrogenase. Membrane topography of the bovine enzyme. *J Biol Chem, 266*, 5728-35. ↗

Figueira, TR., Francisco, A., Castilho, RF. (2022). Mitochondrial NAD(P)⁺ Transhydrogenase: From Molecular Features to Physiology and Disease. *Antioxid Redox Signal, 36*, 864-884. ↗

Peake, SJ., Jackson, JB., Leonard, G., McSweeney, S., White, SA., Cotton, NP. (2000). The high-resolution structure of the NADP(H)-binding component (dIII) of proton-translocating transhydrogenase from human heart mitochondria. *Structure, 8*, 1-12. ↗

Sazanov, LA., Kampjut, D. (2019). Structure and mechanism of mitochondrial proton-translocating transhydrogenase . *Nature, 573*, 291-295. ↗

Editions

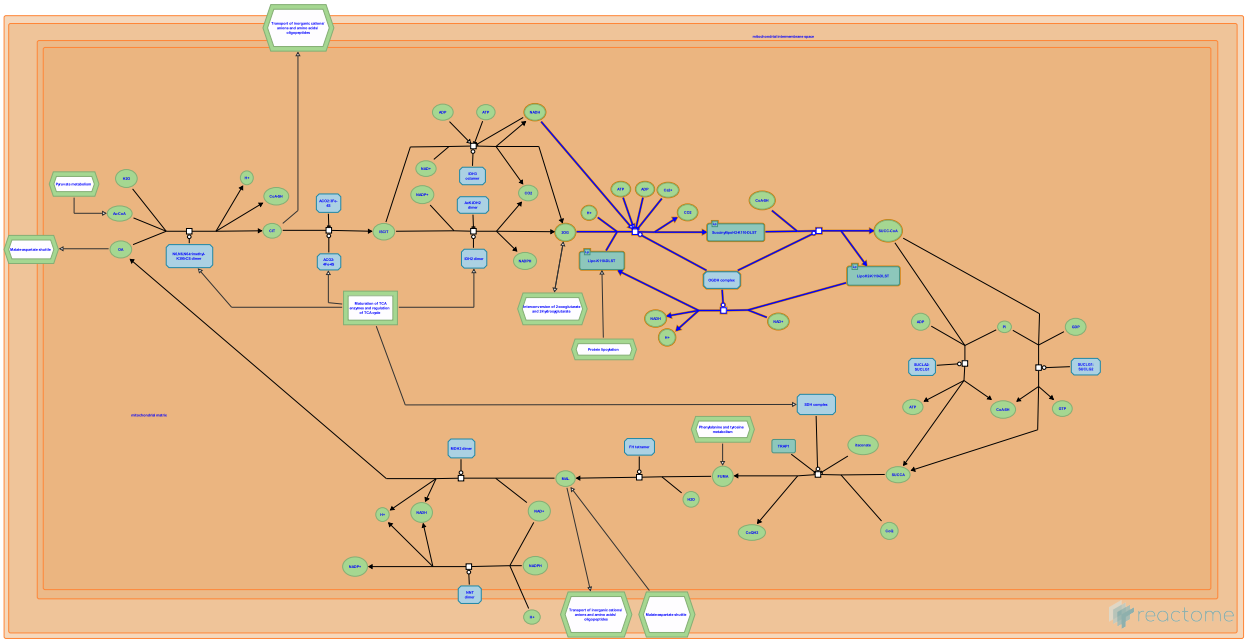
2009-12-26	Authored	D'Eustachio, P.
2024-02-15	Reviewed	Hill, DP.

