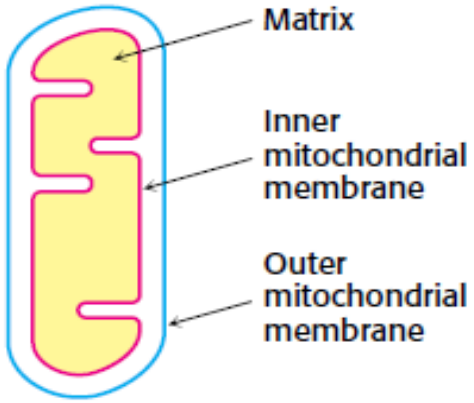
Krebs Cycle

Introduction:

- Most of the ATP generated in metabolism is provided by the aerobic processing of glucose.
- This process starts with the complete oxidation of glucose derivatives to carbon dioxide.
- This oxidation takes place in a series of reactions called the citric acid cycle , also known as the tricarboxylic acid (TCA) cycle or the Krebs cycle .
- The citric acid cycle is the final common pathway for the oxidation of fuel molecules — carbohydrates, fatty acids, and amino acids.
- Most fuel molecules enter the cycle as acetyl coenzyme A .

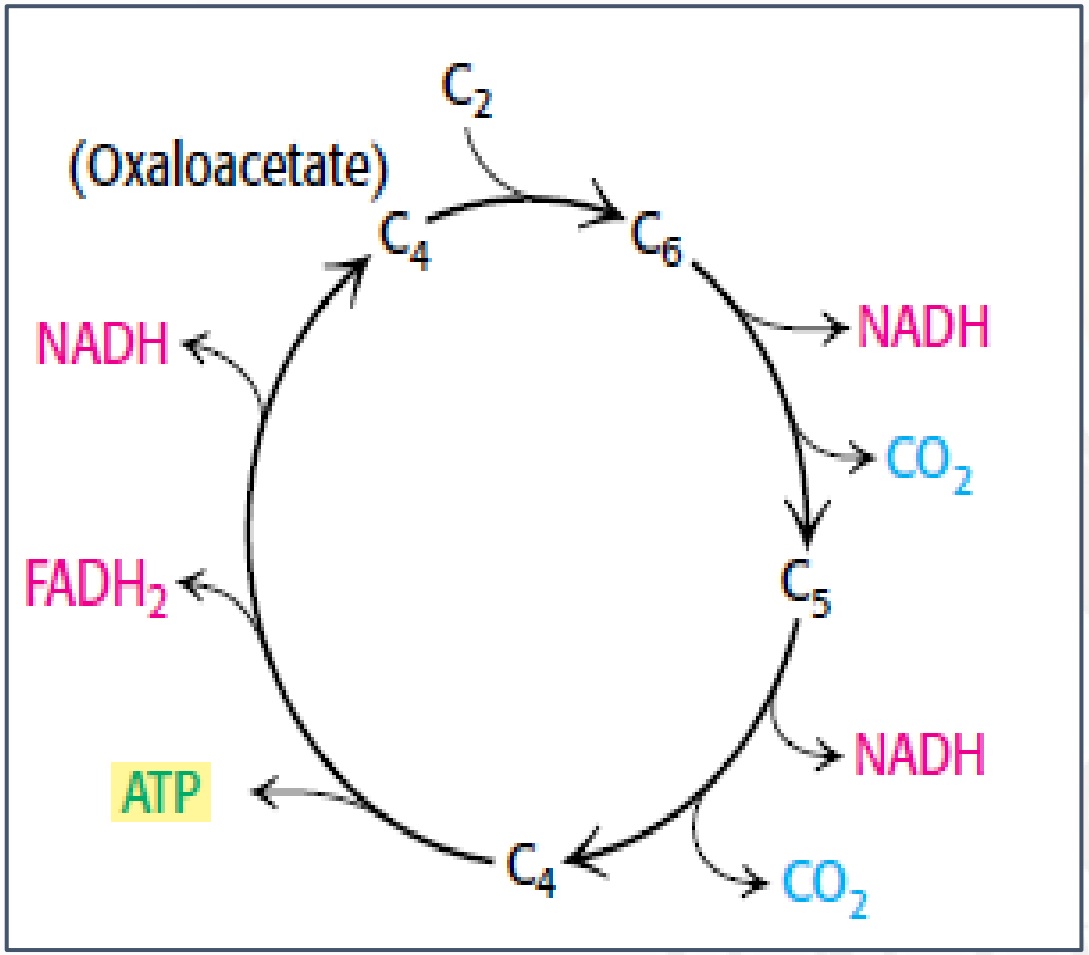
- Under aerobic conditions, the pyruvate generated from glucose is oxidatively decarboxylated to form acetyl CoA.

