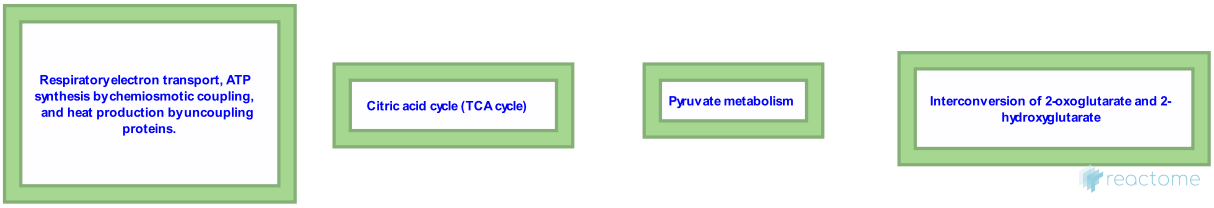
Aerobic respiration and respiratory electron transport



Birney, E., D'Eustachio, P., Ferguson, SJ., Hill, DP., Jassal, B., Rush, MG., Schmidt, EE., Stephan, R.

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20/04/2024

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

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. ↗

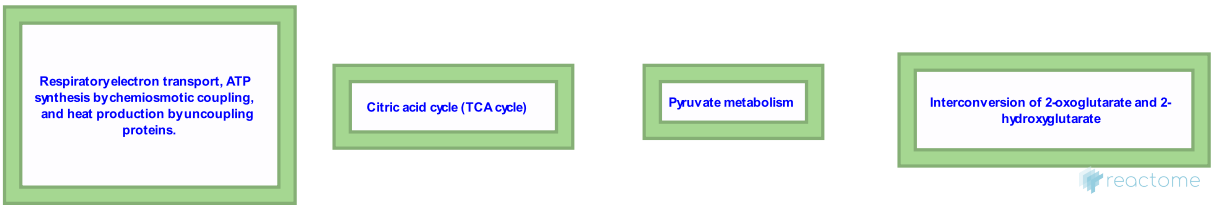
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 5 pathways (see Table of Contents)

Aerobic respiration and respiratory electron transport ↗

Stable identifier: R-HSA-1428517



Pyruvate metabolism and the citric acid (TCA) cycle together link the processes of energy metabolism in a human cell with one another and with key biosynthetic reactions. Pyruvate, derived from the reversible oxidation of lactate or transamination of alanine, can be converted to acetyl CoA. Other sources of acetyl CoA include breakdown of free fatty acids and ketone bodies in the fasting state. Acetyl CoA can enter the citric acid cycle, a major source of reducing equivalents. These reducing equivalents are re-oxidized back to NAD+ in the electron transport chain (ETC), coupling this process with the export of protons across the inner mitochondrial membrane. The chemiosmotic gradient created is used to drive ATP synthesis.

In addition to its role in energy generation, the citric acid cycle is a source of carbon skeletons for amino acid metabolism and other biosynthetic processes. One such process included here is the interconversion of 2-hydroxyglutarate, probably derived from porphyrin and amino acid metabolism, and 2-oxoglutarate (alpha-ketoglutarate), a citric acid cycle intermediate.