OGDH complex synthesizes succinyl-CoA from 2-OG ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-9853506

Compartments: mitochondrial matrix



The mitochondrial alpha-oxoglutarate dehydrogenase complex (αOGDH, αKGDH, OGDHC) catalyzes the reaction of 2-oxoglutarate (2OG), CoASH, and NAD+ to form succinyl-CoA, CO2, and NADH. The enzyme complex ("metabolon") contains multiple copies of three different proteins, E1 (OGDH), E2 (DLST), and E3 (DLD), each with distinct catalytic activities (Reed and Hackert 1990; Zhou et al 2001). Specifically, it is composed of a core of 24 E2 subunits exhibiting octahedral symmetry. To these subunits are bound up to six E1 dimers and to each of these is bound an E3 dimer (Nagy et al., 2021; Skalidis et al., 2023) and to an adaptive MRPS36 unit (Hevler et al., 2023). The reaction starts with the oxidative decarboxylation of 2OG catalyzed by E1alpha and beta (alpha ketoglutarate dehydrogenase). Lipoamide cofactor associated with E2 is reduced at the same time. Next, the succinyl group derived from alpha ketoglutarate is transferred to coenzyme A in two steps catalyzed by E2 (dihydrolipolyl transacetylase). Finally, the oxidized form of lipoamide is regenerated and electrons are transferred to NAD+ in two steps catalyzed by E3 (dihydrolipoyl dehydrogenase). The biochemical details of this reaction have been worked out first with alpha ketoglutarate dehydrogenase complex and subunits purified from bovine tissue (McCartney et al. 1998).

Generation of reactive oxygen species by OGDHC is a major source of mitochondrial oxidative stress under certain pathological conditions.

Literature references

Reed, LJ., Hackert, ML. (1990). Structure-function relationships in dihydrolipoamide acyltransferases. *J Biol Chem, 265*, 8971-4. ↗

Hevler, JF., Albanese, P., Cabrera-Orefice, A., Scheltema, RA., Arnold, S., Potter, A. et al. (2023). MRPS36 provides a structural link in the eukaryotic 2-oxoglutarate dehydrogenase complex. *Open Biol, 13*, 220363. ↗

Zambo, Z., Jordan, F., Adam-Vizi, V., Novaček, J., Ambrus, A., Szabo, E. et al. (2021). Structure of the dihydrolipoamide succinyltransferase (E2) component of the human alpha-ketoglutarate dehydrogenase complex (hKGDHc) revealed by cryo-EM and cross-linking mass spectrometry: Implications for the overall hKGDHc structure. *Biochim Biophys Acta Gen Subj, 1865*, 129889. ↗

Reed, LJ., Stoops, JK., McCarthy, DB., O'Connor, CM., Zhou, ZH. (2001). The remarkable structural and functional organization of the eukaryotic pyruvate dehydrogenase complexes. *Proc Natl Acad Sci U S A, 98*, 14802-7. ↗

O'Reilly, FJ., Kastritis, PL., Skalidis, I., Belapure, J., Tüting, C., Fratini, M. et al. (2023). Structural analysis of an endogenous 4-megadalton succinyl-CoA-generating metabolon. *Commun Biol, 6*, 552. ↗

Editions

2023-11-05	Authored	Stephan, R.
2024-01-22	Edited	Stephan, R.
2024-02-15	Reviewed	Hill, DP.

