Citric acid cycle

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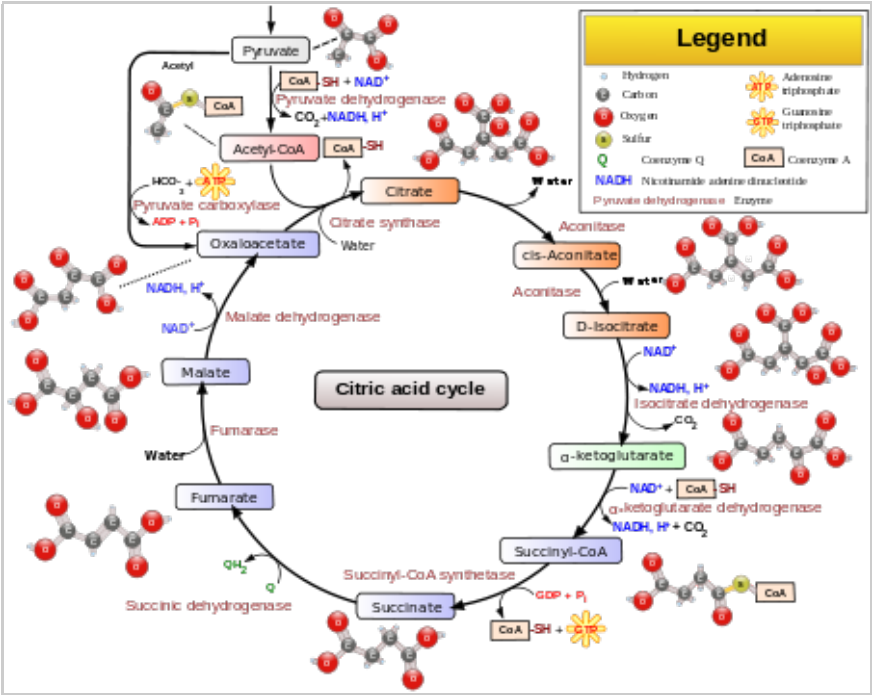

Overview of the citric acid cycle *(click to enlarge)*

The **citric acid cycle** — also known as the **tricarboxylic acid cycle** (**TCA cycle**), or the **Krebs cycle**,[1][2][3] — is a series of chemical reactions used by all aerobic organisms to generate energy through the oxidation of acetate derived from carbohydrates, fats and proteins into carbon dioxide and chemical energy in the form of adenosine triphosphate (ATP). In addition, the cycle provides precursors of certain amino acids as well as the reducing agent NADH that is used in numerous other biochemical reactions. Its central importance to many biochemical pathways suggests that it was one of the earliest established components of cellular metabolism and may have originated abiogenically.[4]

The name of this metabolic pathway is derived from citric acid (a type of tricarboxylic acid) that is consumed and then regenerated by this sequence of reactions to complete the cycle. In addition, the cycle consumes acetate (in the form of acetyl-CoA) and water, reduces NAD^+ to NADH, and produces carbon dioxide as a waste byproduct. The NADH generated by the TCA cycle is fed into the oxidative phosphorylation (electron transport) pathway. The net result of these two closely linked pathways is the oxidation of nutrients to produce usable chemical energy in the form of ATP.

In eukaryotic cells, the citric acid cycle occurs in the matrix of the mitochondrion. In prokaryotic cells, such as bacteria which lack mitochondria, the TCA reaction sequence is performed in the cytosol with the proton gradient for ATP production being across the cell's surface (plasma membrane) rather than the inner membrane of the mitochondrion.

Several of the components and reactions of the citric acid cycle were established in the 1930s by the research of the Nobel laureate Albert Szent-Györgyi, for which he

received the Nobel Prize in 1937 for his discoveries pertaining to fumaric acid, a key component of the cycle.[5]

The citric acid cycle itself was finally identified in 1937 by Hans Adolf Krebs while at the University of Sheffield, for which he received the Nobel Prize for Physiology or Medicine in 1953.[6]

Contents

Evolution

Components of the TCA cycle were derived from anaerobic bacteria, and the TCA cycle itself may have evolved more than once.[7] Theoretically there are several alternatives to the TCA cycle; however, the TCA cycle appears to be the most efficient. If several TCA alternatives had evolved independently, they all appear to have converged to the TCA cycle.[8][9]