Editions

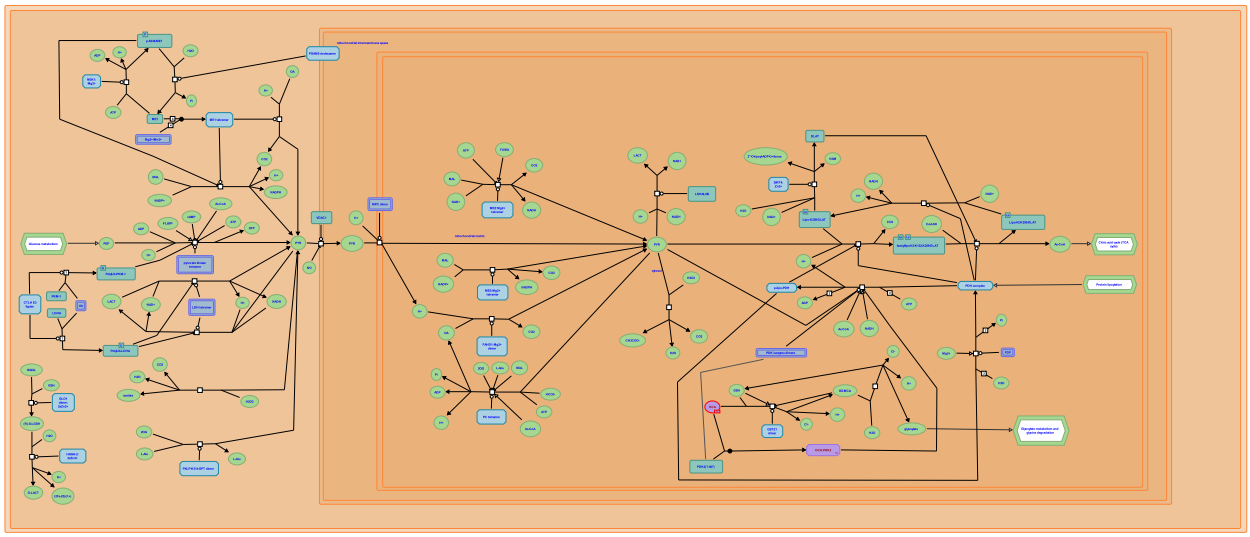
2003-11-03	Authored	Schmidt, EE., Birney, E., D'Eustachio, P.
2011-07-07	Edited	Jassal, B.
2024-02-20	Reviewed	Hill, DP.

Pyruvate metabolism ↗

Location: Aerobic respiration and respiratory electron transport

Stable identifier: R-HSA-70268

Compartments: cytosol, mitochondrial matrix, mitochondrial intermembrane space



Pyruvate sits at an intersection of key pathways of energy metabolism. It is the end product of glycolysis and the starting point for gluconeogenesis and can be generated by the transamination of alanine. The pyruvate dehydrogenase complex can convert it to acetyl CoA (Reed and Hackert 1990), which can enter the TCA cycle or serve as the starting point for the syntheses of long-chain fatty acids, steroids, and ketone bodies depending on the tissue and metabolic state in which it is formed. It also plays a central role in balancing the energy needs of various tissues in the body. Under conditions in which oxygen supply is limiting, e.g., in exercising muscle, or in the absence of mitochondria, e.g., in red blood cells, re-oxidation of NADH produced by glycolysis cannot be coupled to the generation of ATP. Instead, re-oxidation is coupled to the reduction of pyruvate to lactate. This lactate is released into the blood and taken up primarily by the liver, where it is oxidized to pyruvate and can be used for gluconeogenesis (Cori 1981). For a recent review, see Prochownik & Wang, 2021.

Literature references

Cori, CF. (1981). The glucose-lactic acid cycle and gluconeogenesis. *Curr Top Cell Regul, 18*, 377-87. ↗

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

Prochownik, EV., Wang, H. (2021). The Metabolic Fates of Pyruvate in Normal and Neoplastic Cells. *Cells, 10*. ↗

Editions

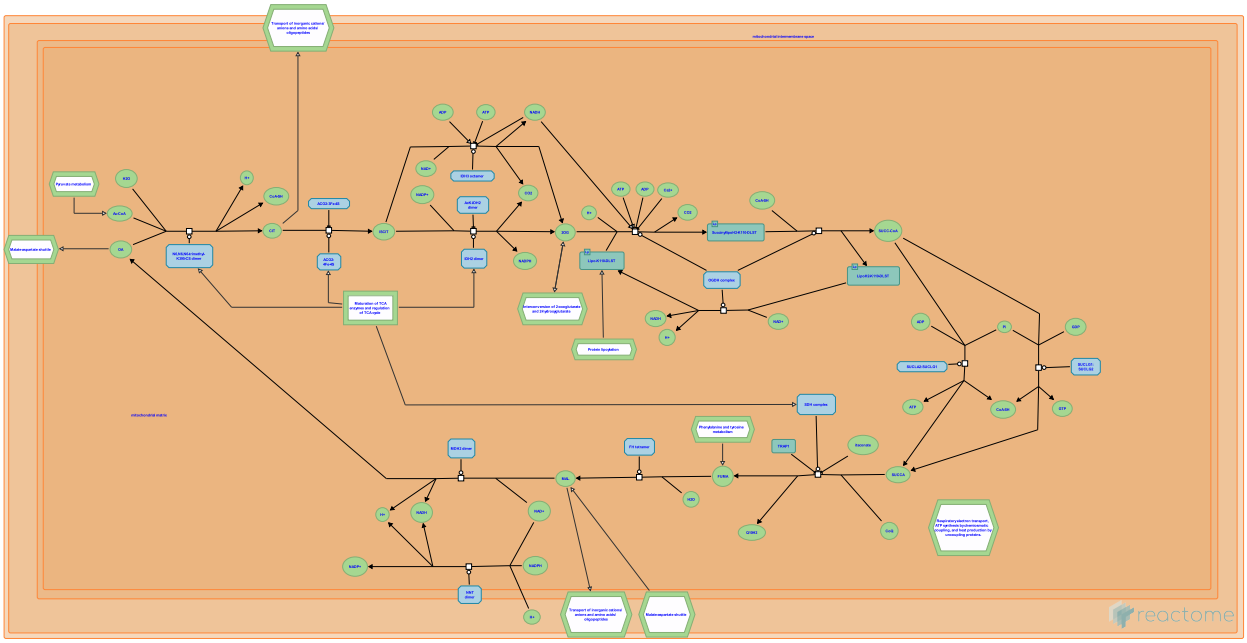
2009-12-18	Revised	D'Eustachio, P.
2024-02-15	Revised	Hill, DP.
2024-02-21	Edited	Stephan, R.
2024-03-01	Reviewed	Hill, DP.