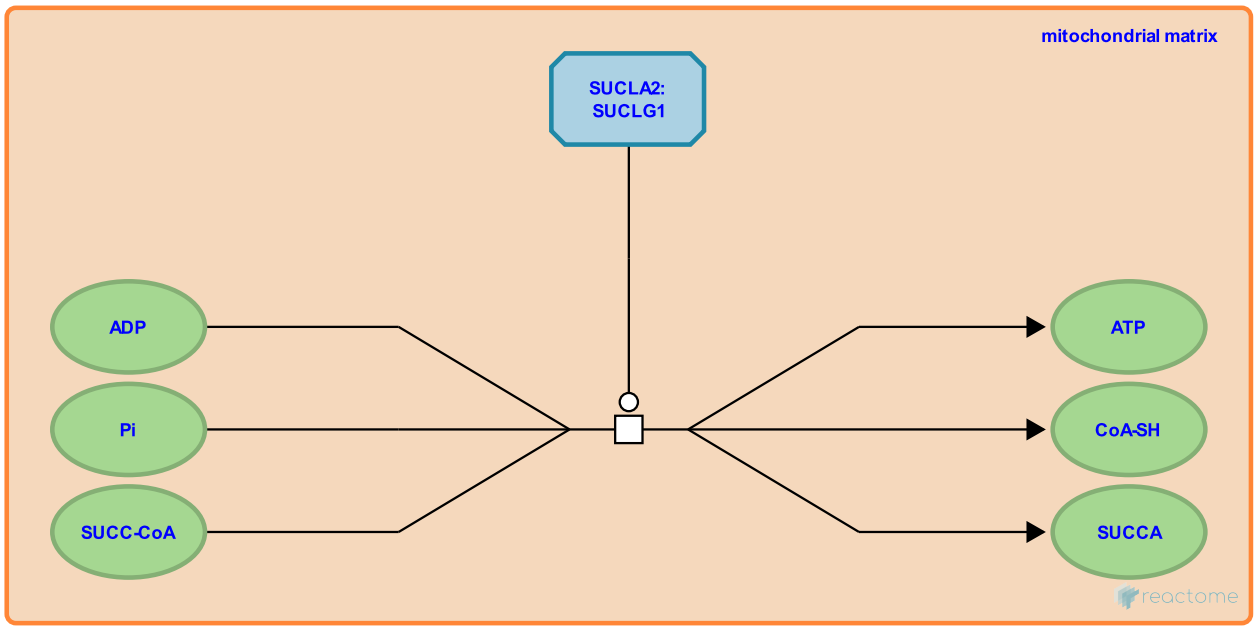
SUCLG1/A2 cleaves succinyl-CoA ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-70997

Type: transition

Compartments: mitochondrial matrix



Mitochondrial succinate CoA ligase (ADP-forming) catalyzes the reversible conversion of succinyl CoA to succinate plus Coenzyme A, coupled to the conversion of ADP and orthophosphate to ATP.

The enzyme catalyzing the reaction in vertebrates is a heterodimer of SUCLG1 and SUCLA2 that occurs in two isoforms. The enzymes have been purified from pigeon and rat tissue and characterized in detail. Both isoforms, an alpha:betaA heterodimer and an alpha:betaG heterodimer, catalyze the reversible conversion of succinyl CoA to succinate plus Coenzyme A. The alpha:betaA heterodimer couples this conversion to the synthesis of ATP from ADP and orthophosphate, while the alpha:betaG heterodimer couples it to the synthesis of GTP from GDP and orthophosphate (Johnson et al. 1998a,b; Lambeth et al. 2004). Consistent with these results in model systems, patients homozygous for a mutant allele of the gene encoding the ADP enzyme beta subunit, SUCLA2, are deficient in succinyl CoA ligase activity (Elpeleg et al. 2005).

Both isoforms are found in vivo, and appear to be expressed at different levels in various tissues. Their relative contributions to the flux of carbon atoms through the TCA cycle are unknown. Genetic and biochemical data suggest that the alpha:betaA isoform may be required to catalyze the reverse reaction, conversion of succinate, Coenzyme A, and ATP to succinyl CoA, ADP, and orthophosphate for heme biosynthesis (Furuyama and Sassa 2000).

Mutations in SUCLG1 are the cause of the infantile metabolic disease named mitochondrial DNA depletion syndrome 9 (MTDPS9; MIM:245400; reviewed by Molaei Ramsheh et al., 2020).

Followed by: SDH complex dehydrogenates succinate

Literature references

Sanadi, DR., Ayengar, P., Gibson, M. (1954). Guanosine triphosphate, the primary product of phosphorylation coupled to the breakdown of succinyl coenzyme A. *Biochim Biophys Acta, 14*, 434-6. ↗

Rahman, S., Elpeleg, O., Hershkovitz, E., Miller, C., Bondi-Rubinstein, G., Saada, A. et al. (2005). Deficiency of the ADP-forming succinyl-CoA synthase activity is associated with encephalomyopathy and mitochondrial DNA depletion. *Am J Hum Genet, 76*, 1081-6. ↗

