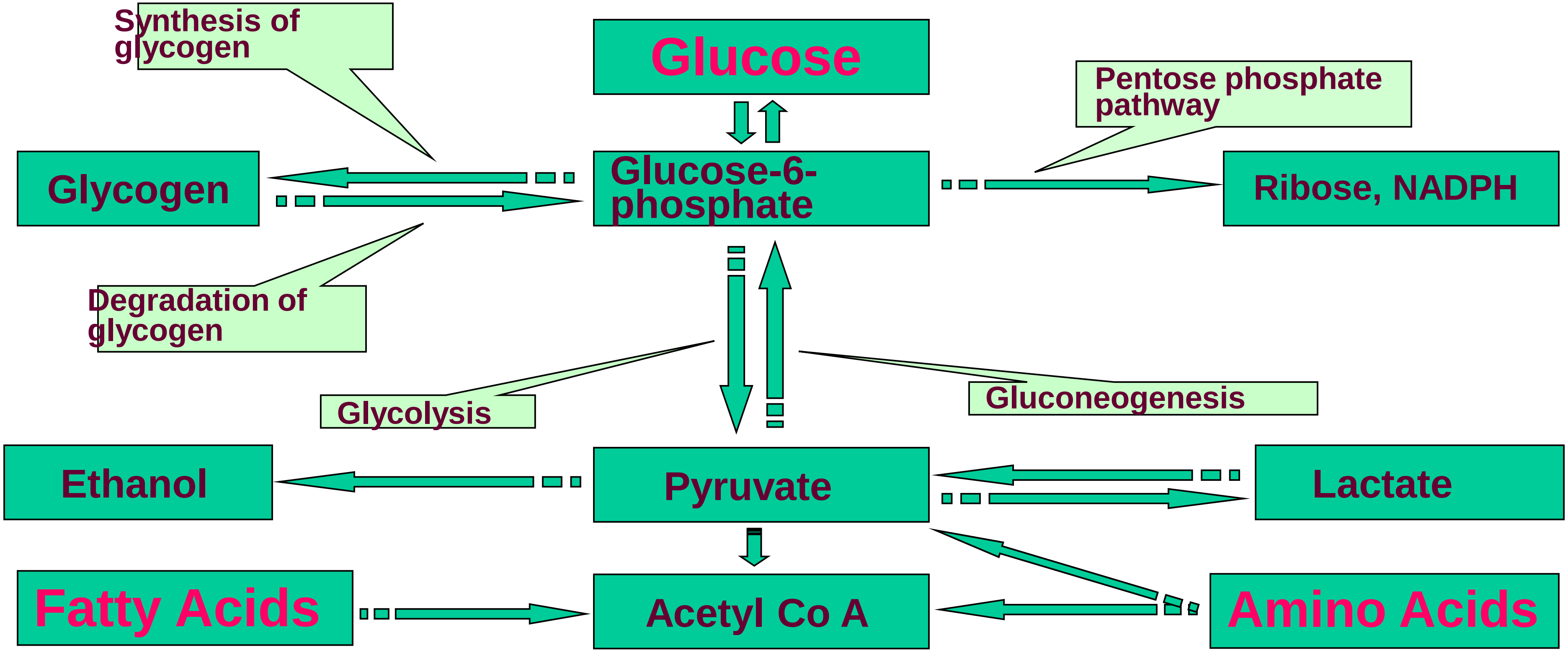
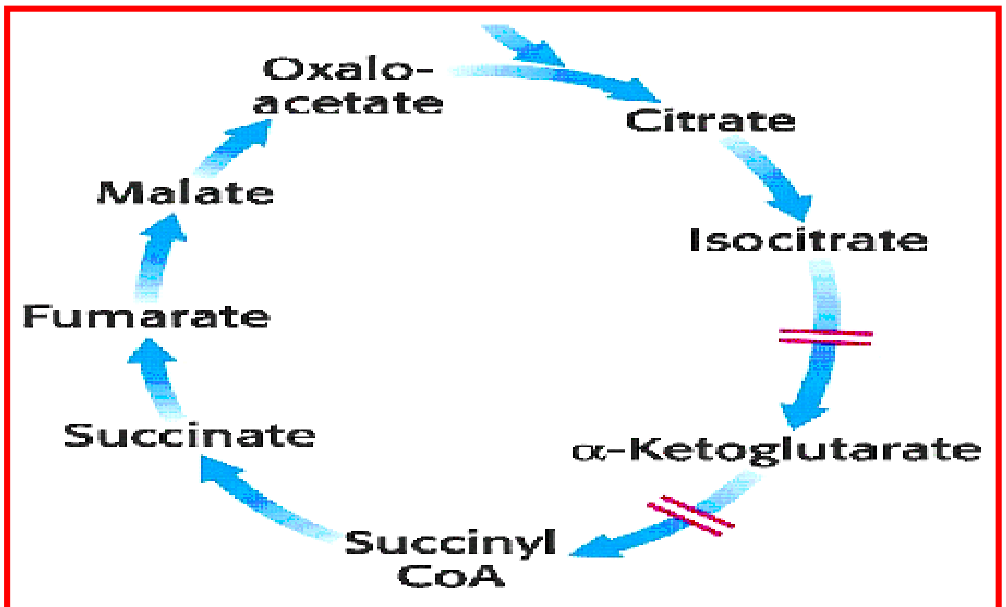
The Citric Acid Cycle