Overview

The citric acid cycle is a key component of the metabolic pathway by which all aerobic organisms generate energy. Through catabolism of sugars, fats, and proteins, a two-carbon organic product acetate in the form of acetyl-CoA is produced. Acetyl-CoA along with two equivalents of water (H_2O) is consumed by the citric acid cycle producing two equivalents of carbon dioxide (CO_2) and one equivalent of HS-CoA. In addition, one complete turn of the cycle converts three equivalents of nicotinamide adenine dinucleotide (NAD^+) into three equivalents of reduced NAD^+ (NADH), one equivalent of ubiquinone (Q) into one equivalent of reduced ubiquinone (QH_2), and one equivalent each of guanosine diphosphate (GDP) and inorganic phosphate (P_i) into one equivalent of guanosine triphosphate (GTP). The NADH and QH_2 generated by the citric acid cycle are in turn used by the oxidative

phosphorylation pathway to generate energy-rich adenosine triphosphate (ATP).

One of the primary sources of acetyl-CoA is sugars that are broken down by glycolysis to produce pyruvate that in turn is decarboxylated by the enzyme pyruvate dehydrogenase generating acetyl-CoA according to the following reaction scheme:[1]

- $CH_3C(=O)C(=O)O^-$ (pyruvate) + HSCoA + NAD^+ → $CH_3C(=O)SCoA$ (acetyl-CoA) + NADH + CO_2

The product of this reaction, acetyl-CoA, is the starting point for the citric acid cycle. Below is a schematic outline of the cycle:[1]

- The citric acid cycle begins with the transfer of a two-carbon acetyl group from acetyl-CoA to the four-carbon acceptor compound (oxaloacetate) to form a six-carbon compound (citrate).
- The citrate then goes through a series of chemical transformations, losing two carboxyl groups as CO_2. The carbons lost as CO_2 originate from what was oxaloacetate, not directly from acetyl-CoA. The carbons donated by acetyl-CoA become part of the oxaloacetate carbon backbone after the first turn of the citric acid cycle. Loss of the acetyl-CoA-donated carbons as CO_2 requires several turns of the citric acid cycle. However, because of the role of the citric acid cycle in anabolism, they may not be lost, since many TCA cycle intermediates are also used as precursors for the biosynthesis of other molecules.[10]
- Most of the energy made available by the oxidative steps of the cycle is transferred as energy-rich electrons to NAD^+, forming NADH. For each acetyl group that enters the citric acid cycle, three molecules of NADH are produced.
- Electrons are also transferred to the electron acceptor Q, forming QH_2.
- At the end of each cycle, the four-carbon oxaloacetate has been regenerated, and the cycle continues.

Steps

Two carbon atoms are oxidized to CO_2, the energy from these reactions being transferred to other metabolic processes by GTP (or ATP), and as electrons in NADH and QH_2. The NADH generated in the TCA cycle may later donate its electrons in oxidative phosphorylation to drive ATP synthesis; $FADH_2$ is covalently attached to succinate dehydrogenase, an enzyme functioning both in the TCA cycle and the mitochondrial electron transport chain in oxidative phosphorylation. $FADH_2$, therefore, facilitates transfer of electrons to coenzyme Q, which is the final electron acceptor of the reaction catalyzed by the Succinate:ubiquinone oxidoreductase complex, also acting as an intermediate in the electron transport chain.[11]

The citric acid cycle is continuously supplied with new carbon in the form of acetyl-CoA, entering at step 1 below.[1][12]

	Substrates	Products	Enzyme	Reaction type	Comment
1	Oxaloacetate + Acetyl CoA + H_2O	Citrate + CoA-SH	Citrate synthase	Aldol condensation	irreversible, extends the 4C oxaloacetate to a 6C molecule
2	Citrate	*cis*-Aconitate + H_2O	Aconitase	Dehydration	reversible isomerisation
3	*cis*-Aconitate + H_2O	Isocitrate		Hydration	
4	Isocitrate + NAD^+	Oxalosuccinate + NADH + H^+	Isocitrate dehydrogenase	Oxidation	generates NADH (equivalent of 2.5 ATP)
5	Oxalosuccinate	α-Ketoglutarate + CO_2		Decarboxylation	rate-limiting, irreversible stage, generates a 5C molecule
6	α-Ketoglutarate + NAD^+ + CoA-SH	Succinyl-CoA + NADH + H^+ + CO_2	α-Ketoglutarate dehydrogenase	Oxidative decarboxylation	irreversible stage, generates NADH (equivalent of 2.5 ATP), regenerates the 4C chain (CoA excluded)
7	Succinyl-CoA + GDP + P_i	Succinate + CoA-SH + GTP	Succinyl-CoA synthetase	substrate-level phosphorylation	or ADP→ATP instead of GDP→GTP,[11] generates 1 ATP or equivalent Condensation reaction of GDP + P_i and hydrolysis of Succinyl-CoA involve the