Sassa, S., Furuyama, K. (2000). Interaction between succinyl CoA synthetase and the heme-biosynthetic enzyme ALAS-E is disrupted in sideroblastic anemia. *J Clin Invest, 105*, 757-64. ↗

Mehus, JG., Lambeth, DO., Milavetz, BI., Tews, KN., Johnson, JD. (1998). Genetic evidence for the expression of ATP- and GTP-specific succinyl-CoA synthetases in multicellular eucaryotes. *J Biol Chem, 273*, 27580-6. ↗

Lambeth, DO., Frohlich, D., Milavetz, BI., Adkins, S., Tews, KN. (2004). Expression of two succinyl-CoA synthetases with different nucleotide specificities in mammalian tissues. *J Biol Chem, 279*, 36621-4. ↗

Editions

2009-12-26	Revised	D'Eustachio, P.
2024-02-15	Reviewed	Hill, DP.
2024-08-27	Edited	D'Eustachio, P.

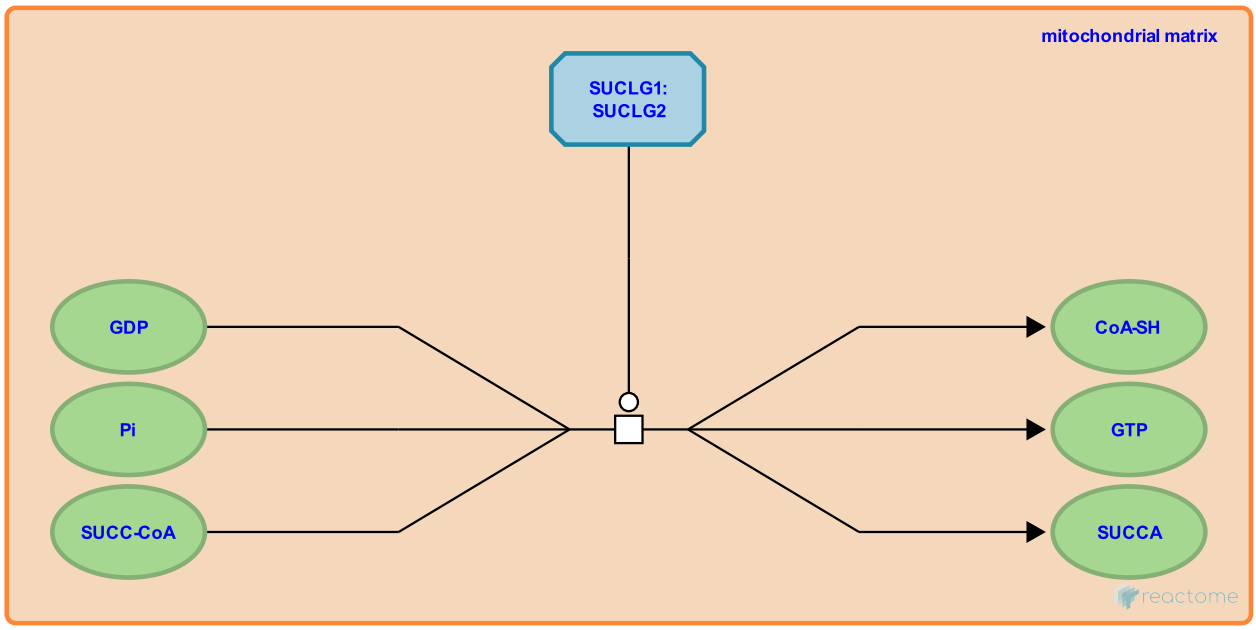
SUCLG1/G2 cleaves succinyl-CoA ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-71775

Type: transition

Compartments: mitochondrial matrix



Mitochondrial succinate CoA ligase (GDP-forming) catalyzes the reversible conversion of succinyl CoA to succinate plus Coenzyme A, coupled to the conversion of GDP and orthophosphate to GTP. The enzyme is a heterodimer containing SUCLG1 and SUCLG2 monomers.

