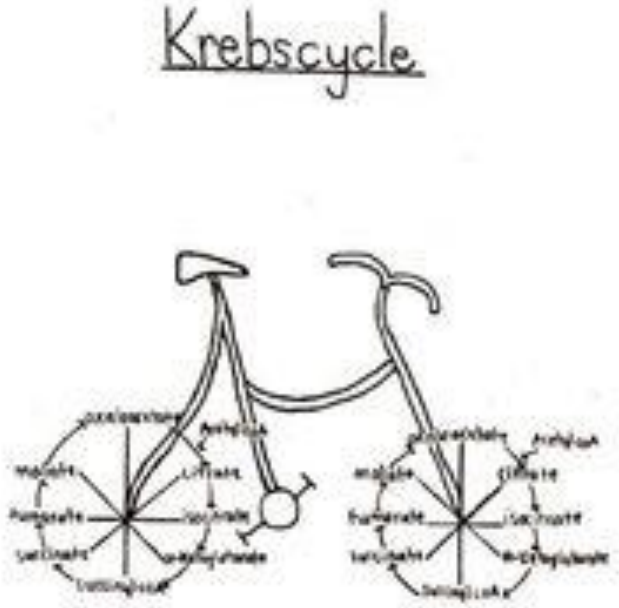
Citric Acid Cycle

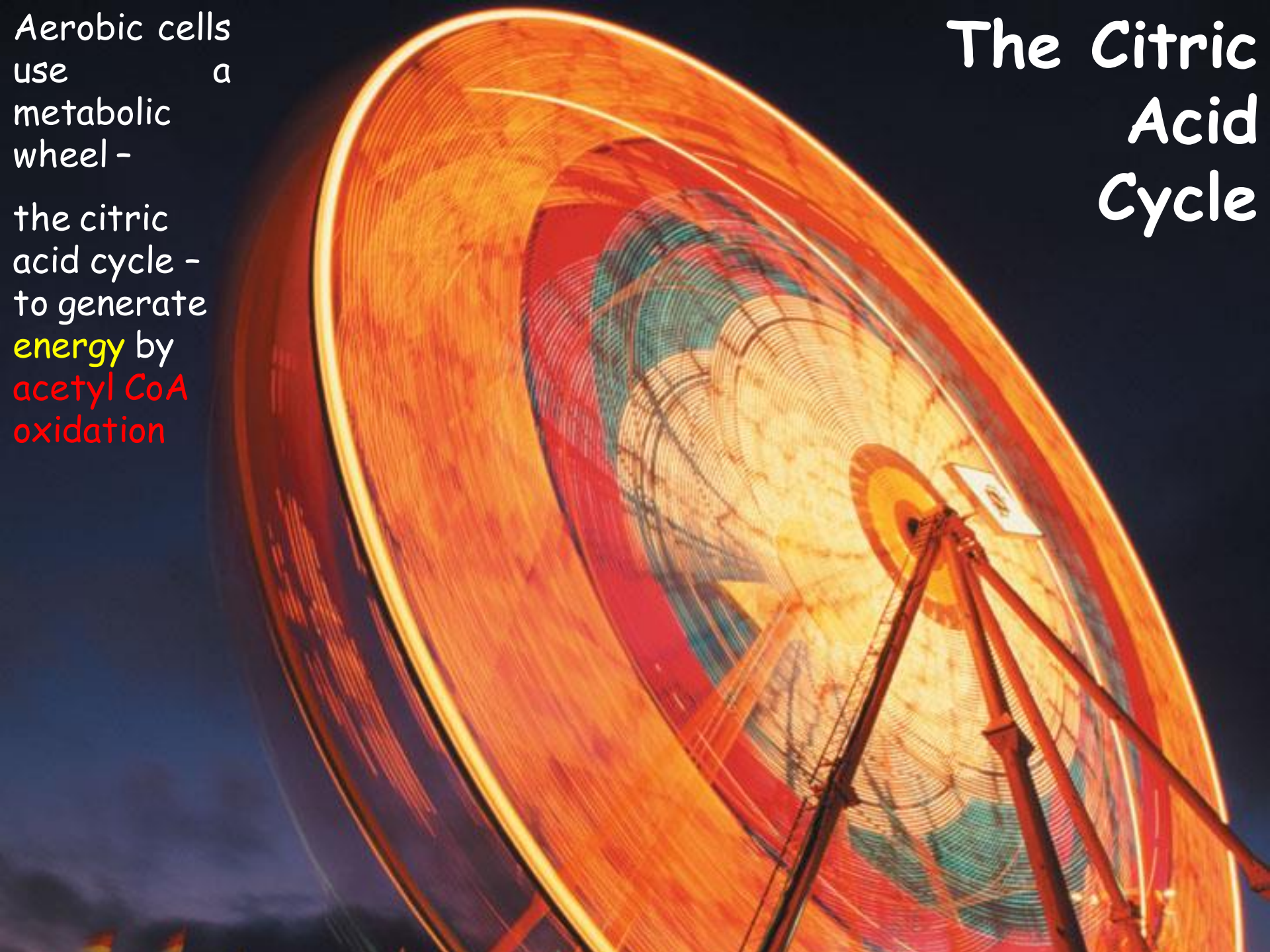
Krebs Cycle



The Citric Acid Cycle

Aerobic cells use a metabolic wheel –

the citric acid cycle – to generate energy by acetyl CoA oxidation



Synthesis of glycogen

Glucose

Pentose phosphate pathway

Glycogen

Glucose-6-phosphate

Ribose, NADPH

Degradation of glycogen

Glycolysis

Gluconeogenesis

Ethanol

Pyruvate

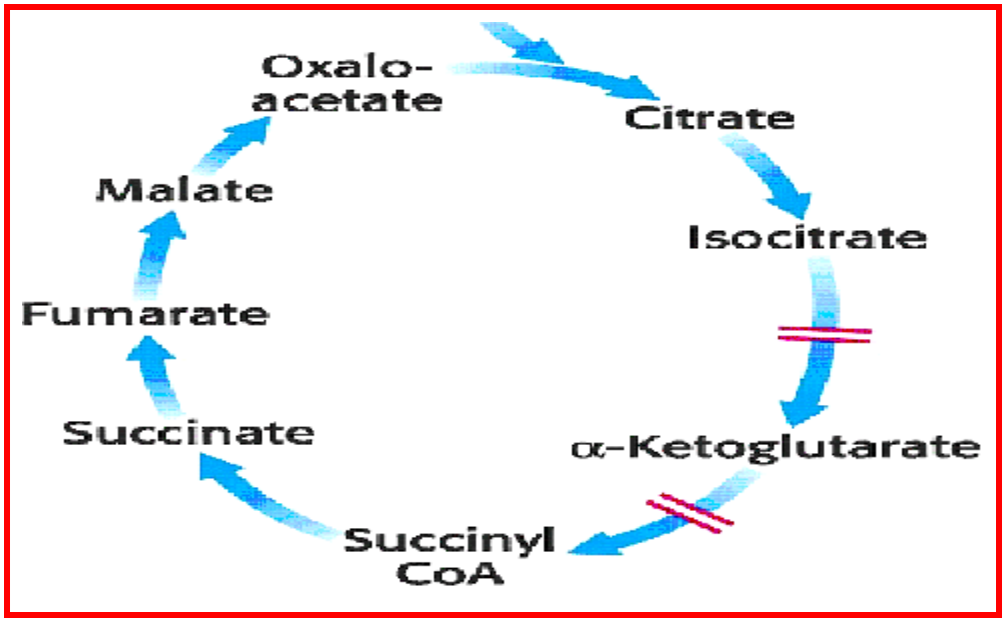
Lactate

Fatty Acids

Acetyl Co A

Amino Acids

The citric acid cycle is the final common pathway for the oxidation of fuel molecules — amino acids, fatty acids, and carbohydrates.



Most fuel molecules enter the cycle as acetyl coenzyme A.

Names:

The Citric Acid Cycle

Tricarboxylic Acid Cycle

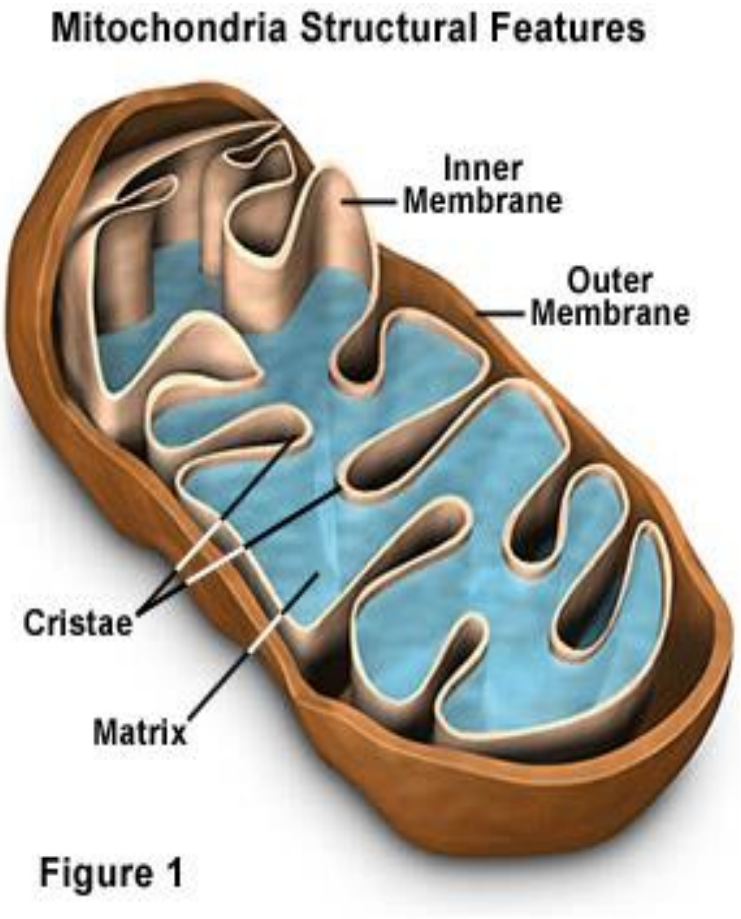
Krebs Cycle

Hans Adolf Krebs.

