

Highlights Citric Acid Cycle

1. The citric acid cycle occurs in mitochondria. The most important structural feature of mitochondria are the inner membrane, the matrix (where the enzymes are dissolved), and the cristae (the infoldings of the inner membrane).
2. The oxidative decarboxylation of pyruvate (oxidative = NADH produced), is a reaction that occurs AFTER glycolysis in the mitochondrion, but BEFORE the Citric Acid Cycle. The reaction is catalyzed by the pyruvate dehydrogenase complex, to form acetyl-CoA and is another "big bang" reaction. It has a very large negative free energy (ΔG), AND makes an activated form of acetate - a thioester bond in acetyl-CoA. Five coenzymes are involved - TPP (thiamine pyrophosphate), NAD, FAD, Coenzyme A, and lipoic acid.
3. The cyclic pathway of the citric acid cycle (also called TCA cycle or Krebs' Cycle) is generally considered to "start" with addition of acetyl-CoA to oxaloacetate (OAA) to form citrate. This first reaction uses energy of the high energy thioester bond to form citrate. Coenzyme A is released in the process.
4. Rearrangement of citrate to isocitrate is catalyzed by aconitase. This enzyme was targeted by coyote killers in the 1960s.
4. The first oxidative decarboxylation in the citric acid cycle (oxidative = NADH or $FADH_2$ produced, decarboxylation = carbon dioxide produced) occurs in the third step, yielding NADH and a five carbon compound, alpha-ketoglutarate. The enzyme is isocitrate dehydrogenase.
5. Oxidative decarboxylation of alpha-ketoglutarate by alpha-ketoglutarate dehydrogenase (alphaKGDH) occurs in the fourth step. The product of the reaction is a four carbon molecule, succinyl-CoA. AlphaKGDH uses the same coenzymes and almost exactly the same mechanism as pyruvate dehydrogenase.
6. The fifth step is the only step where a triphosphate is directly produced (substrate level phosphorylation). GTP is the triphosphate produced, and coenzyme A is released in the process. This is catalyzed by succinyl-CoA synthetase.
7. The remaining steps of the citric acid cycle are devoted to regenerating the four carbon oxaloacetate molecule. Step six involves oxidation of succinate (by FAD, to produce $FADH_2$), catalyzed by succinate dehydrogenase. It is the only enzyme of the cycle not found in the mitochondrial matrix. Instead, it is embedded in the inner mitochondrial membrane. Fumarate is the product of this reaction. The oxidation reaction that makes fumarate is different in being a reaction where protons and electrons are taken away to make a double bond and for this reason, FAD is needed instead of NAD.
8. Addition of water to the double bond in fumarate yields L-malate in the seventh reaction, catalyzed by fumarase. The eighth step of the citric acid cycle involves oxidation of malate (by NAD^+ to produce NADH) to yield oxaloacetate. This reaction is the simple oxidation of an alcohol to a ketone and is catalyzed by malate dehydrogenase. It is unusual in being a rare oxidation that requires input energy. This reaction is "pulled" by the next reaction (first reaction) in which oxaloacetate is made into citrate. Breaking of the bond between acetate and coenzyme A (CoA) releases energy, which drives that reaction forward.
9. Both alpha-ketoglutarate and oxaloacetate can readily be converted into the amino acids glutamate and aspartate, respectively. Remember from previously that pyruvate can be converted to alanine, as well.

10. The citric acid cycle is called anaplerotic, which means "to fill up" because several of its intermediates are important in other anabolic and catabolic pathways. Alpha-ketoglutarate, for example, can be converted easily to glutamic acid (and vice-versa) and oxaloacetate can be converted to glucose or aspartic acid (and vice-versa).

11. The citric acid cycle is regulated largely at the level of availability of NAD⁺ and FAD. When these are low in abundance, the pathway slows or stops.