The enzyme catalyzing the reaction in vertebrates is a heterodimer that occurs in two isoforms. The enzymes have been purified from pigeon and rat tissue and characterized in detail. Both isoforms, an alpha:betaA heterodimer and an alpha:betaG heterodimer, catalyze the reversible conversion of succinyl CoA to succinate plus Coenzyme A. The alpha:betaA heterodimer couples this conversion to the synthesis of ATP from ADP and orthophosphate, while the alpha:betaG heterodimer couples it to the synthesis of GTP from GDP and orthophosphate (Johnson et al. 1998a,b; Lambeth et al. 2004). Consistent with these results in model systems, patients homozygous for a mutant allele of the gene encoding the ADP enzyme beta subunit, SUCLA2, are deficient in succinyl CoA ligase activity (Elpeleg et al. 2005).

Both isoforms are found in vivo, and appear to be expressed at different levels in various tissues. Their relative contributions to the flux of carbon atoms through the TCA cycle are unknown. Genetic and biochemical data suggest that the alpha:betaA isoform may be required to catalyze the reverse reaction, conversion of succinate, Coenzyme A, and ATP to succinyl CoA, ADP, and orthophosphate for heme biosynthesis (Furuyama and Sassa 2000).

Mutations in SUCLG1 are the cause of the infantile metabolic disease named mitochondrial DNA depletion syndrome 9 (MTDPS9; MIM:245400; reviewed by Molaei Ramsheh et al., 2020).

Followed by: SDH complex dehydrogenates succinate

Literature references

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Editions

2009-12-26	Revised	D'Eustachio, P.
2024-02-15	Reviewed	Hill, DP.
2024-08-27	Edited	D'Eustachio, P.

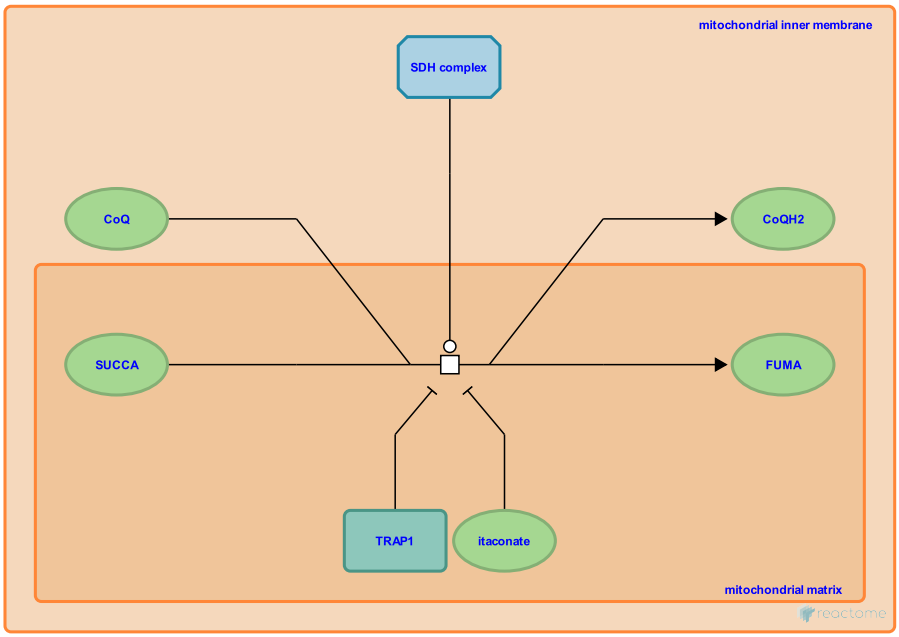
SDH complex dehydrogenates succinate ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-70994

Type: transition

Compartments: mitochondrial matrix, mitochondrial inner membrane



The succinate dehydrogenase complex (SDH, complex II), associated with the inner mitochondrial membrane, catalyzes the dehydrogenation of succinate to fumarate, reducing ubiquinone (Q10) to ubiquinol (Q10H2) on the membrane part of the enzyme. FAD is covalently bound to His-99 of the SDHA subunit (PDB 6VAX; Sharma et al., 2020). The redox potential of Q10H2 is then used in the electron transfer chain to drive a proton motive force to generate ATP (Devertanian et al., 1964; Renkema et al., 2015)