Biochemist; born in Germany..

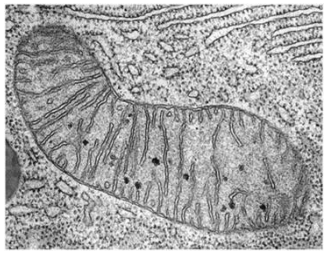
His discovery in 1937 of the 'Krebs cycle' was critical to the understanding of cell metabolism and earned him the 1953 Nobel Prize for Physiology or Medicine.

The **Krebs Cycle** is the **Third Stage** of Aerobic Respiration



Takes place in the **matrix** of the mitochondria.

It happens once for every pyruvate molecule in glycolysis….

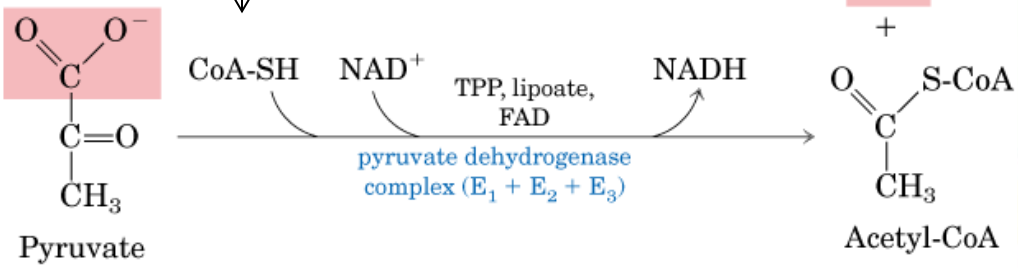


..and so it goes round twice for every glucose molecule that enters the respiration pathway.

Citric acid cycle

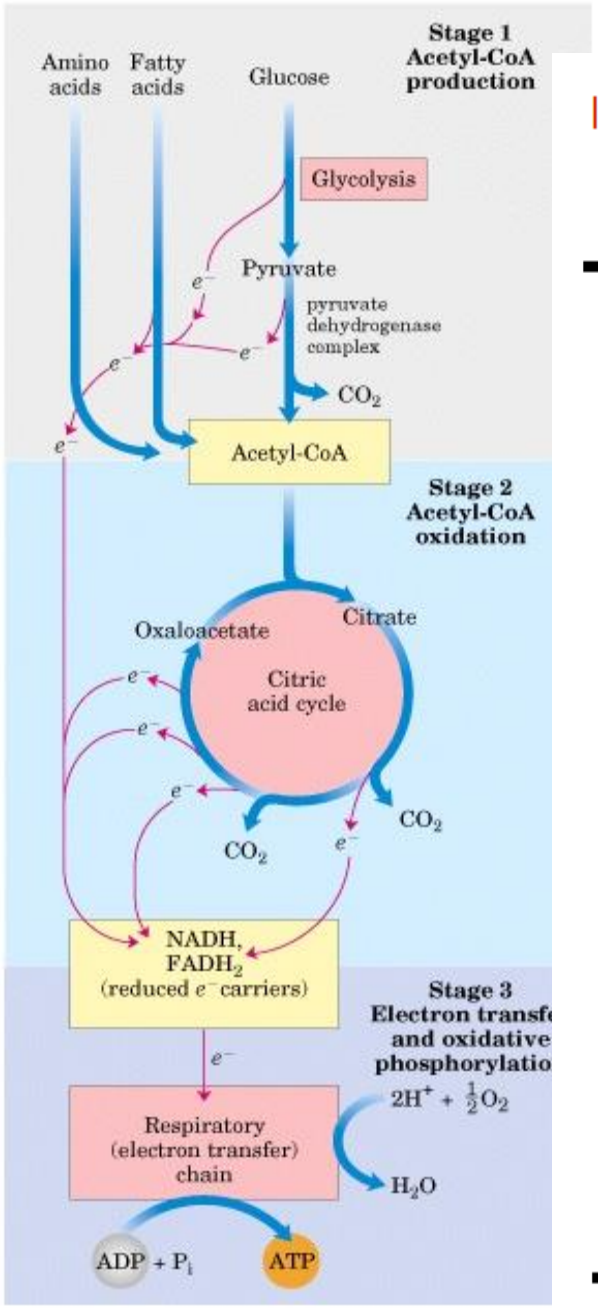
Function of the citric acid cycle is the harvesting of high-energy electrons from acetyl CoA.

مرافق الإنزيم-أ هو مرافق إنزيمي يعرف بدوره البارز في تكوين وأكسدة البيروفات في دورة حمض الستريك



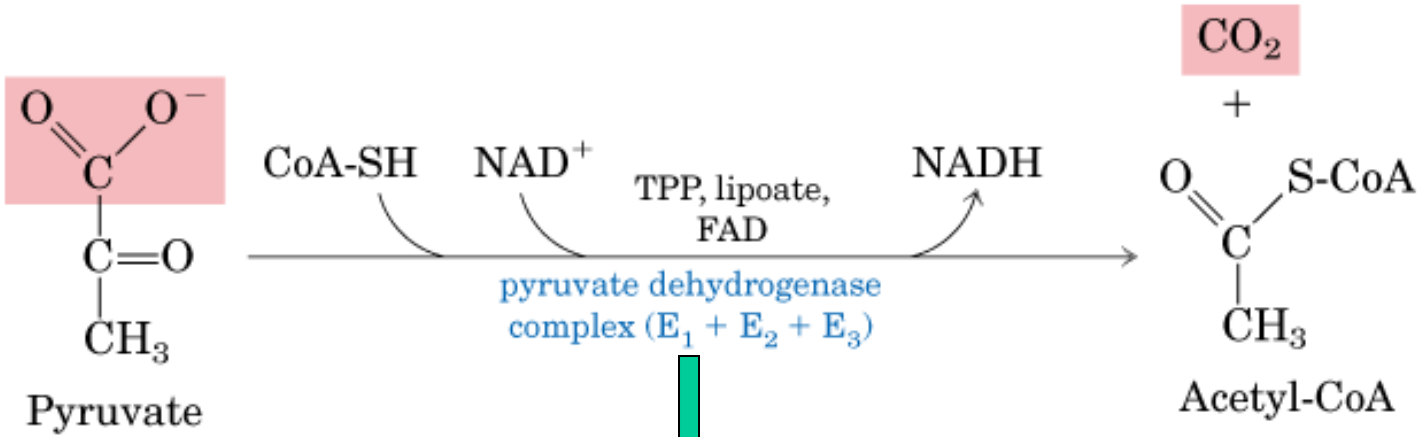
$\Delta G'^{\circ} = -33.4$ kJ/mol

استيل التميم أ



In Cytosol

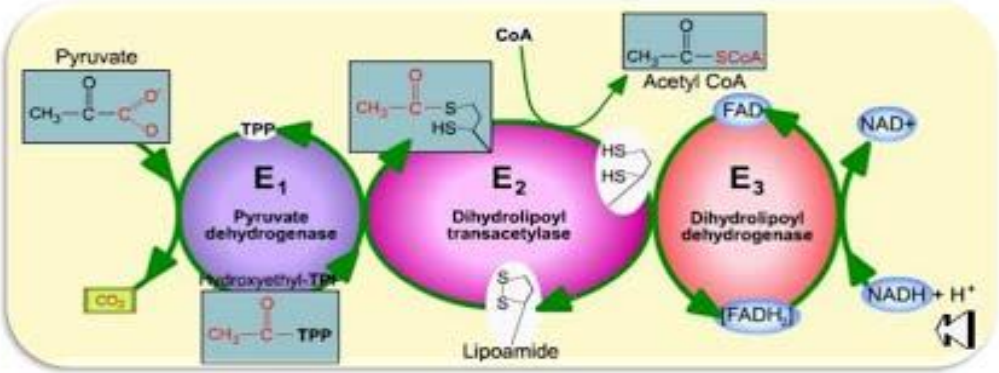
In Mitochondria



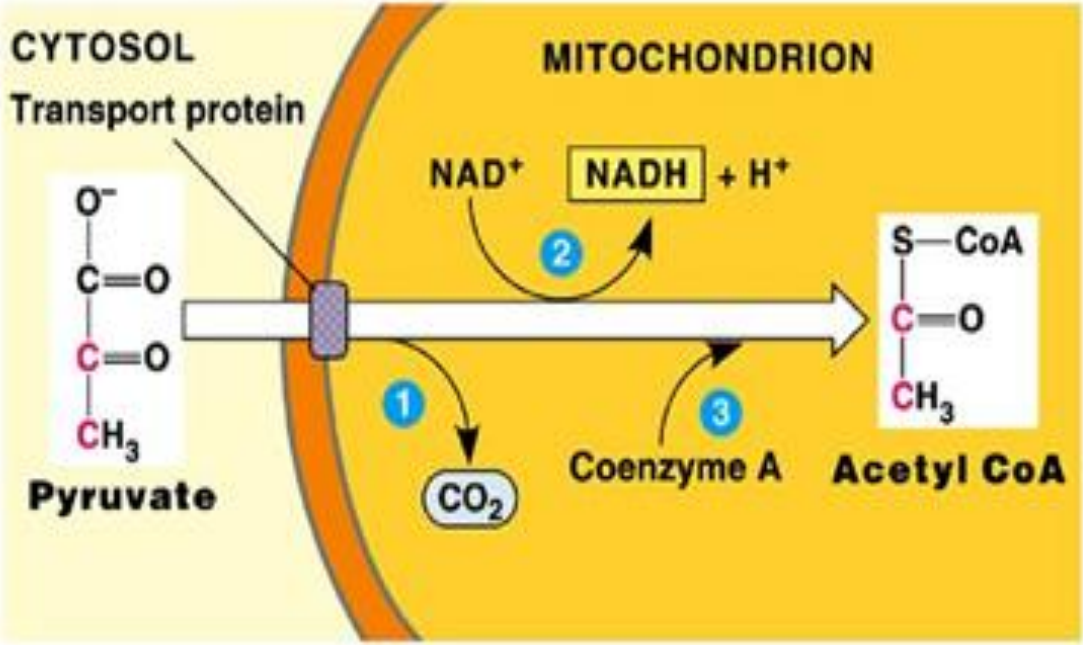
$\Delta G'^{\circ} = -33.4$ kJ/mol

Pyruvate dehydrogenase

complex mechanism



- As pyruvate enters the mitochondrion which modifies pyruvate to acetyl-CoA which enters the Krebs cycle in the matrix.
  - A carboxyl group is removed as CO_2.
  - A pair of electrons is transferred from the remaining two-carbon fragment to NAD^+ to form NADH.
  - The oxidized fragment, acetate, combines with coenzyme A to form acetyl-CoA.