- The reactions of the citric acid cycle take place in the matrix of the mitochondria in contrast with those of glycolysis, which take place in the cytoplasm.



- The citric acid cycle is the central metabolic hub of the cell.

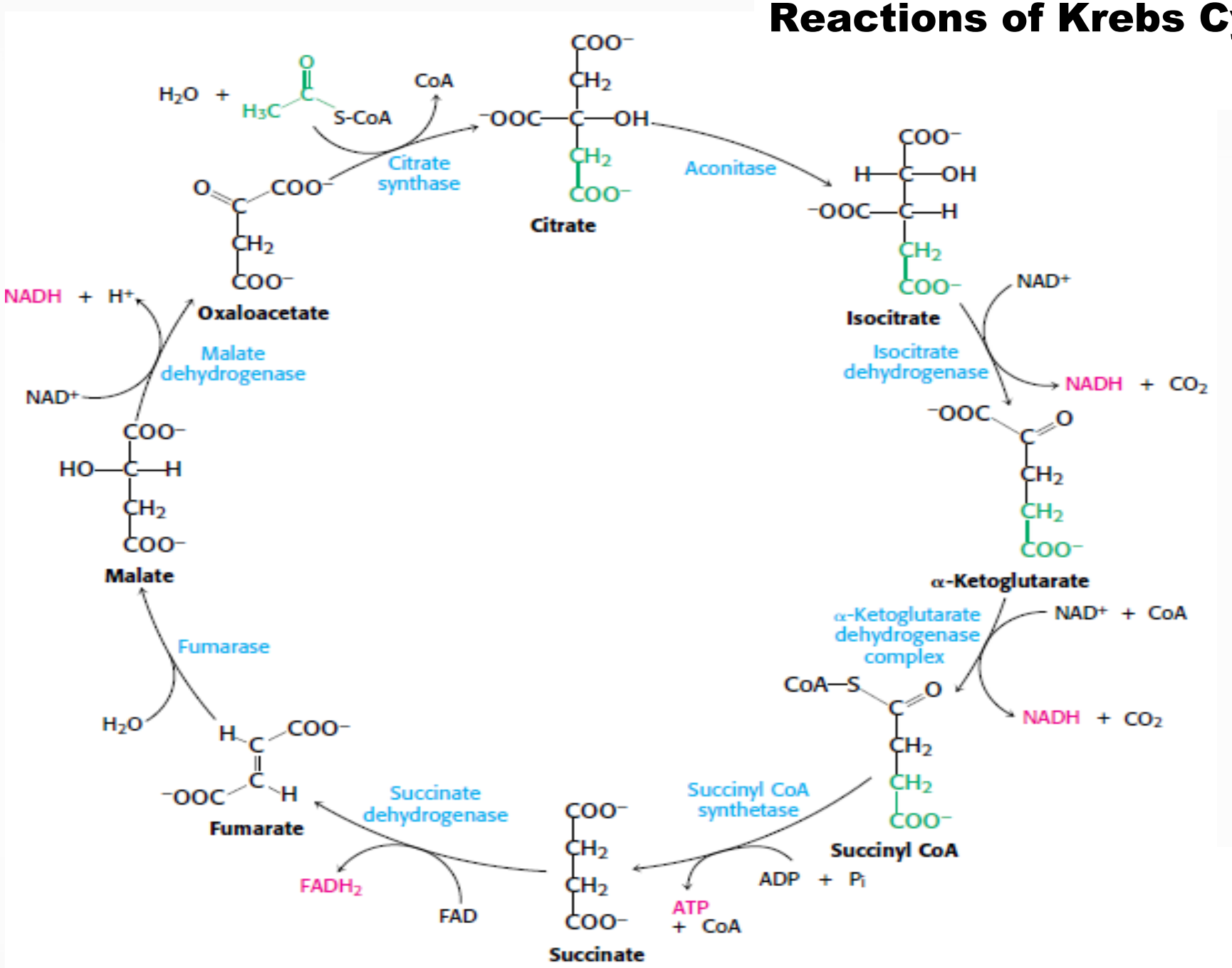
Overview of the citric acid cycle.