The endogenous metabolite itaconate has been shown to bind and inhibit Complex II, leading to an accumulation of succinate. Elevated succinate levels modulate immune, hypoxic and metabolic reprogramming pathways, including during oncogenesis (Booth et al, 1952; Selak et al., 2005; Cordes et al., 2016; reviewed by Hayash et al., 2018; Peace & O'Neill, 2022). The mitochondrial heat shock protein 75 kDa (TRAP1) inhibits Complex II which elicits respiratory downregulation, leading to a pseudohypoxic state. This state is caused by succinate-dependent HIF1-alpha stabilisation which, in turn, can promote tumorigenesis (Sciacovelli et al. 2013, Yoshida et al. 2013, Guzzo et al. 2014).

Mutations in all four SDH subunits (SDHA, SDHB, SDHC, SDHD) have been reported, leading to distinct phenotypes of SDH deficiency and tumors (reviewed by Briere et al., 2005).

Preceded by: SUCLG1/A2 cleaves succinyl-CoA, SUCLG1/G2 cleaves succinyl-CoA

Followed by: FH tetramer hydrates fumarate to L-malate

Literature references

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Lee, MJ., Miyajima, N., Picard, D., Trepel, J., Tsutsumi, S., Tatokoro, M. et al. (2013). Molecular chaperone TRAP1 regulates a metabolic switch between mitochondrial respiration and aerobic glycolysis. *Proc. Natl. Acad. Sci. U.S.A., 110*, E1604-12. ↗

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Editions

2009-12-26	Revised	D'Eustachio, P.
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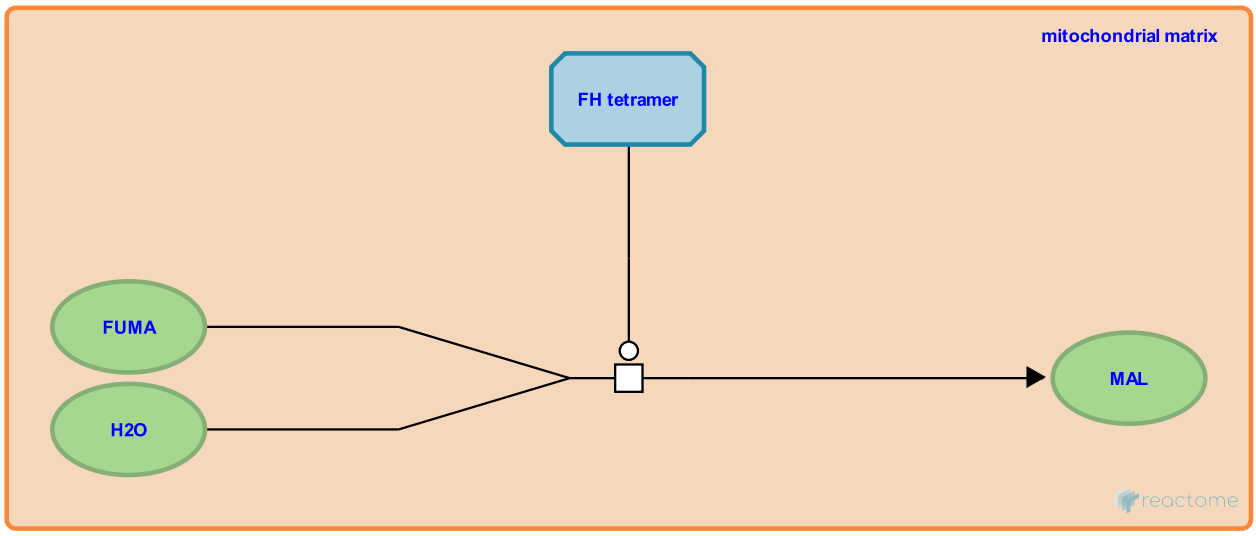
FH tetramer hydrates fumarate to L-malate ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-70982

Type: transition

Compartments: mitochondrial matrix



Mitochondrial fumarate hydratase (FH) tetramer catalyzes the reversible reaction of fumarate and water to form malate, the seventh step of the TCA cycle (Ajalla Aleixo et al., 2019; Wang et al., 2020). Mutations in the FH gene can lead to fumarase deficiency (FMRD, MIM:606812) or to leiomyomatosis and renal cell cancer (HLRCC, MIM:150800) (Bourgeron et al., 1994; reviewed by Giallongo et al, 2023).