Pyruvate dehydrogenase Complex (PDC)

PDC Is a multi-enzyme complex containing three enzymes associated together non-covalently:

E-1 : Pyruvate carboxylase , uses Thiamine pyrophosphate as cofactor (TPP)

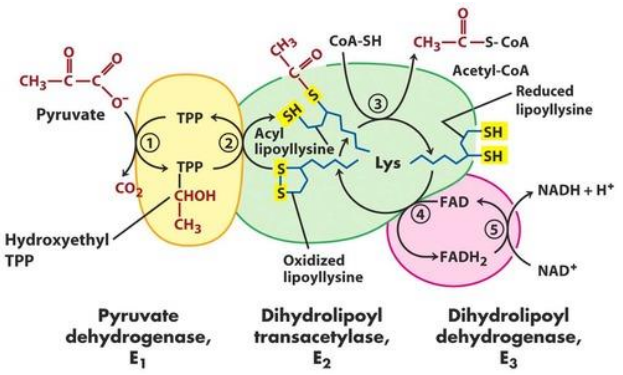
E-2 : Dihydrolipoyl transacetylase, Lipoic acid and CoA

E-3 : Dihydrolipoyl Dehydrogenase requires FAD, NAD^+ as substrate

Each catalyzes a part of the overall reaction. Their physical association links the reactions in proper sequence without the release of intermediates.

Advantages of multienzyme complex:

1. **Higher rate of reaction:**
2. **Minimum side reaction.**
3. **Coordinated control.**



Pyruvate Dehydrogenase Subunits

Enzyme	Abbreviated	Prosthetic Group
Pyruvate Dehydrogenase	E_1	Thiamine pyrophosphate (TPP)
Dihydrolipoyl Transacetylase	E_2	Lipoamide
Dihydrolipoyl Dehydrogenase	E_3	FAD

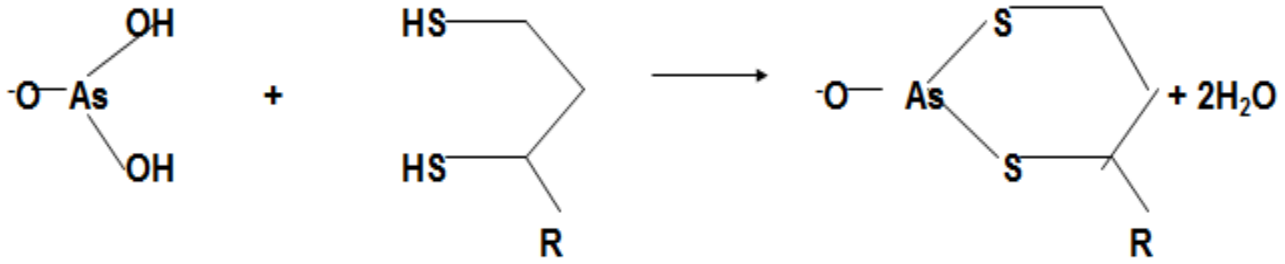
Thiamin (Vitamine B1) deficiency causes Beriberi:

Thiamine pyrophosphate (TPP) is an important cofactor of pyruvate dehydrogenase complex

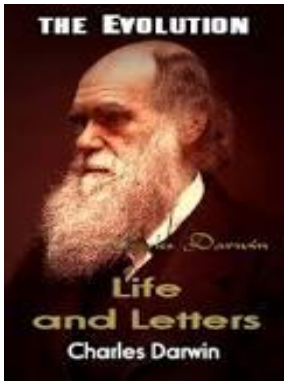
Thiamine is neither synthesized nor stored in good amounts by most vertebrates. Thiamine deficiency ultimately causes a fatal disease called Beriberi characterized by neurological disturbances, paralysis, atrophy of limbs and cardiac failure.

Note that brain exclusively uses aerobic glucose catabolism for energy and PDC is very critical for aerobic catabolism. Therefore thiamine deficiency causes severe neurological symptoms.

Arsenic Poisoning: Arsenic compounds such as arsenite (AsO3---) are poisonous because they covalently bind to sulfhydryl compounds (SH-groups of proteins and cofactors). Dihydrolipoamide is a critical cofactor of PDC, and it has two-SH groups, which are important for the PDC. These –SH groups are covalently inactivated by arsenic compounds as shown below;



Arsenic compounds in low doses are very toxic to microorganisms, therefore these compounds were used for the treatment of syphilis and other diseases in earlier days. Arsenicals were first antibiotics.

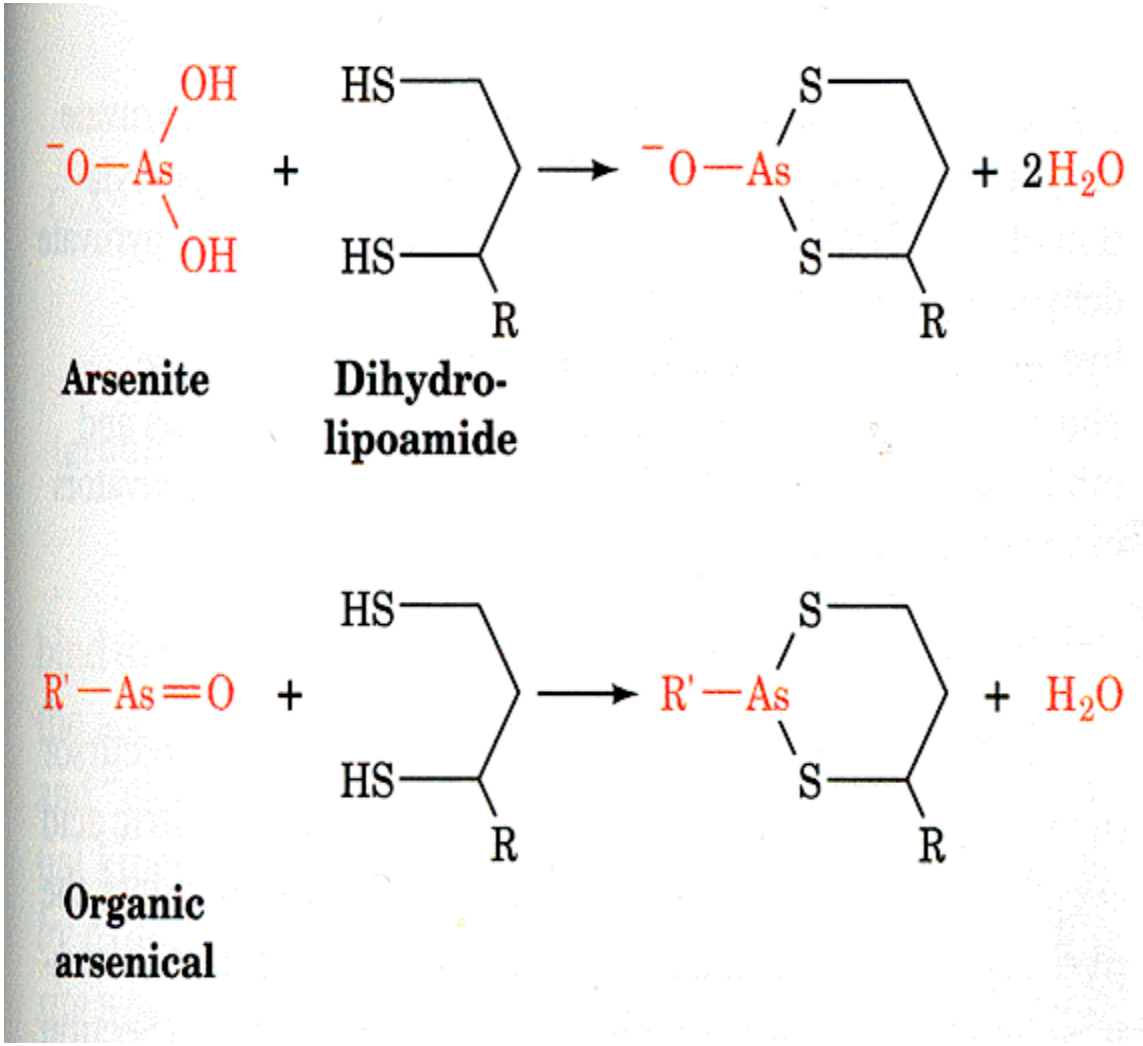


Arsenic Compound poisoning: Inactivation of E-2 of PDC, and other proteins.

Fowler's solution, the famous 19th century tonic contained 10mg/ml As.

Charles Darwin died of As poisoning by taking this tonic.

Napoleon Bonaparte's death was also suspected to be due to As poisoning.