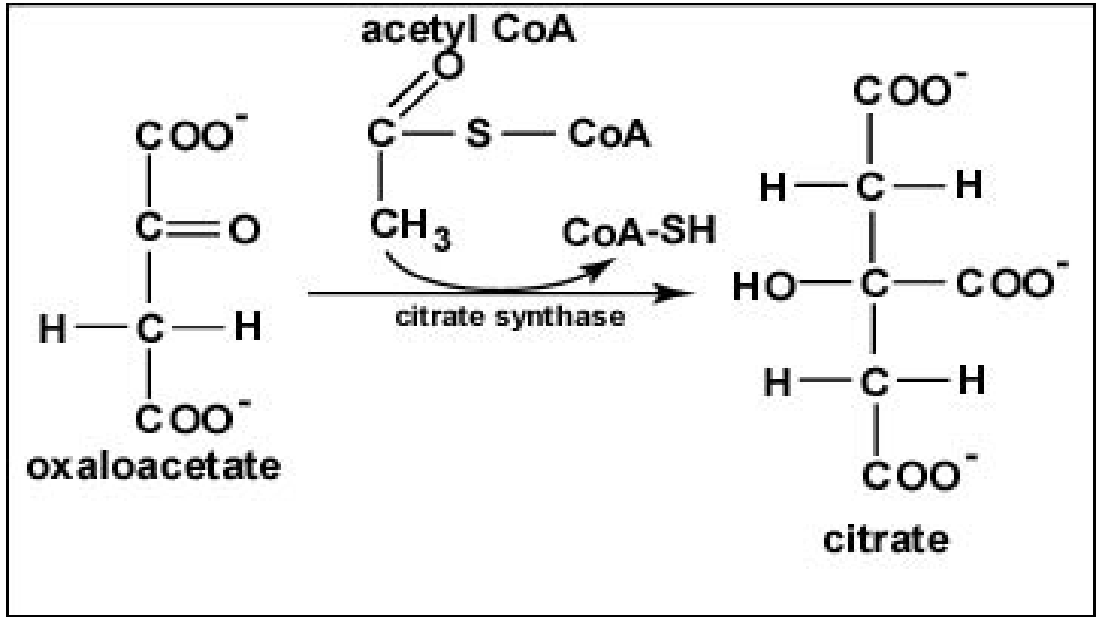
The citric acid cycle oxidizes two carbon units, producing

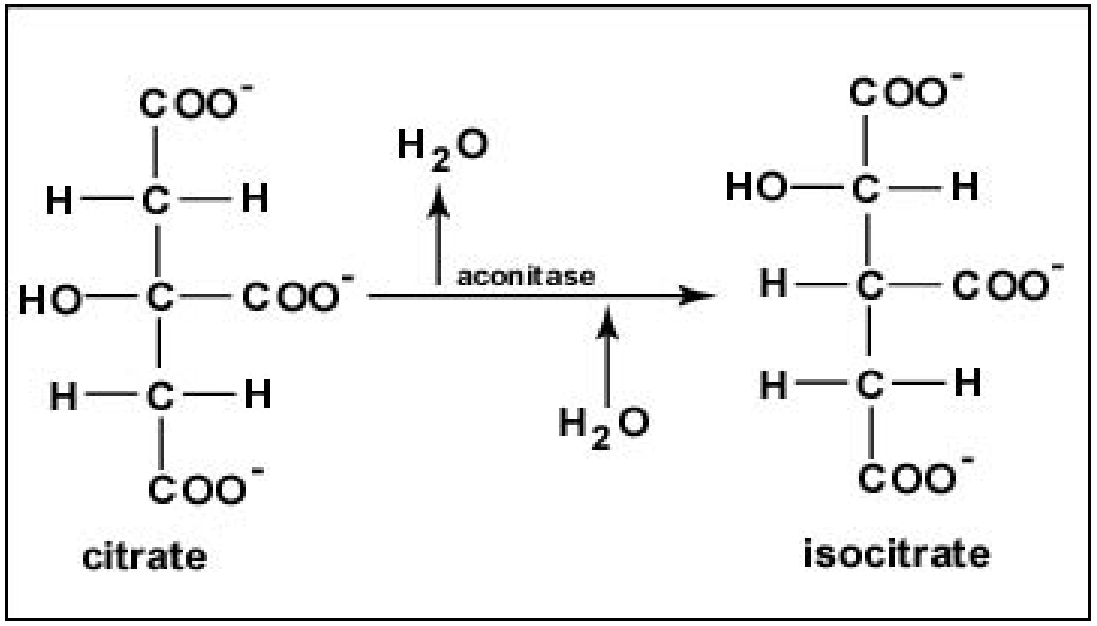
- Two molecules of CO2
- one molecule of ATP
- High-energy electrons in the form of NADH and FADH2.