					H_2O needed for balanced equation.
8	Succinate + ubiquinone (Q)	Fumarate + ubiquinol (QH_2)	Succinate dehydrogenase	Oxidation	uses FAD as a prosthetic group (FAD→$FADH_2$ in the first step of the reaction) in the enzyme,[11] generates the equivalent of 1.5 ATP
9	Fumarate + H_2O	*L*-Malate	Fumarase	Hydration	
10	*L*-Malate + NAD^+	Oxaloacetate + NADH + H^+	Malate dehydrogenase	Oxidation	reversible (in fact, equilibrium favors malate), generates NADH (equivalent of 2.5 ATP)

Mitochondria in animals, including humans, possess two succinyl-CoA synthetases: one that produces GTP from GDP, and another that produces ATP from ADP.[13] Plants have the type that produces ATP (ADP-forming succinyl-CoA synthetase).[12] Several of the enzymes in the cycle may be loosely associated in a multienzyme protein complex within the mitochondrial matrix.[14]

The GTP that is formed by GDP-forming succinyl-CoA synthetase may be utilized by nucleoside-diphosphate kinase to form ATP (the catalyzed reaction is GTP + ADP → GDP + ATP).[11]

Products

Products of the first turn of the cycle are: *one GTP (or ATP), three NADH, one QH_2, two CO_2*.

Because two acetyl-CoA molecules are produced from each glucose molecule, two

cycles are required per glucose molecule. Therefore, at the end of two cycles, the products are: two GTP, six NADH, two QH_2, and four CO_2

Description	**Reactants**	**Products**
The sum of all reactions in the citric acid cycle is:	Acetyl-CoA + 3 NAD^+ + Q + GDP + P_i + 3 H_2O	→ CoA-SH + 3 NADH + 3 H^+ + QH_2 + GTP + 2 CO_2
Combining the reactions occurring during the pyruvate oxidation with those occurring during the citric acid cycle, the following overall pyruvate oxidation reaction is obtained:	Pyruvate ion + 4 NAD^+ + Q + GDP + P_i + 2 H_2O	→ 4 NADH + 4 H^+ + QH_2 + GTP + 3 CO_2
Combining the above reaction with the ones occurring in the course of glycolysis, the following overall glucose oxidation reaction (excluding reactions in the respiratory chain) is obtained:	Glucose + 10 NAD^+ + 2 Q + 2 ADP + 2 GDP + 4 P_i + 2 H_2O	→ 10 NADH + 10 H^+ + 2 QH_2 + 2 ATP + 2 GTP + 6 CO_2

The above reactions are balanced if P_i represents the $H_2PO_4^-$ ion, ADP and GDP the ADP^{2-} and GDP^{2-} ions, respectively, and ATP and GTP the ATP^{3-} and GTP^{3-} ions, respectively.

The total number of ATP obtained after complete oxidation of one glucose in glycolysis, citric acid cycle, and oxidative phosphorylation is estimated to be between 30 and 38.[15]

Efficiency

The theoretical maximum yield of ATP through oxidation of one molecule of glucose in glycolysis, citric acid cycle, and oxidative phosphorylation is 38 (assuming 3 molar equivalents of ATP per equivalent NADH and 2 ATP per $FADH_2$). In eukaryotes, two equivalents of NADH are generated in glycolysis, which takes place in the cytoplasm. Transport of these two equivalents into the mitochondria consumes two equivalents of ATP, thus reducing the net production of ATP to 36. Furthermore, inefficiencies in oxidative phosphorylation due to leakage of protons across of the mitochondrial membrane and slippage of the ATP synthase/proton pump commonly reduces the ATP yield from NADH and $FADH_2$ to less than the theoretical maximum yield.[15] The observed yields are, therefore, closer to ~2.5 ATP per NADH and ~1.5 ATP per $FADH_2$, further reducing the total net production of ATP to approximately 30.[16] An assessment of the total ATP yield with newly revised proton-to-ATP ratios provides an estimate of 29.85 ATP per glucose molecule.[17] However, the total amount of ATP generated from just the Krebs Cycle for one molecule of glucose is around 25.[1]