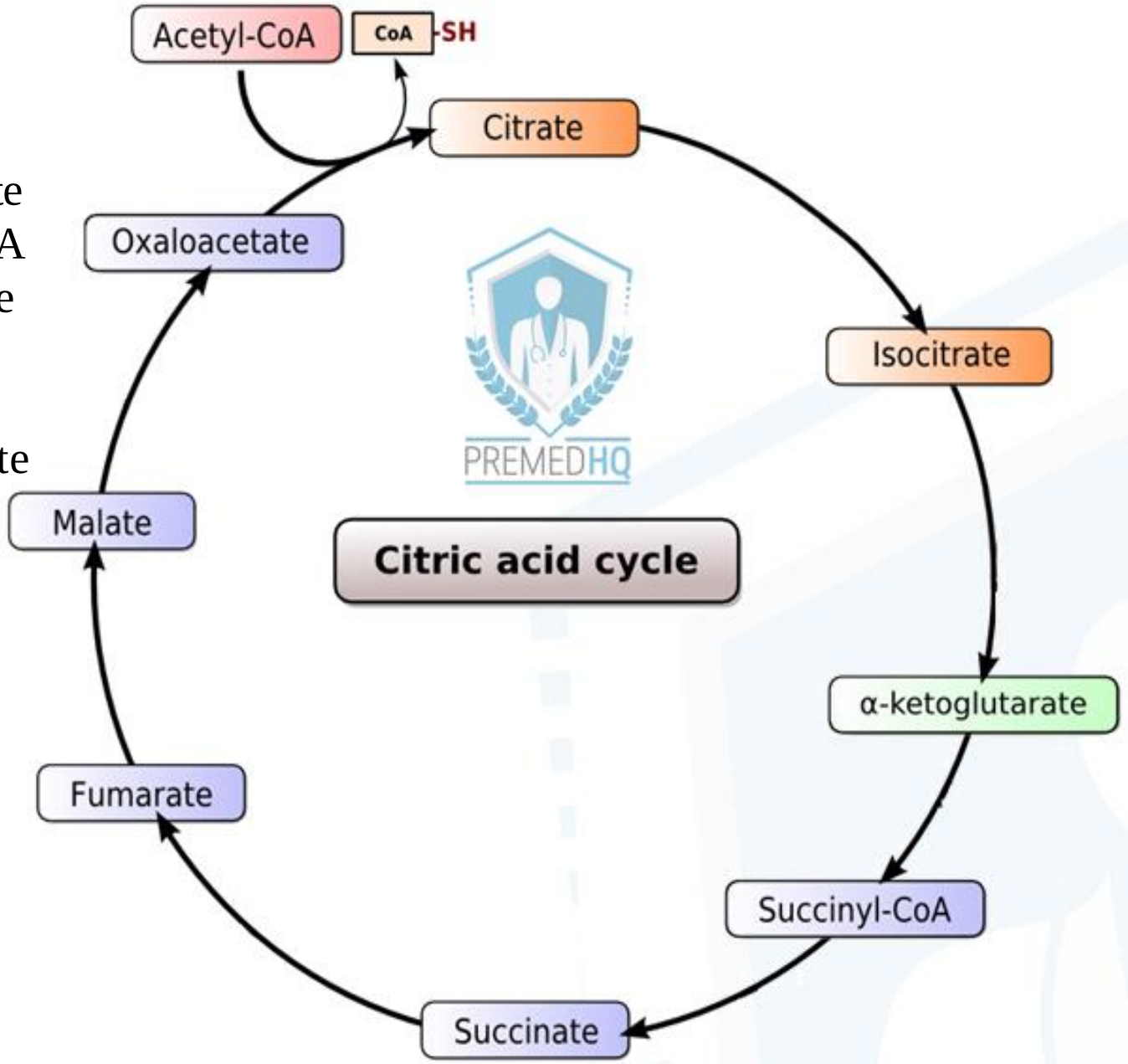


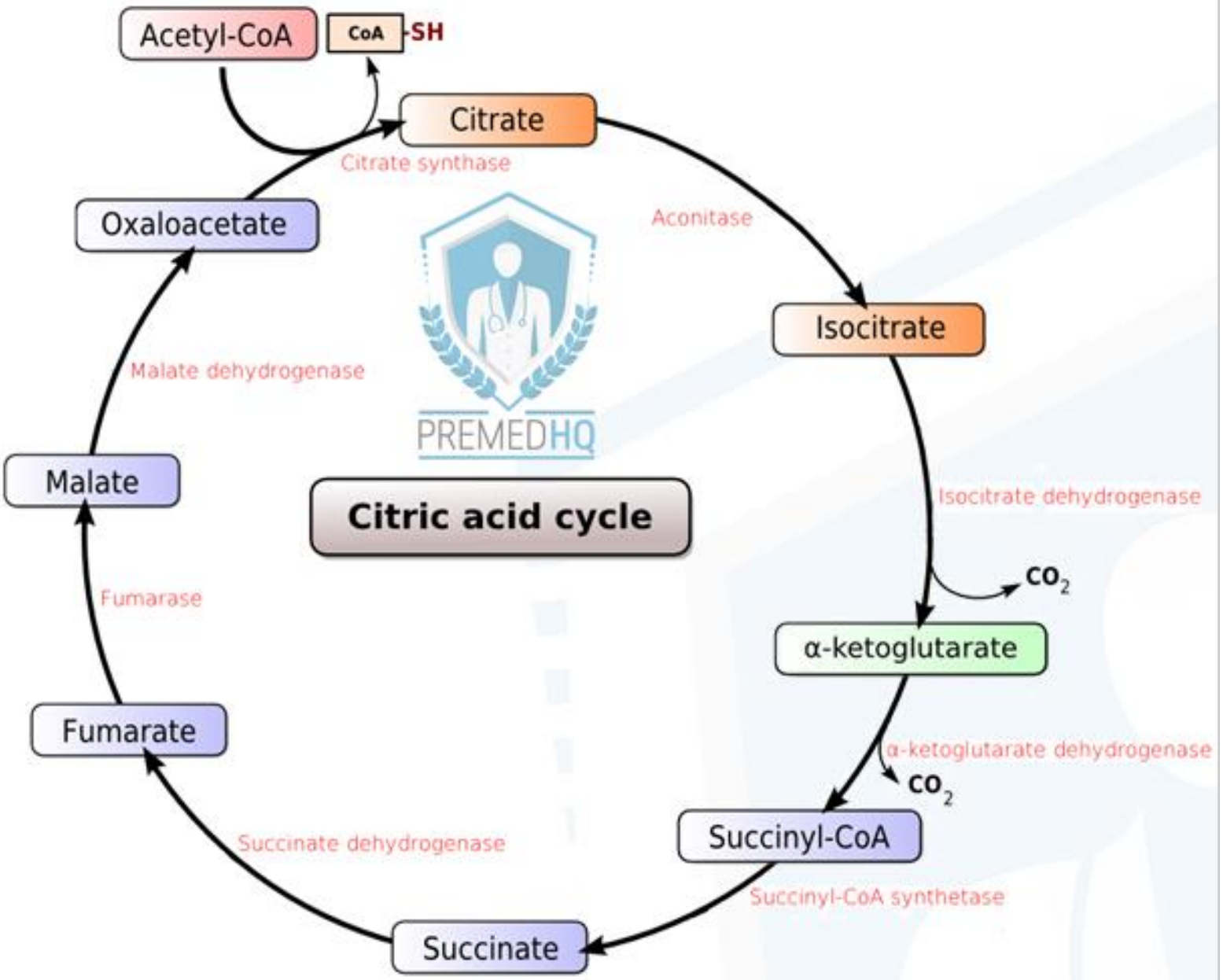
The first step to memorizing the Krebs Cycle is to know the 8 key players.

The 8 key players are:

1. Citrate
2. Isocitrate
3. α-Ketoglutarate
4. Succinyl-CoA
5. Succinate
6. Fumarate
7. Malate
8. Oxaloacetate

Can – **C**itrate
I – **I**socitrate
Keep – α-**K**etoglutarate
Selling – **S**uccinyl-CoA
Substances – **S**uccinate
For – **F**umarate
Money – **M**alate
Officer? – **O**xaloacetate




Acetyl-CoA
CoA
SH
Citrate
Citrate synthase
Aconitase
Isocitrate
Isocitrate dehydrogenase
CO_2
α-ketoglutarate
α-ketoglutarate dehydrogenase
CO_2
Succinyl-CoA
Succinyl-CoA synthetase
Succinate
Succinate dehydrogenase
Fumarate
Fumarase
Malate
Malate dehydrogenase
Oxaloacetate
PREMEDHQ
Citric acid cycle

An Overview of the Citric Acid Cycle

A **four-carbon oxaloacetate** condenses with a **two-carbon acetyl** unit to yield a **six-carbon citrate**.

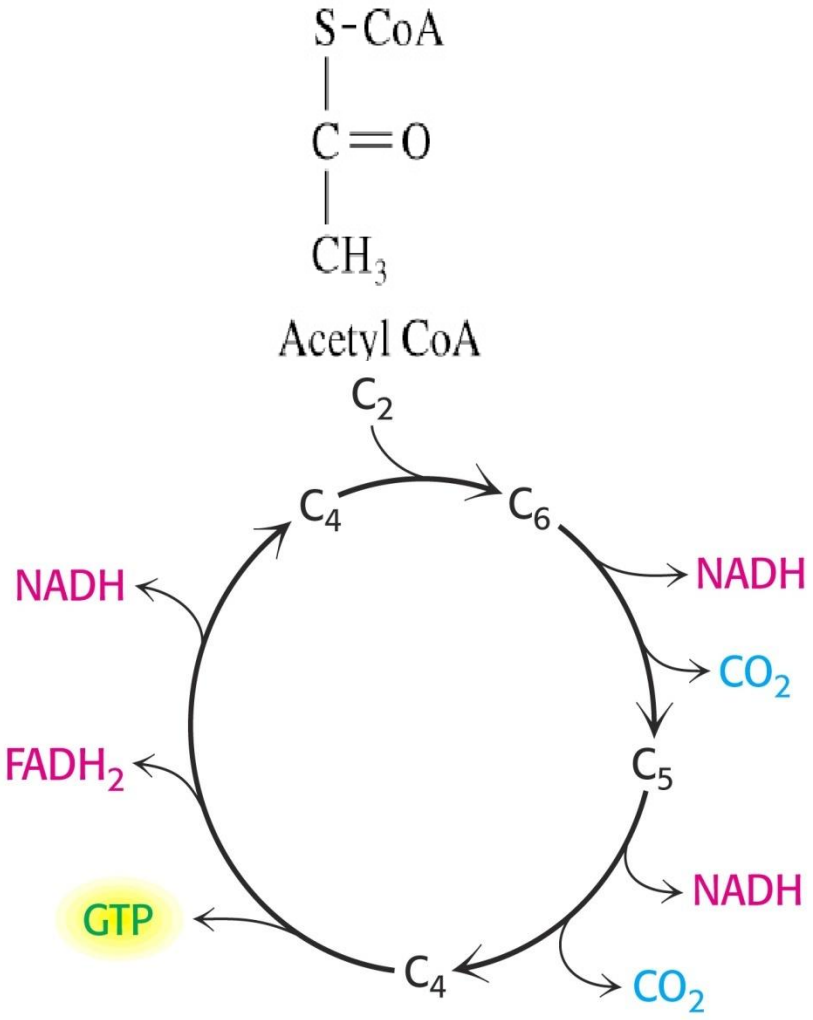
An isomer of citrate is oxidatively decarboxylated and **five-carbon α-ketoglutarate** is formed.