Citric acid cycle (TCA cycle) ↗

Location: Aerobic respiration and respiratory electron transport

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

Krebs, HA., Johnson, WA., Salvin, E. (1938). The formation of citric and alpha-ketoglutaric acids in the mammalian body. *Biochem J, 32*, 113-117. ↗

Saito, T., Miyado, K., Suzuki, M., Kang, W. (2021). Emerging Role of TCA Cycle-Related Enzymes in Human Diseases. *Int J Mol Sci, 22*. ↗

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. ↗

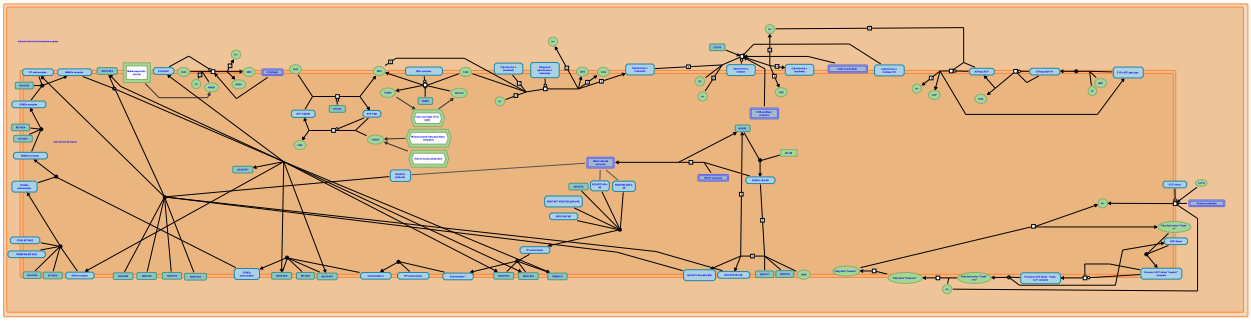
Editions

2003-01-28	Authored	Birney, E.
2009-12-26	Revised	D'Eustachio, P.
2024-02-15	Reviewed	Hill, DP.
2024-03-06	Edited	D'Eustachio, P.

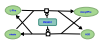
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins. ↗

Location: Aerobic respiration and respiratory electron transport

Stable identifier: R-HSA-163200



reactome



Oxidation of fatty acids and pyruvate in the mitochondrial matrix yield large amounts of NADH. The respiratory electron transport chain couples the re-oxidation of this NADH to NAD+ to the export of protons from the mitochonrial matrix, generating a chemiosmotic gradient across the inner mitochondrial membrane. This gradient is used to drive the synthesis of ATP; it can also be bypassed by uncoupling proteins to generate heat, a reaction in brown fat that may be important in regulation of body temperature in newborn children.