Reactions of Krebs Cycle



Steps in Krebs Cycle



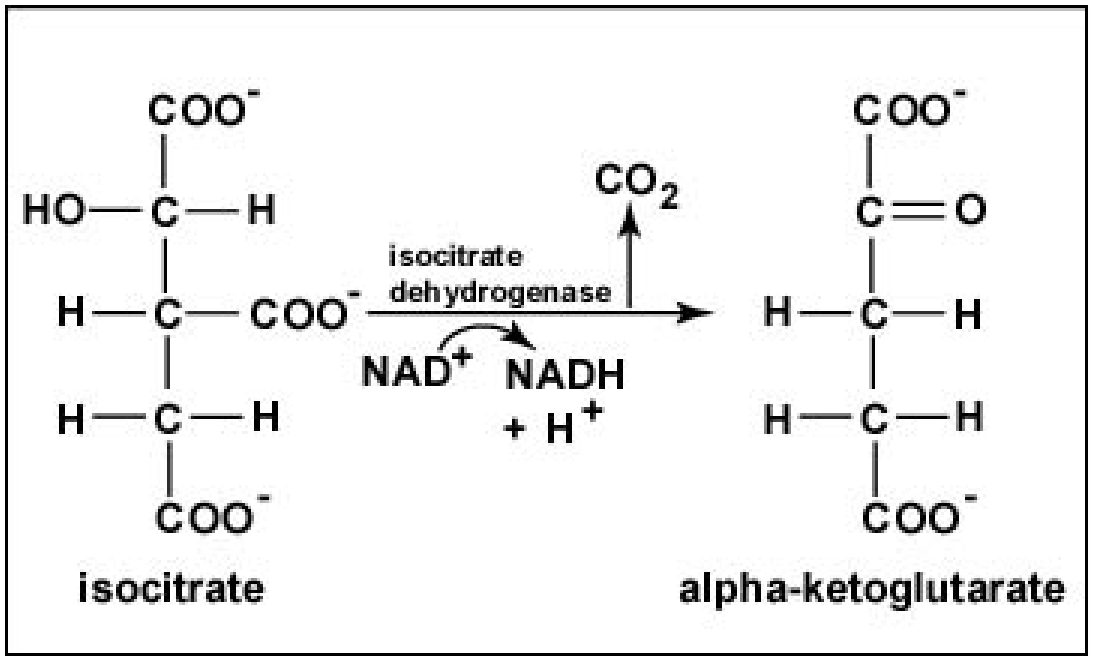


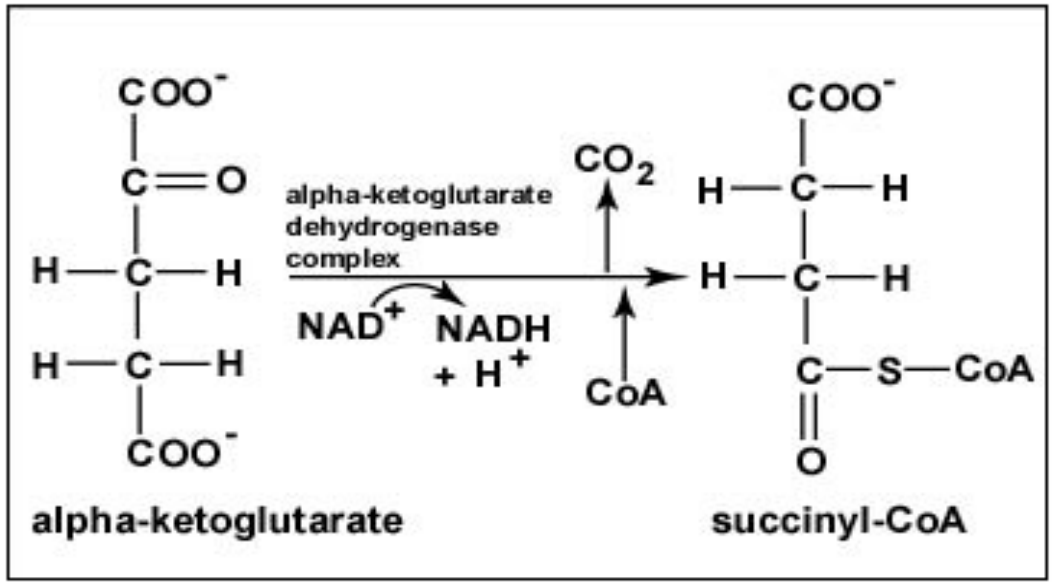
❖ **Citrate synthase forms citrate from oxaloacetate and acetyl coenzyme A**

