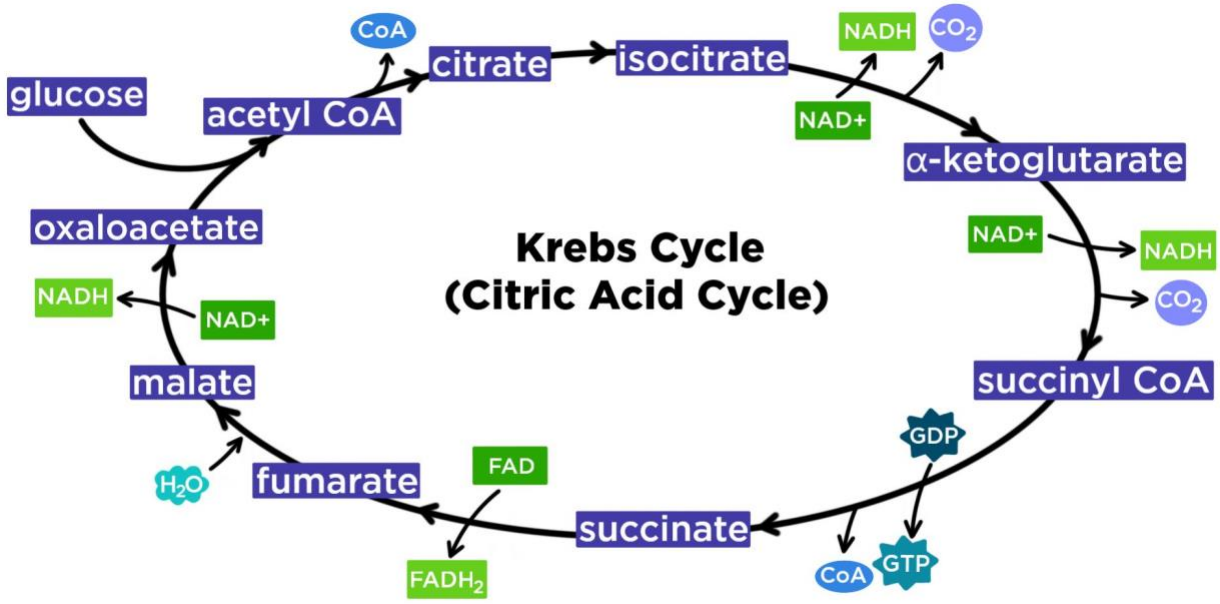
KREB CYCLE



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INTRODUCTION: The **citric acid cycle** (**CAC**) – also known as the **TCA cycle** **(tricarboxylic acid cycle)** or the **Krebs cycle** – is a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl-coenzyme A derived from carbohydrate, fats, and proteins into adenosine tri phosphate (ATP) and carbon-dioxide. In addition, the cycle provides precursors of certain amino acids, as well as the reducing agents like NADH, that are used in numerous other reactions. The name of this metabolic pathway is derived from the citric acid, that is consumed and then regenerated by this sequence of reactions to complete the cycle. The cycle consumes acetate (in the form of acetyl co-enzyme A) and water, reduces NAD+ to NADH, and produces carbon dioxide as a waste by product. The NADH generated by the citric acid cycle is fed into the oxidative phosphorylation.

DISCOVERY AND LOCATION: The citric acid cycle itself was finally identified in 1937 by Hans Adolf Kreb and William Arthur Johnson at the university of Sheffield for which the former received the noble prize for medicine in 1953, and for whom the cycle is sometimes named (Krebs cycle). The citric acid or TCA cycle is located in the mitochondrial matrix in close proximity to electron transport chain. Kreb Cycle basically involves combination of a 2-c-actyle-co enzyme A with a 4-C oxalo acetate to produce a 6 C tri-carboxylic acid citrate. In this reaction carbon is oxidized to CO_2 and oxalo acetate is generated, which is considered to play a central role in citric acid cycle.

STEPS OF TCA CYCLE: The TCA cycle starts with the condensation of acetyl group with oxaloacetic acid (OAA) and water to yield. Steps of kreb cycle are following-

FORMATION OF CITRATE: Acetyl Co-A adds its 2 carbon fragments to oxaloacetate, a four carbon compound. The unstable bond is broken as oxaloacetate displaces the coenzyme and attaches to acetyl group. The

product is 6 carbon citrate Co-A is then free to prime with other two carbon fragment derived from pyruvate. Oxaloacetate is generated at end of cycle.

CONVERTION OF CITRATE TO ISOCITRATE: A molecule of water is removed and other is added. The net result is the conversion of citrate to its isomer, isocitrate

CONVERSION OF ISOCITRATE TO ∝ KETOGLUTARATE: The substrate looses a CO_2 molecule and remaining 5 carbon compound is oxidized, reducing NAD+ to NADH. Formation of ∝ ketoglutarate takes place.