Preceded by: SDH complex dehydrogenates succinate

Followed by: MDH2 dimer dehydrogenates MAL

Literature references

Lehming, N., Lim, TK., Lin, Q., Ramamurthy, D., Tan, J., Yip, J. et al. (2020). Post-translational Modifications of Fumarase Regulate its Enzyme Activity and Function in Respiration and the DNA Damage Response. *J Mol Biol, 432*, 6108-6126. ↗

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Editions

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

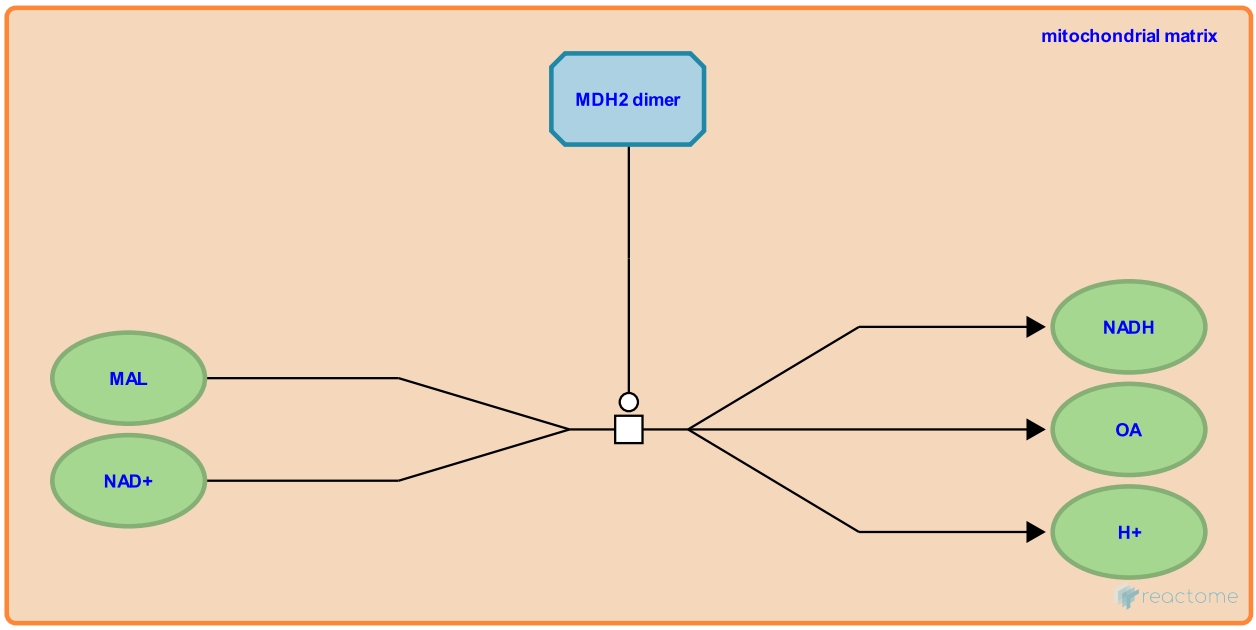
MDH2 dimer dehydrogenates MAL ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-70979

Type: transition

Compartments: mitochondrial matrix



Mitochondrial malate dehydrogenase (MDH2) dimer catalyzes the reversible reaction of malate and NAD+ to form oxaloacetate (OA) and NADH + H+ (Luo et al. 2006; Eo et al., 2022). This reaction is highly endergonic but is pulled in the direction annotated here when the TCA cycle is operating. The active enzyme is a palmitoylated homodimer (Sanchez et al. 1998; Pei et al., 2022). Mutations in MDH2 can cause infantile epileptic encephalopathy (DEE51, MIM:617339; see Priestley et al., 2022).