- The citric acid cycle begins with the condensation of a four-carbon unit, oxaloacetate, and a two-carbon unit, the acetyl group of acetyl CoA.
- Oxaloacetate reacts with acetyl CoA and H2O to yield citrate and CoA.

❖ **Citrate is isomerized into isocitrate**

- Citrate is isomerized into isocitrate to enable the six-carbon unit to undergo oxidative decarboxylation.
- The isomerization of citrate is accomplished by a dehydration step followed by a hydration step.
- The enzyme catalyzing both steps is called aconitase



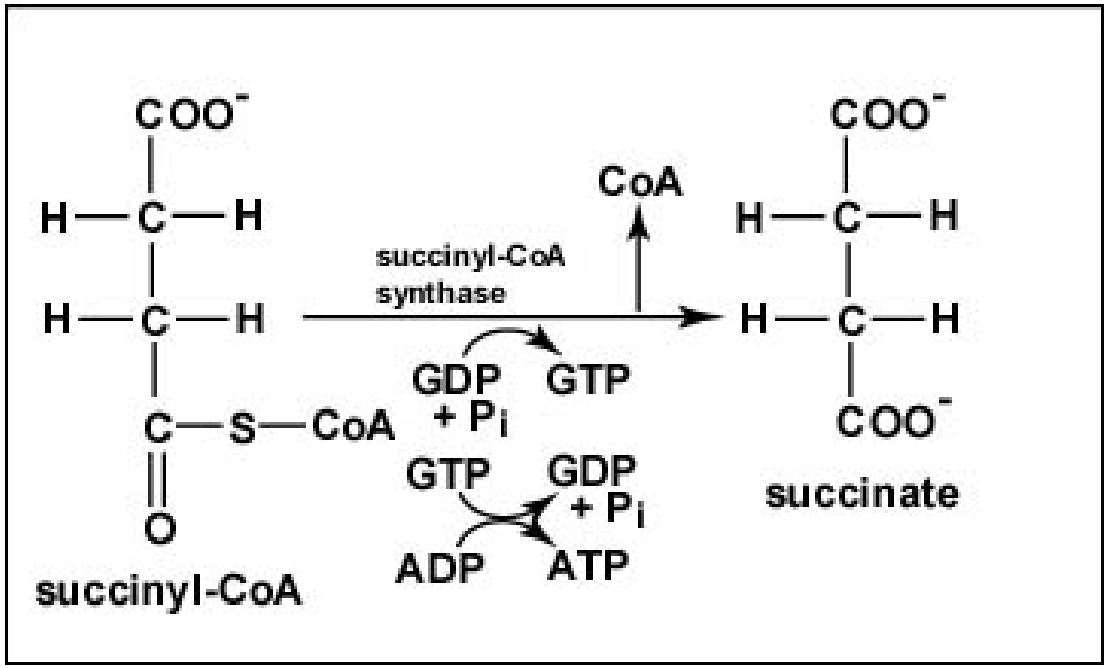


- **Isocitrate is oxidized and decarboxylated to alpha-ketoglutarate**

  - The oxidative decarboxylation of isocitrate is catalyzed by isocitrate dehydrogenase.