Regulation

The regulation of the TCA cycle is largely determined by product inhibition and substrate availability. The major eventual substrate of the cycle is ADP which gets converted to ATP. A reduced amount of ADP causes accumulation of precursor NADH which in turn can inhibit a number of enzymes.[1] NADH, a product of all dehydrogenases in the TCA cycle with the exception of succinate dehydrogenase, inhibits pyruvate dehydrogenase, isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, and also citrate synthase. Acetyl-coA inhibits pyruvate dehydrogenase, while succinyl-CoA inhibits alpha-ketoglutarate dehydrogenase and citrate synthase. When tested in vitro with TCA enzymes, ATP inhibits citrate synthase and α-ketoglutarate dehydrogenase; however, ATP levels do not change more than 10% in vivo between rest and vigorous exercise. There is no known allosteric mechanism that can account for large changes in reaction rate from an allosteric effector whose concentration changes less than 10%.[18]

Calcium is used as a regulator. Mitochondrial matrix calcium levels can reach the tens of micromolar levels during cellular activation.[19] It activates pyruvate dehydrogenase phosphatase which in turn activates the pyruvate dehydrogenase complex. Calcium also activates isocitrate dehydrogenase and α-ketoglutarate dehydrogenase.[20] This increases the reaction rate of many of the steps in the cycle, and therefore increases flux throughout the pathway.

Citrate is used for feedback inhibition, as it inhibits phosphofructokinase, an enzyme involved in glycolysis that catalyses formation of fructose 1,6-bisphosphate,a precursor of pyruvate. This prevents a constant high rate of flux when there is an accumulation of citrate and a decrease in substrate for the enzyme.

Recent work has demonstrated an important link between intermediates of the citric acid cycle and the regulation of hypoxia-inducible factors (HIF). HIF plays a role in the regulation of oxygen homeostasis, and is a transcription factor that targets angiogenesis, vascular remodeling, glucose utilization, iron transport and apoptosis. HIF is synthesized consititutively, and hydroxylation of at least one of two critical proline residues mediates their interaction with the von Hippel Lindau E3 ubiquitin ligase complex, which targets them for rapid degradation. This reaction is catalysed by prolyl 4-hydroxylases. Fumarate and succinate have been identified as potent inhibitors of prolyl hydroxylases, thus leading to the stabilisation of HIF.[21]

Major metabolic pathways converging on the TCA cycle

Several catabolic pathways converge on the TCA cycle. Reactions that form intermediates of the TCA cycle in order to replenish them (especially during the scarcity of the intermediates) are called anaplerotic reactions.

The citric acid cycle is the third step in carbohydrate catabolism (the breakdown of sugars). Glycolysis breaks glucose (a six-carbon-molecule) down into pyruvate (a three-carbon molecule). In eukaryotes, pyruvate moves into the mitochondria. It is converted into acetyl-CoA by decarboxylation and enters the citric acid cycle.

In protein catabolism, proteins are broken down by proteases into their constituent amino acids. The carbon backbone of these amino acids can become a source of energy by being converted to acetyl-CoA and entering into the citric acid cycle.

In fat catabolism, triglycerides are hydrolyzed to break them into fatty acids and glycerol. In the liver the glycerol can be converted into glucose via dihydroxyacetone phosphate and glyceraldehyde-3-phosphate by way of gluconeogenesis. In many tissues, especially heart tissue, fatty acids are broken down through a process known as beta oxidation, which results in acetyl-CoA, which can be used in the citric acid cycle. Beta oxidation of fatty acids with an odd number of methylene bridges produces propionyl CoA, which is then converted into succinyl-CoA and fed into the citric acid cycle.[22]

The total energy gained from the complete breakdown of one molecule of glucose by glycolysis, the citric acid cycle, and oxidative phosphorylation equals about 30 ATP molecules, in eukaryotes. The citric acid cycle is called an amphibolic pathway because it participates in both catabolism and anabolism.

Interactive pathway map

Click on genes, proteins and metabolites below to link to respective articles. [§ 1]

1. ^ The interactive pathway map can be edited at WikiPathways: "TCACycle_WP78" (http://www.wikipathways.org/index.php/Pathway:WP78).