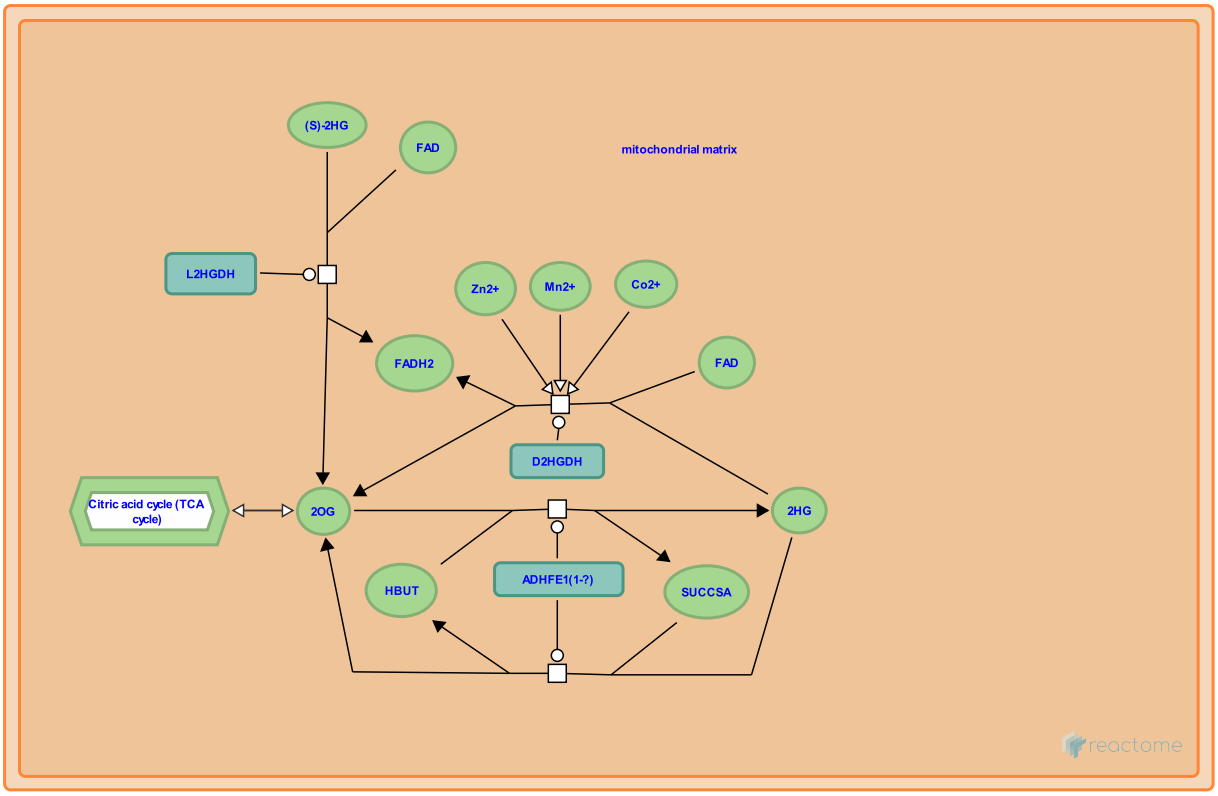
Editions

2005-04-21	Authored	Jassal, B.
2005-05-12	Reviewed	Ferguson, SJ.

Interconversion of 2-oxoglutarate and 2-hydroxyglutarate ↗

Location: Aerobic respiration and respiratory electron transport

Stable identifier: R-HSA-880009



The two stereoisomers of 2-hydroxyglutarate are normally converted to 2-oxoglutarate in the mitochondrial matrix, and can then be metabolized by the citric acid cycle. The physiological sources of 2-hydroxyglutarate have not been established although plausible hypotheses are that it is generated by lysine breakdown or as a byproduct of delta-aminolevulinate metabolism. The stereoisomers are oxidized to 2-oxoglutarate in FAD-dependent reactions catalyzed by the enzymes D2HGDH (specific for R(-)-2-hydroxyglutarate) and L2HGDH (specific for S(-)-2-hydroxyglutarate). An inherited deficiency in either enzyme is associated with accumulation of 2-hydroxyglutarate and variable neurological symptoms. R(-)-2-hydroxyglutarate also reacts reversibly with succinate semialdehyde to form 4-hydroxybutyrate and 2-oxoglutarate, catalyzed by ADHFE1. No deficiencies of this enzyme have been found in patients with elevated 2-hydroxyglutarate levels (Struys 2006).

Literature references

Keenan, MC., White, DW., Su, SM., Liau, LM., Yen, KE., Bittinger, MA. et al. (2009). Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature, 462*, 739-44. ↗

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Editions

2010-06-26	Authored, Edited	D'Eustachio, P.
2010-11-09	Reviewed	Jassal, B.
2011-01-31	Reviewed	Rush, MG.

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