α-ketoglutarate is oxidatively decarboxylated to yield a **four-carbon succinate**.

Oxaloacetate is then regenerated from **succinate**.

Two carbon atoms (**acetyl CoA**) **enter the cycle** and **two carbon atoms leave the cycle** in the form of two molecules of **carbon dioxide**.

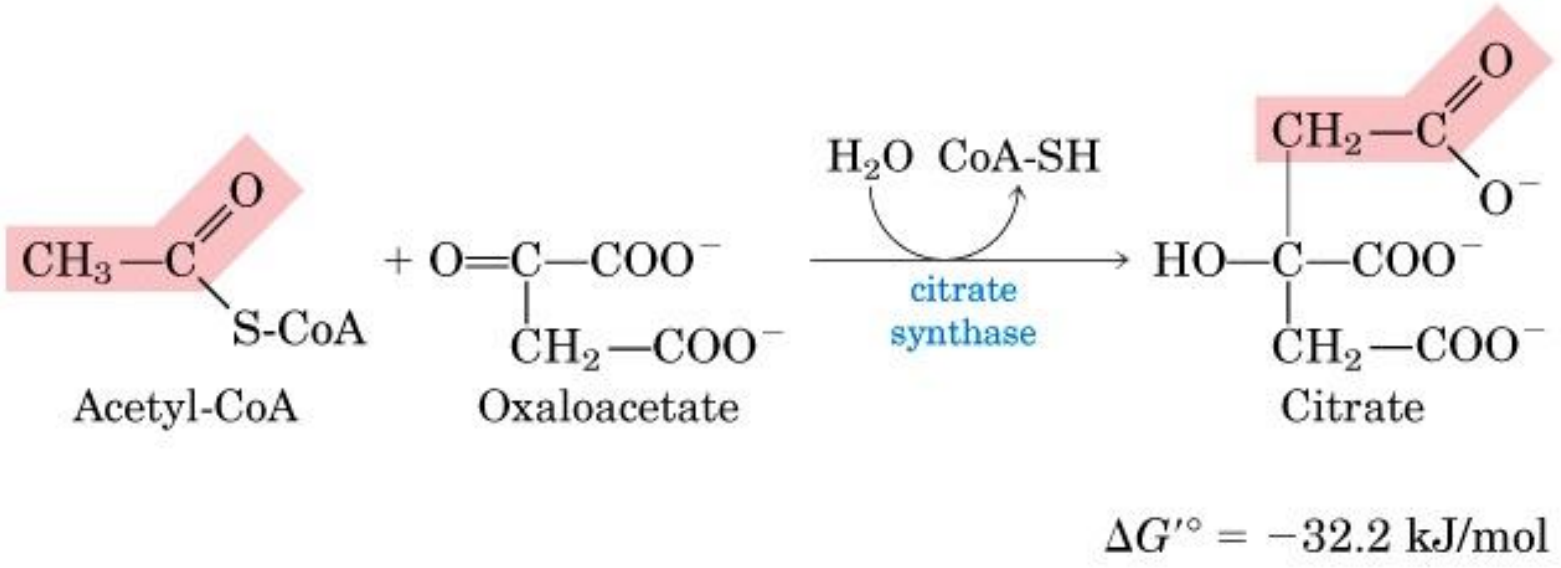
Three hydride ions (**six electrons**) are transferred to three molecules of **NAD^+**, **one pair of hydrogen atoms** (**two electrons**) is transferred to one molecule of **FAD**.



Reactions of Citric Acid Cycle

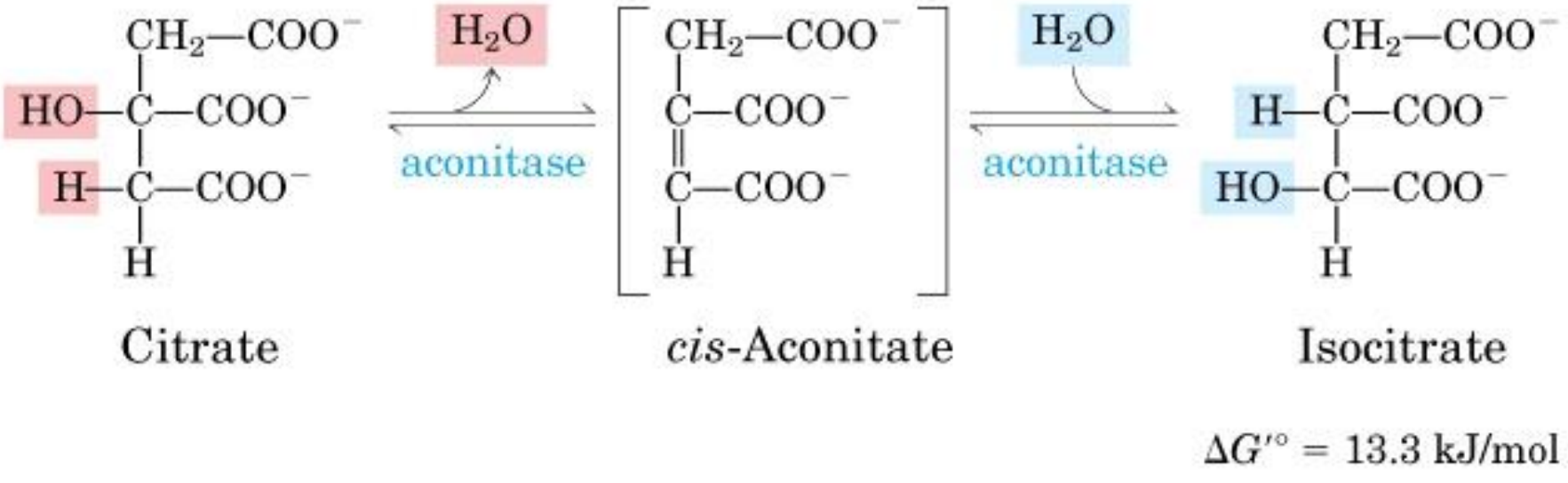
The citric acid cycle has eight steps :

1.Formation of citrate: the first reaction of the cycle is the condensation of acetyl-coA with oxaloacetate to form citrate, catalyzed by **citrate synthase**.



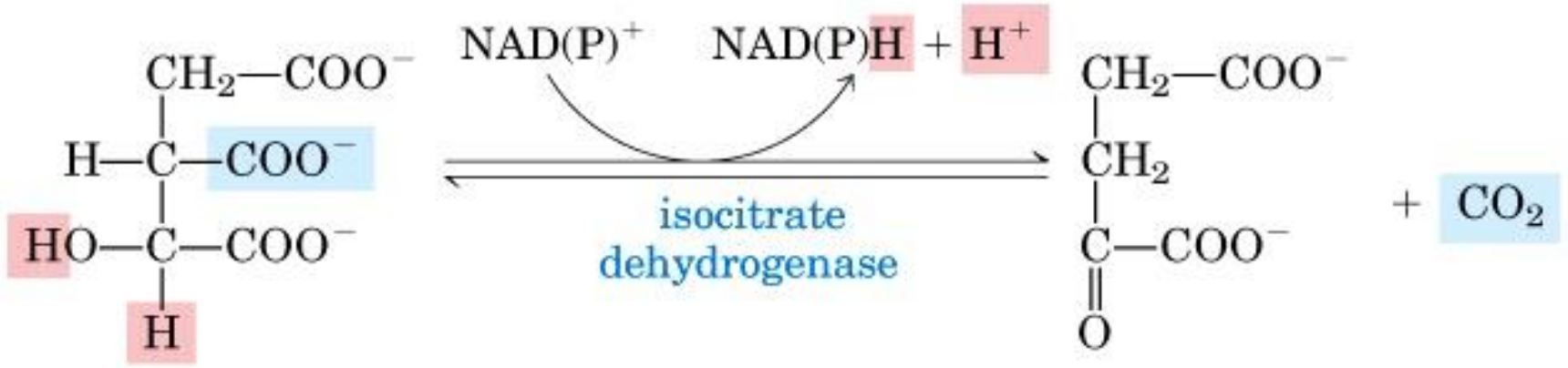
$\Delta G'^{\circ} = -32.2$ kJ/mol

2. Aconitase: This enzyme catalyses the isomerization reaction by removing and then adding back the water to cis-aconitate in at different positions. Isocitrate is consumed rapidly by the next step thus deriving the reaction in forward direction.