See also

- Calvin cycle
- Glyoxylate cycle
- Reverse (Reductive) Krebs cycle

References

1. ^ ***a b c d e f*** The Kreb's Cycle or Citric Acid Cycle or Tricarboxylic Cycle-explained with animation (http://pharmaxchange.info/press/2013/09/krebs-cycle-citric-acid-cycle-tricarboxylic-acid-cycle-animation/)
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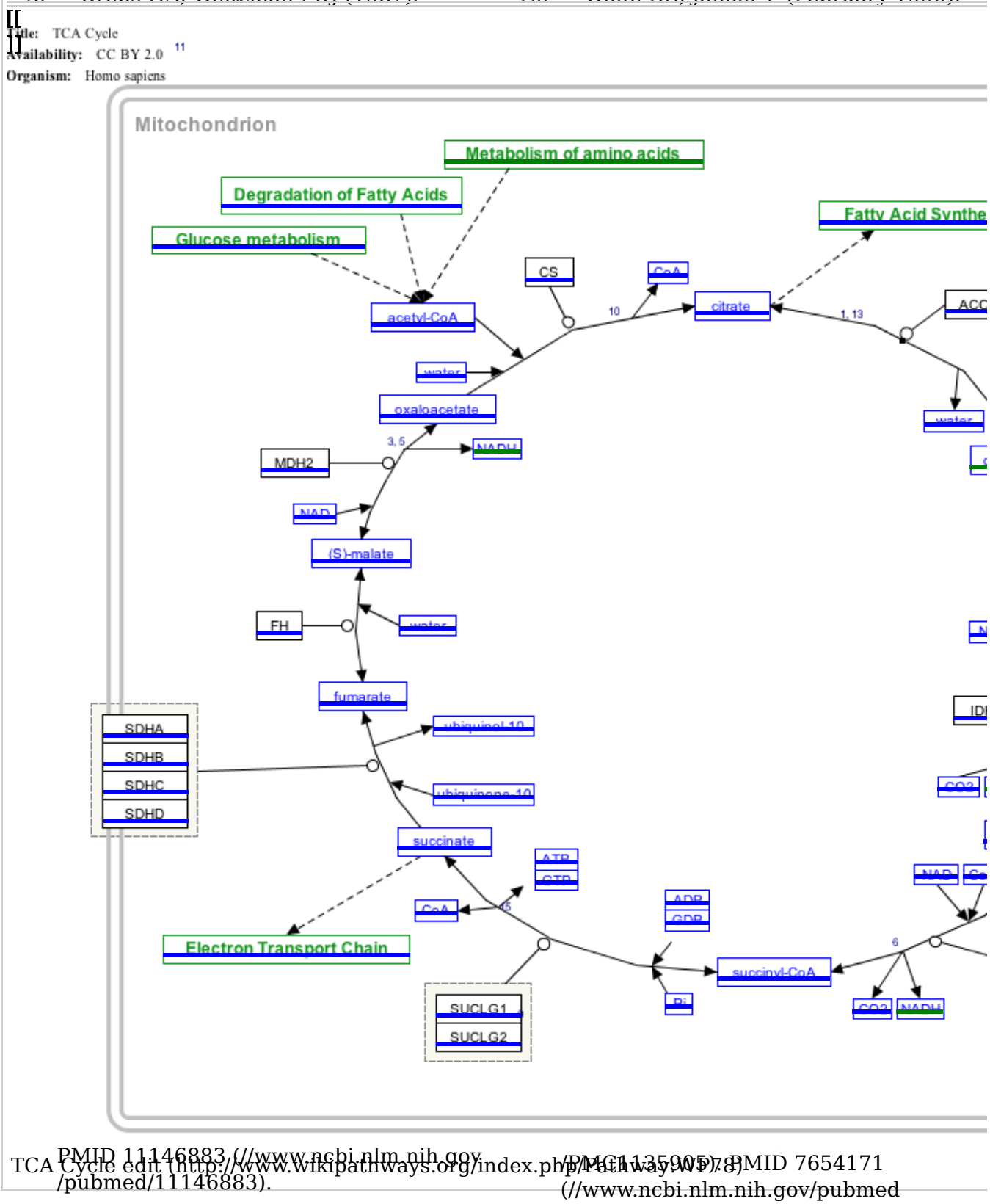

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External links

- An animation of the citric acid cycle (http://www.science.smith.edu/departments/Biology/Bio231/krebs.html) at Smith College
- Citric acid cycle variants (http://biocyc.org/META/NEW-IMAGE?object=TCA-VARIANTS) at MetaCyc
- Pathways connected to the citric acid cycle (http://www.genome.ad.jp/kegg/pathway/map/map00020.html) at Kyoto Encyclopedia of Genes and Genomes
- Introduction at Khan Academy (https://www.khanacademy.org/science/biology/cellular-respiration/v/krebs---citric-acid-cycle)
- Quiz the Citric Acid Cycle (http://www.gbgmed.se/biochemistry/cac.aspx)