Citric acid cycle (TCA cycle)

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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**


Reactome database release: 79

This document contains 1 pathway and 17 reactions (see Table of Contents)

https://reactome.org
**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). The NADH and FADH2 are then oxidized by the electron transport chain 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. Six additional reactions are included here. Three reversible reactions, the interconversions of citrate and isocitrate, of fumarate and malate, and of malate and oxaloacetate are annotated in both their canonical (forward) and reverse directions. The synthesis of succinate from succinyl-CoA can be coupled to the phosphorylation of either GDP (the canonical reaction) or ADP; both reactions are annotated. 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 reduction of NADP+, a reaction whose normal physiological function is unclear. Both reactions are annotated. Finally, a reaction is annotated in which reducing equivalents are transferred from NADPH to NAD+ coupled to proton import across the inner mitochondrial membrane.

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). Many of the molecular details of individual reactions were worked out by Ochoa and colleagues, largely...
through studies of enzymes purified from pig heart (Ochoa 1980). While the human homologues 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.

**Literature references**


**Editions**

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https://reactome.org
Acetyl-CoA + H2O + Oxaloacetate => Citrate + CoA

Location: Citric acid cycle (TCA cycle)

Stable identifier: R-HSA-70975