3. Isocitrate dehydrogenase:

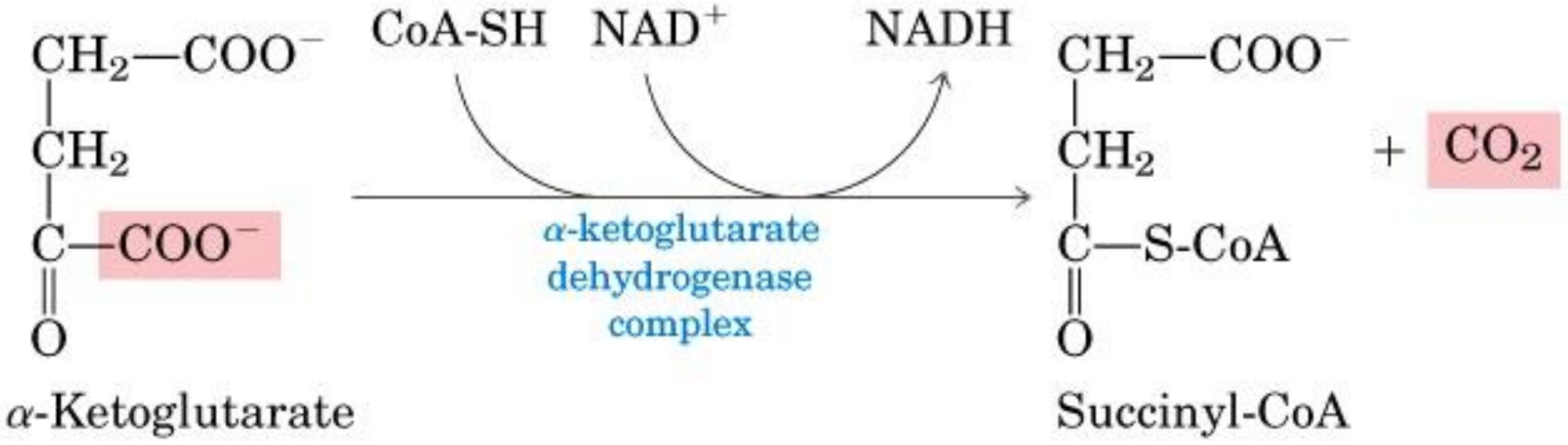
Oxidation ; Decarboxylation ناشر للطاقة



$\Delta G'^{\circ} = -20.9$ kJ/mol

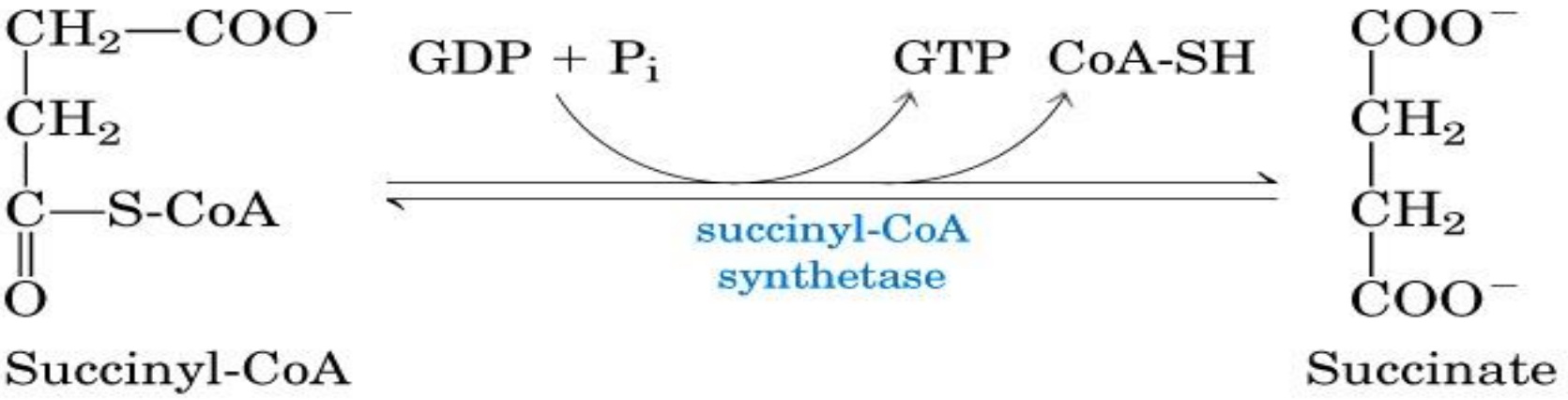
4. a-Ketoglutarate dehydrogenase: Oxidative decarboxylation of α-ketoglutarate..

-In this irreversible reaction, α-ketoglutarate is converted to succinyl-CoA and CO2 , this reaction uses enzymatic activities similar to the pyruvate dyhdogenase complex



$\Delta G'^{\circ} = -33.5$ kJ/mol

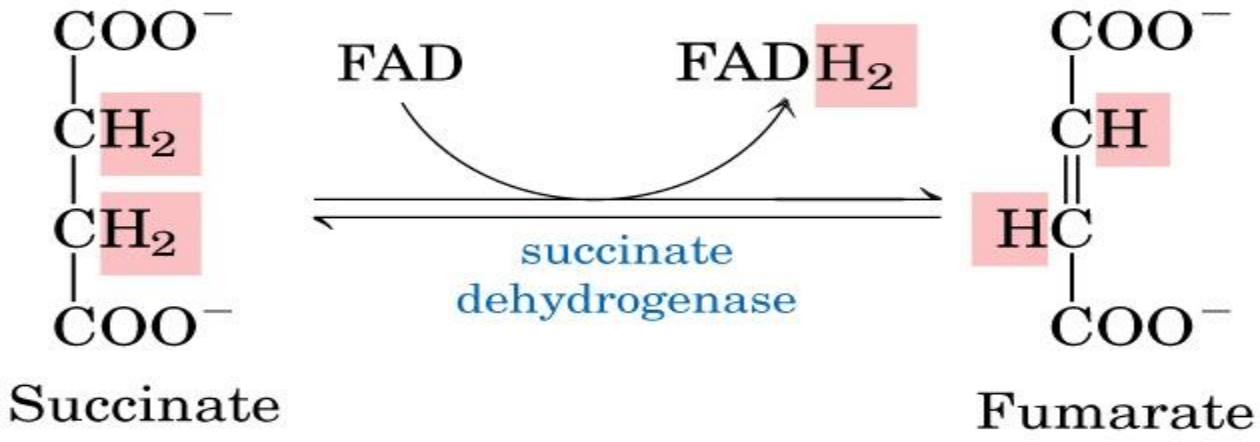
5. Conversion of Succinyl-CoA to Succinate: Succinyl- CoA, like acetyl-CoA, has a thioester bond. Energy released in the breakage of this bond is used to drive the synthesis of GTP (or ATP). Succinate is formed in this process. The enzyme that catalyzes this reversible reaction is called succinyl-CoA synthetase (or succinic thiokinase).



Succinyl-CoA Succinate

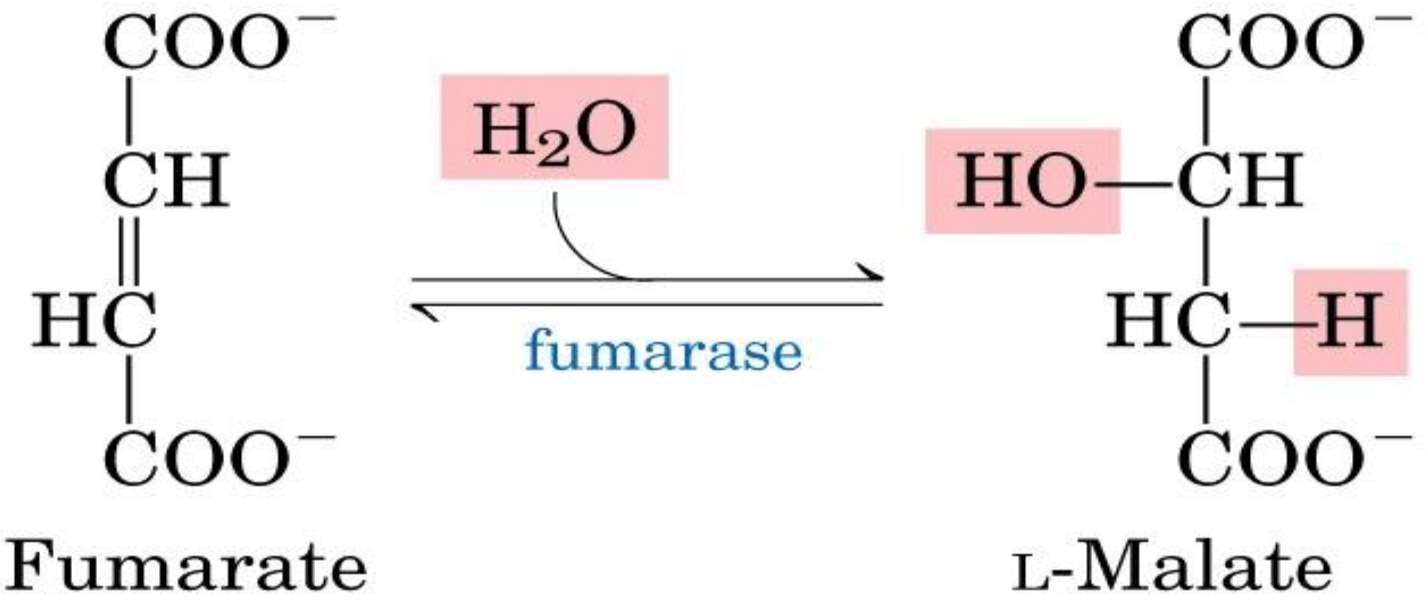
$$\Delta G'^{\circ} = -2.9 \text{ kJ/mol}$$

6. Succinate Dehydrogenase: Oxidation of succinate to fumarate. This is the only citric acid cycle enzyme that is tightly bound to the inner mitochondrial membrane. It is an FAD dependent enzyme.



$$\Delta G'^{\circ} = 0 \text{ kJ/mol}$$

7. Hydration of Fumarate to malate by Fumarase: It is a highly stereospecific enzyme. Cis-Maleate (the cis form of fumarate is not recognized by this enzyme.