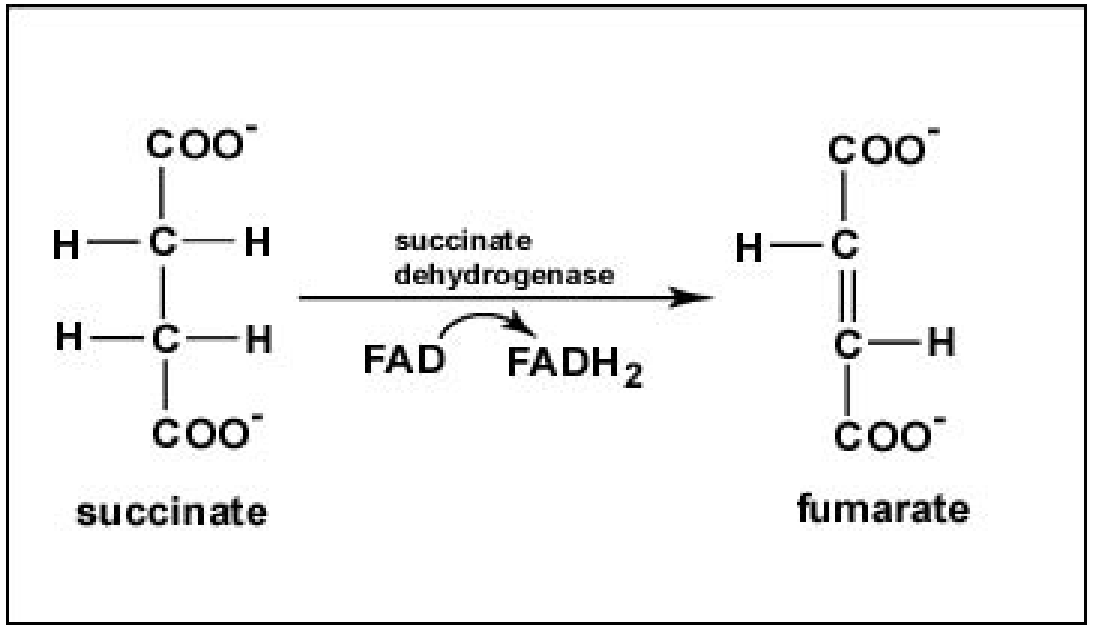
- **Succinyl coenzyme A is formed by the oxidative decarboxylation of alpha-ketoglutarate**

  - The conversion of isocitrate into a -ketoglutarate is followed by a second oxidative decarboxylation reaction, the formation of succinyl CoA from alpha -ketoglutarate.



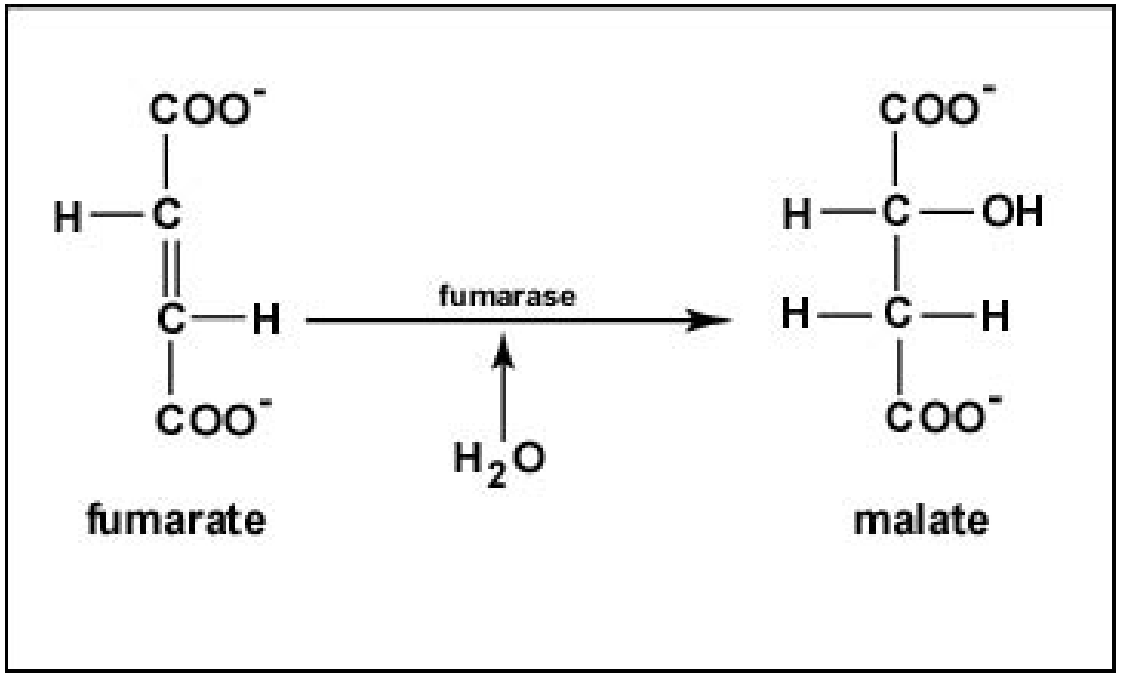
❖ Conversion of Succinyl-CoA to Succinate