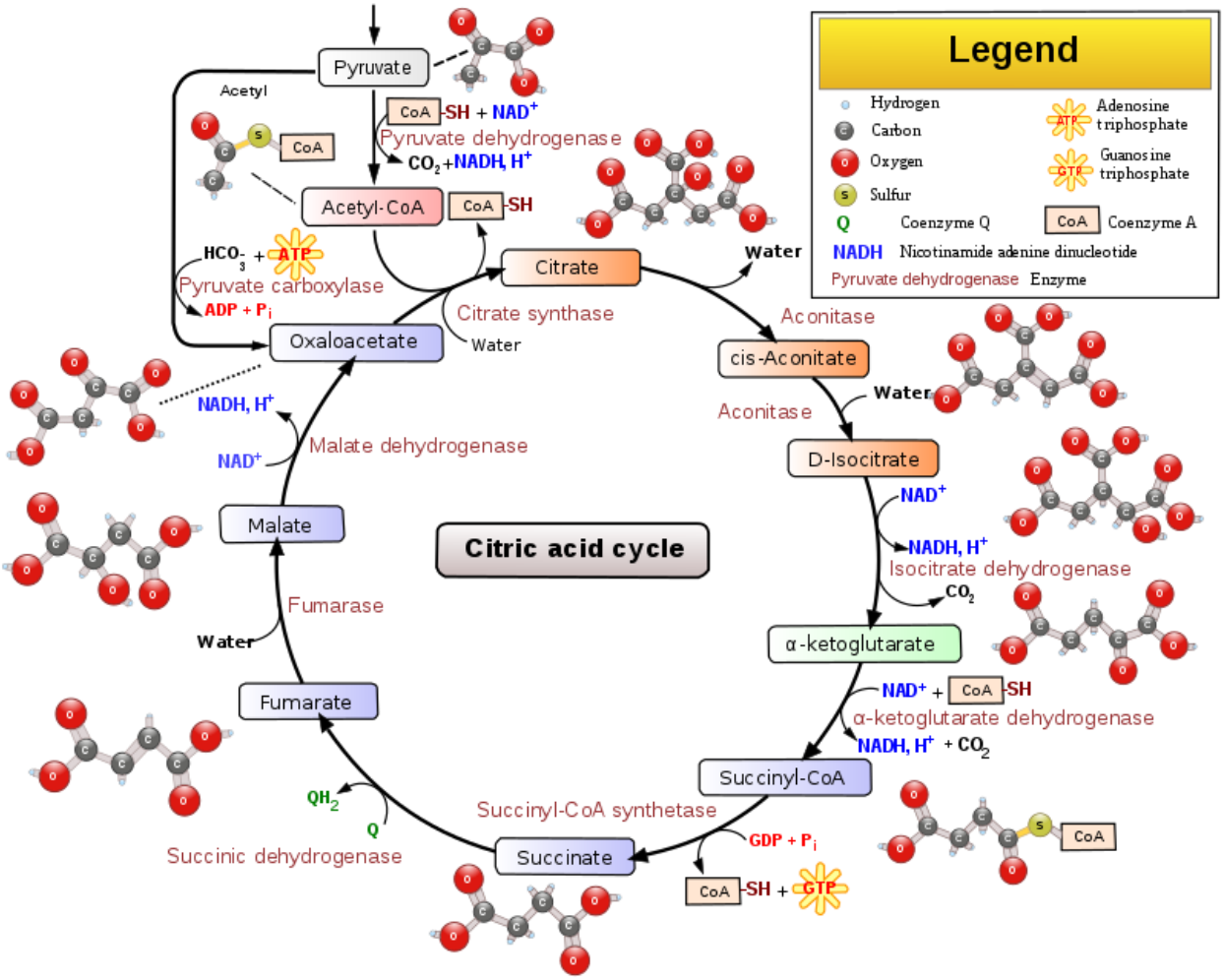
CONVERSION OF ∝ KETOGLUTARATE TO SUCCINYL CO-A: The step is catalyzed by a multienzyme complex very similar to the one that converts pyruvate to acetyl Co-A. CO_2 is lost the remaining four carbon compound is oxidized by the transfer of electrons to NAD+ to form NADH and is then attached to coenzyme- A, formation of succinyl CO-A takes place.

CONVERSION OF SUCCINYL CO-A TO SUCCINATE: Substrate level phosphorylation takes place, CO-A is displaced by a phosphate group, which is then transferred to GDP to form Guanosine triphosphate (GTP). GTP is similar to ATP, which is formed when GTP donates a phosphate group to ATP. Formation of GTP, ATP and succinate takes place.

FORMATION OF FUMARATE: In another oxidative step, two hydrogen atoms are transferred to FAD to form $FADH_2$. Formation of fumarate takes place.

FORMATION OF MALATE: Bonds in the substrate are rearranged in this step by the addition of water and fumarate gets converted to malate.

FORMATION OF OXALOACETATE: The last step is an oxidative step, which produces another molecule of NADH and regenerates oxaloacetate, which accepts a two-carbon fragment from acetyl Co-A for another turn of cycle.



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NET GAIN OF KREB CYCLE: The net gain of Kreb cycle can be summed up as following-

Pyruvic Acid + $4NAD^+$ + FAD^+ +2 H_2O+ ADP +Pi ⟶

$3CO_2$+ 4 $NADH^+$ +4 H^++ $FADH_2$+ ATP.

In Kreb cycle, glucose has been broken down to release CO_2 and eight molecules of NADH + H+; two of $FADH_2$ and two molecules of ATP. Total gain of Kreb cycle is 30 ATP molecules.

REGULATION OF KREB CYCLE: The cellular demand of ATP is crucial in controlling the rate of TCA cycle. The regulation is brought about either by enzyme or by level of ADP and three enzymes citrate synthetase, isocitrate dehydrogenase and ∞ ketoglutarate dehydrogenase regulate citric acid cycle.

CITRATE SYNTHATASE: It is inhibited by ATP, NADH, acyl-Co enzyme, succinyl coenzyme.

∞-KETOGLUTARATE DEHYDROGENASE: It is inhibited by succinyl co-enzyme and NADH.

ISO-CITRATE AND DEHYDROGENASE: It is activated by ADP and inhibited by ATP and NADH.

AVAILABLITY OF ADP: It is very important for citric acid cycle to proceed. This is due to the fact that unless sufficient level of ADP are available, Kreb cycle cannot proceed, similarly the supply of NAD+ and FAD+ are also essential for TCA cycle to proceed.