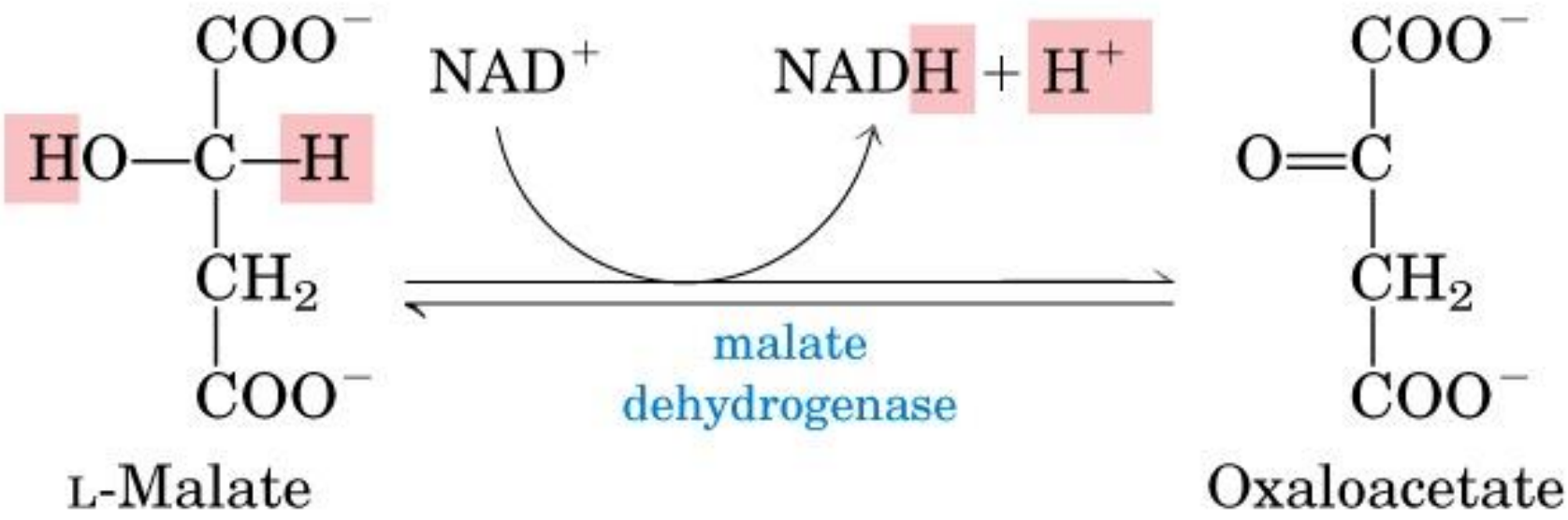


Fumarate L-Malate

$$\Delta G'^{\circ} = -3.8 \text{ kJ/mol}$$

8. L-Malate dehydrogenase: Oxidation of malate to oxaloacetate: It is an NAD^+dependent enzyme.

Oxidation of Malate to Oxaloacetate: In the last reaction of the citric acid cycle, NAD-linked L-malate dehydrogenase catalyzes the oxidation of L-malate to oxaloacetate.



L-Malate Oxaloacetate

$$\Delta G'^{\circ} = 29.7 \text{ kJ/mol}$$

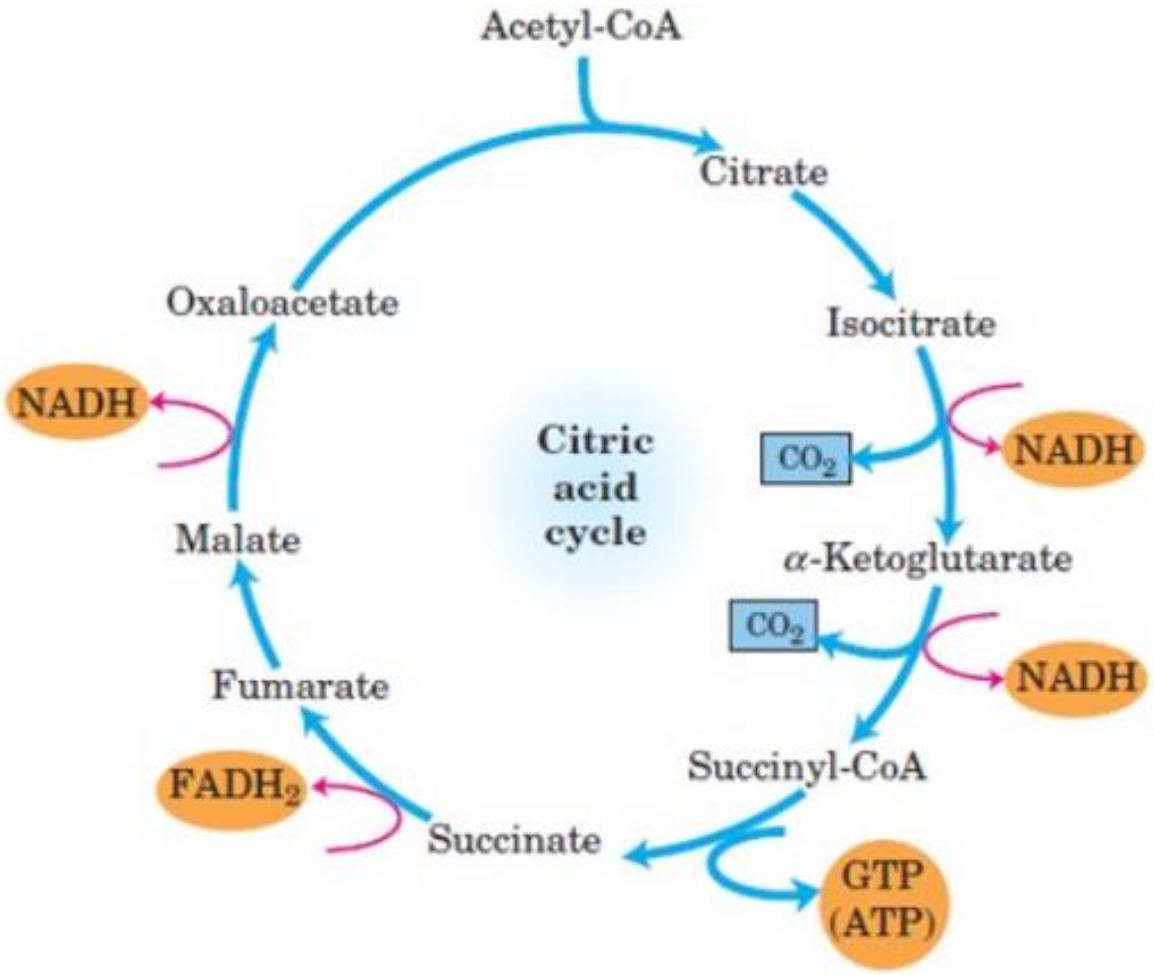
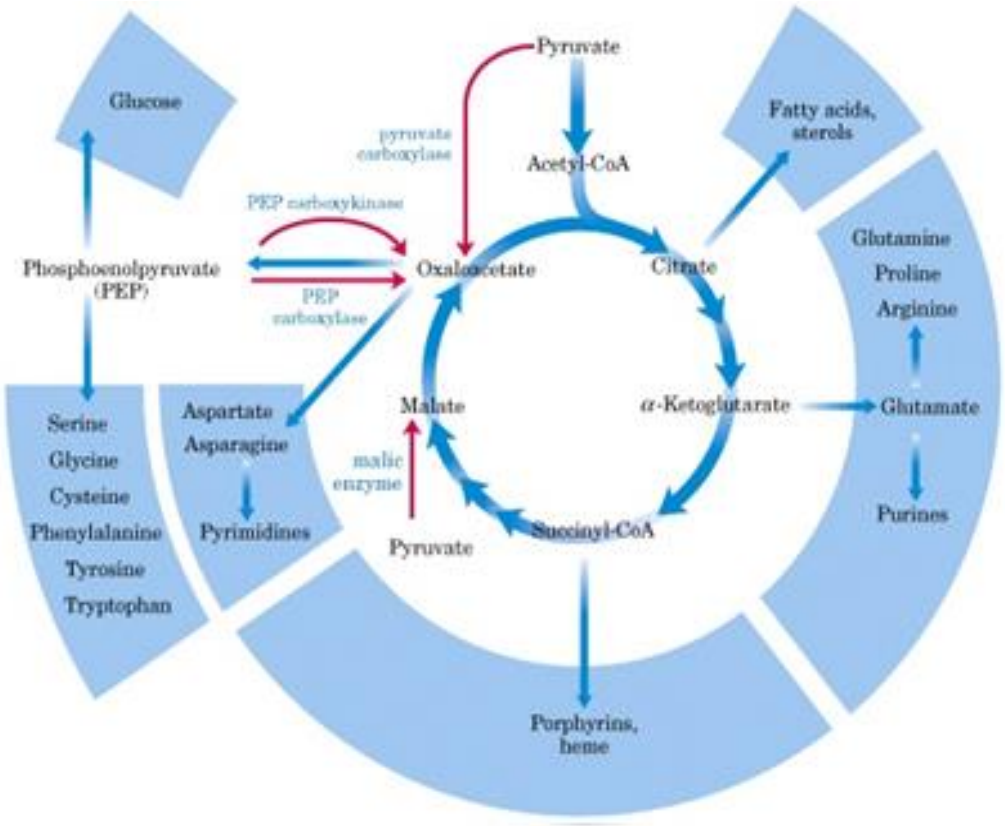


FIGURE 16–13 Products of one turn of the citric acid cycle. At each turn of the cycle, three NADH, one $FADH_2$, one GTP (or ATP), and two CO_2 are released in oxidative decarboxylation reactions. Here and in several following figures, all cycle reactions are shown as proceeding in one direction only, but keep in mind that most of the reactions are reversible (see Fig. 16–7).

Citric acid cycle is an amphibolic pathway, one that serves in both *catabolic and anabolic* processes. Besides its role in the **oxidative catabolism** of carbohydrates, fatty acids and amino acids, the cycle provides **precursors for many biosynthetic pathways**.