- The energy released is used to make guanosine triphosphate (GTP) from guanosine diphosphate (GDP) and Pi by substrate-level phosphorylation.
- The enzyme **succinyl-CoA synthase** catalyzes this reaction of the citric acid cycle.



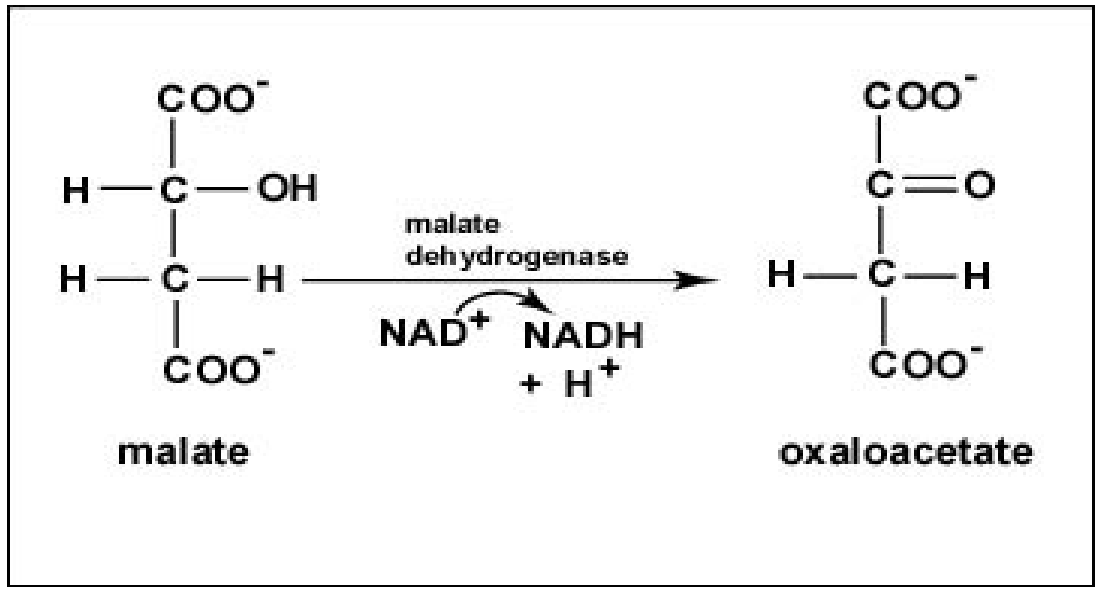
❖ Formation of Succinate to Fumarate

- During this oxidation, FAD is reduced to FADH2. The enzyme **succinate dehydrogenase** catalyzes the removal of two hydrogens from succinate.



❖ Hydration of Fumarate to Malate

- The reversible hydration of **fumarate** to **L-malate** is catalyzed by **fumarase (fumarate hydratase).**



❖ Formation of Oxaloacetate from Malate

- Finally, malate is oxidized to form oxaloacetate. This reaction is catalyzed by malate dehydrogenase, and NAD+ is again the hydrogen acceptor.

Significance of the TCA cycle

- The major significance of the citric acid cycle is to act as the final common pathway for the oxidation of carbohydrates, lipids and proteins, since glucose, fatty acids and many amino acids are all metabolised to acetyl CoA.

- This cycle serves as the mechanism by which much of the free energy liberated during the oxidation of carbohydrate, lipids and amino acids is made available.

- TCA cycle is of further significance since it has dual or amphibolic role thus providing precursor compounds for biosynthesis of other biomolecules (amino acids, fatty acids, and glucose).

References:

Lehninger, Albert L., Cox, Michael M.Nelson, David L.Lehninger Principles Of Biochemistry. New York : W.H. Freeman, 2008.

Biochemistry (9th Edition). Author(s):. Jeremy M. Berg, Lubert Stryer, John Tymoczko, Gregory Gatto. Publisher: WH Freeman.