Preceded by: FH tetramer hydrates fumarate to L-malate

Followed by: CS acetylates OA to citrate

Literature references

Aggarwal, A., Gowda, VK., Jolín García, PC., Hong, X., Srinivasan, VM., Pace, LM. et al. (2022). Malate dehydrogenase 2 deficiency is an emerging cause of pediatric epileptic encephalopathy with a recognizable biochemical signature. *Mol Genet Metab Rep, 33*, 100931. ↗

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Ahn, HC., Eo, Y., Duong, MTH. (2022). Structural Comparison of hMDH2 Complexed with Natural Substrates and Cofactors: The Importance of Phosphate Binding for Active Conformation and Catalysis. *Biomolecules, 12*. ↗

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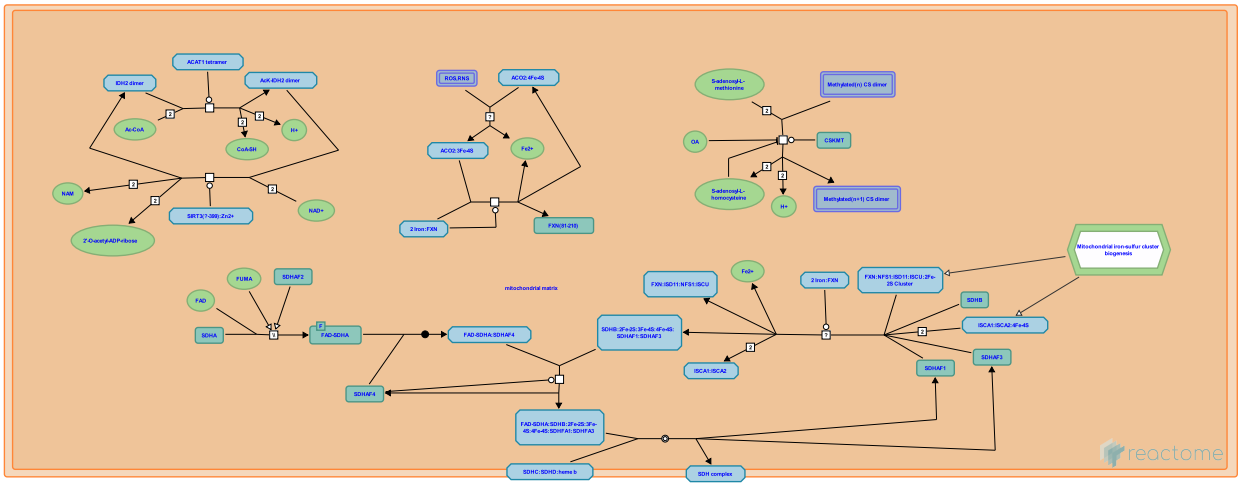
2024-02-15	Reviewed	Hill, DP.

Maturation of TCA enzymes and regulation of TCA cycle ↗

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-9854311

Compartments: mitochondrion



(Citrate-synthase)-lysyl-methyltransferase (CSKMT, METTL12) transfers three methyl groups from S-adenosylmethionine (SAM) to lysine-395 of citrate synthase (CS). The expression of CSKMT is low or absent in many normal organ tissues, but the trimethylated form is predominant in most cell lines tested. The modification is evolutionarily conserved, with contradicting reports on the activity of modified CS, while the effect on the whole CS/ACO2 metabolon was not investigated. Oxalocetate inhibits methyltransferase activity (Malecki et al., 2017; Rhein et al., 2017; reviewed in Qi et al., 2023).

Literature references

Arnold, PK., Finley, LWS. (2023). Regulation and function of the mammalian tricarboxylic acid cycle. *J Biol Chem, 299*, 102838. ↗

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2023-11-25	Authored	Stephan, R.
2024-02-15	Edited	D'Eustachio, P.
2024-02-15	Reviewed	Hill, DP.
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