α-Ketoglutarate and **oxaloacetate** can serve as precursors of the amino acids aspartate and glutamate by simple transamination

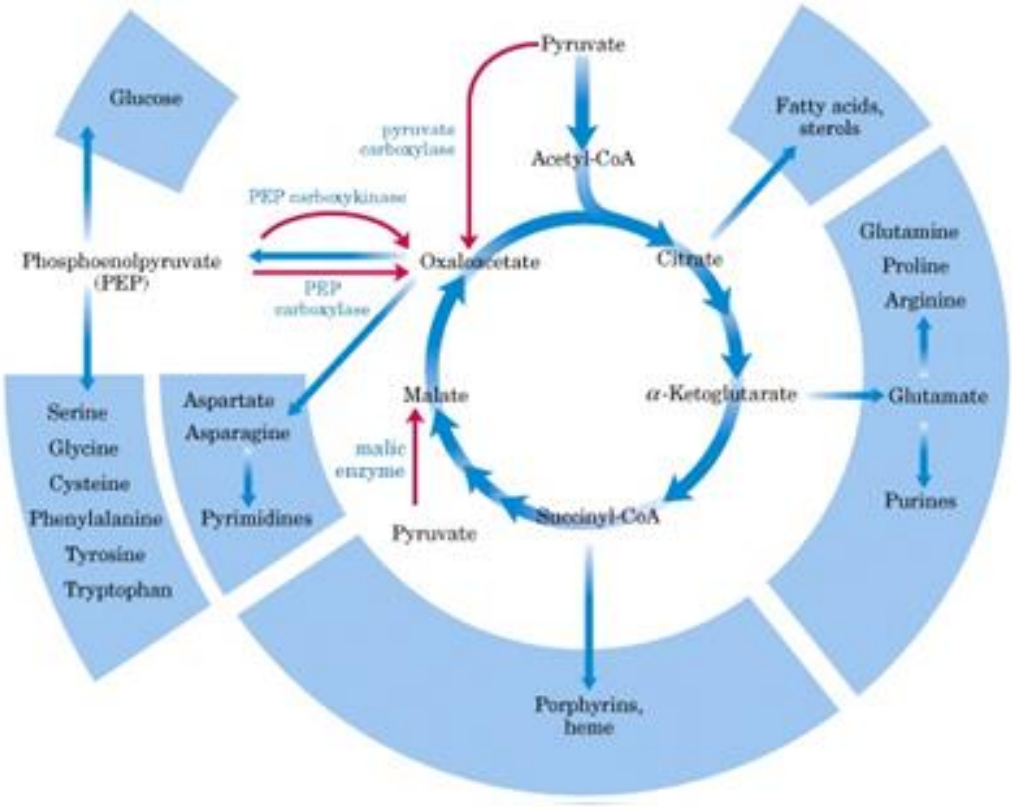
Through aspartate and glutamate, the carbons of oxaloacetate and α-Ketoglutarate are then used to build other amino acids as well as purines and pyrimidine nucleotide



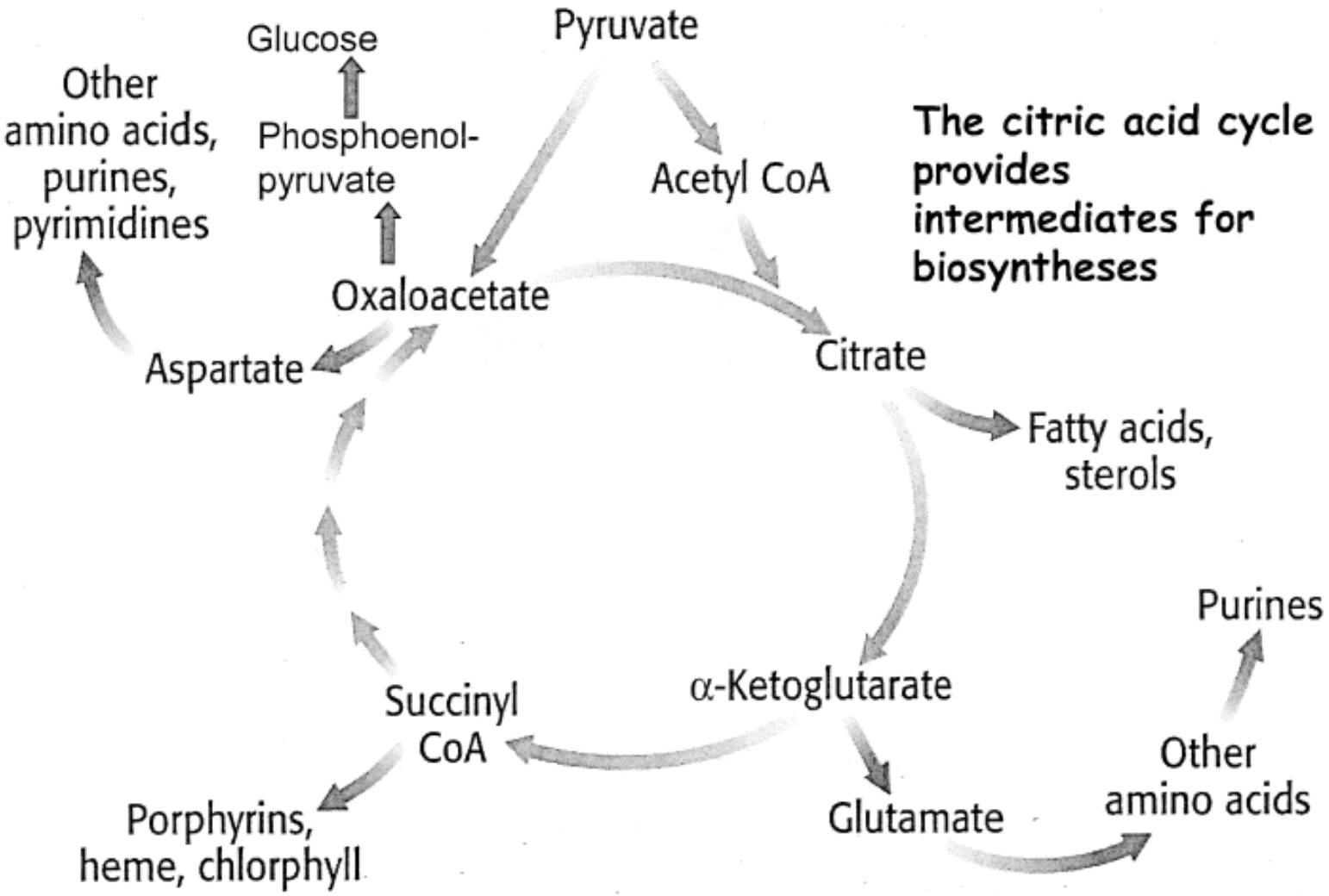
Oxaloacetate is converted to glucose in gluconeogenesis.

Succcinyl-CoA is a central intermediate in the synthesis of the porphyrin ring of heme group, which serve as oxygen carriers (in hemoglobin and myoglobin)

Citrate plays various purposes: fatty acids



Krebs Cycle is a Source of Biosynthetic Precursors



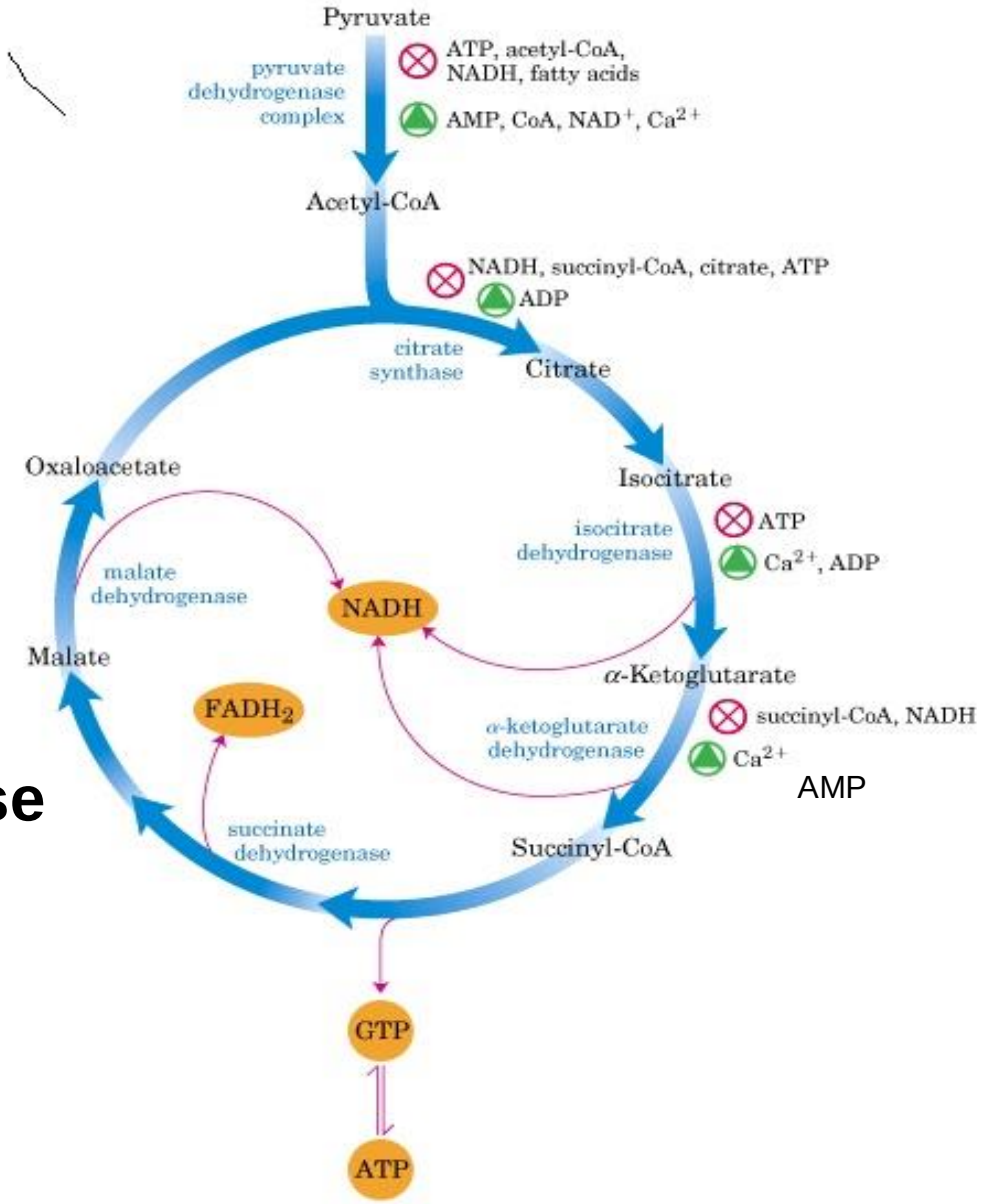
Regulation of CAC:

Rate controlling enzymes:

Citrate synthatase

Isocitrate dehydrogenase

α-keoglutaratedehydrogenase



Regulation of the TCA Cycle

Again, 3 reactions are the key sites

- **Citrate synthase** - ATP, NADH and succinyl-CoA inhibit
- **Isocitrate dehydrogenase** - ATP inhibits, ADP and NAD^+ activate
- **α -Ketoglutarate dehydrogenase** - NADH and succinyl-CoA inhibit, AMP activates