Aerobic cells use a metabolic wheel – the citric acid cycle – to generate energy by acetyl CoA oxidation



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

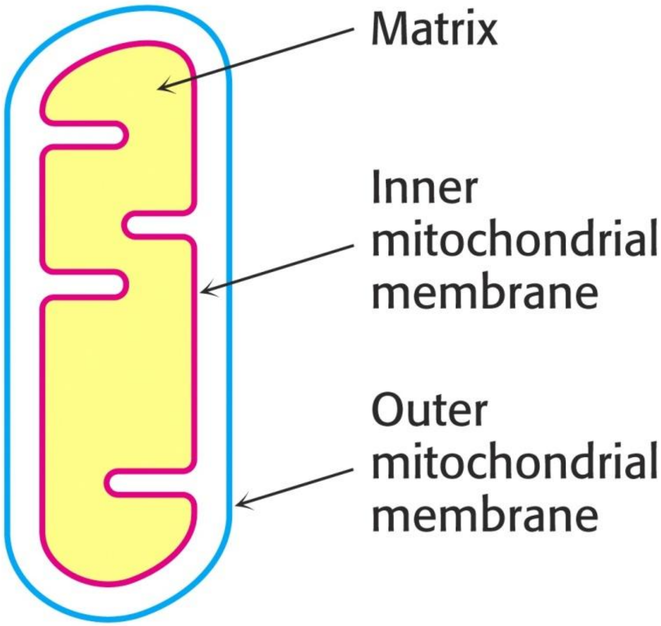
Tricarboxylic Acid Cycle

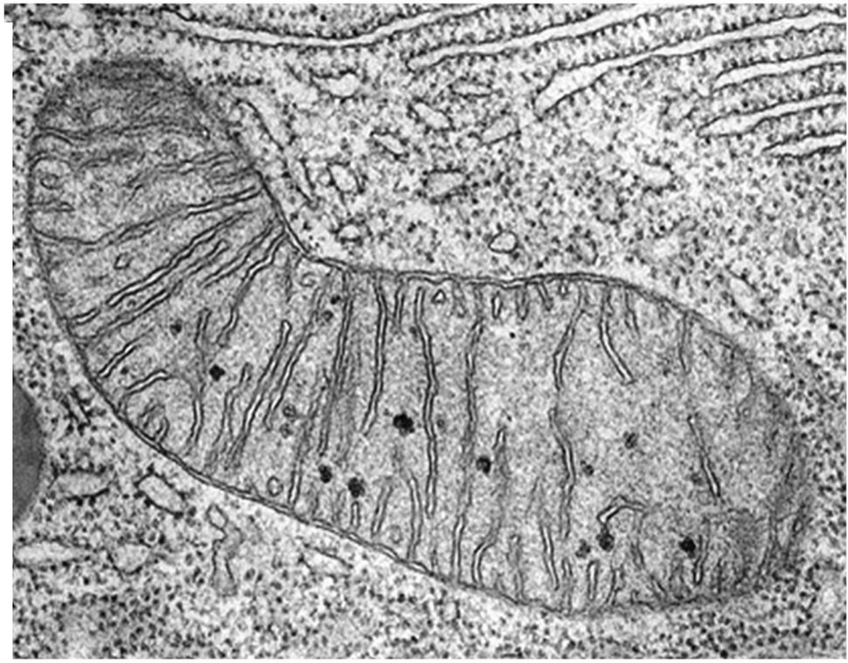
Krebs Cycle

Hans Adolf Krebs.

Biochemist; born in Germany. Worked in Britain. His discovery in 1937 of the 'Krebs cycle' of chemical reactions was critical to the understanding of cell metabolism and earned him the 1953 Nobel Prize for Physiology or Medicine.

In eukaryotes the reactions of the citric acid cycle take place inside mitochondria





An Overview of the Citric Acid Cycle

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

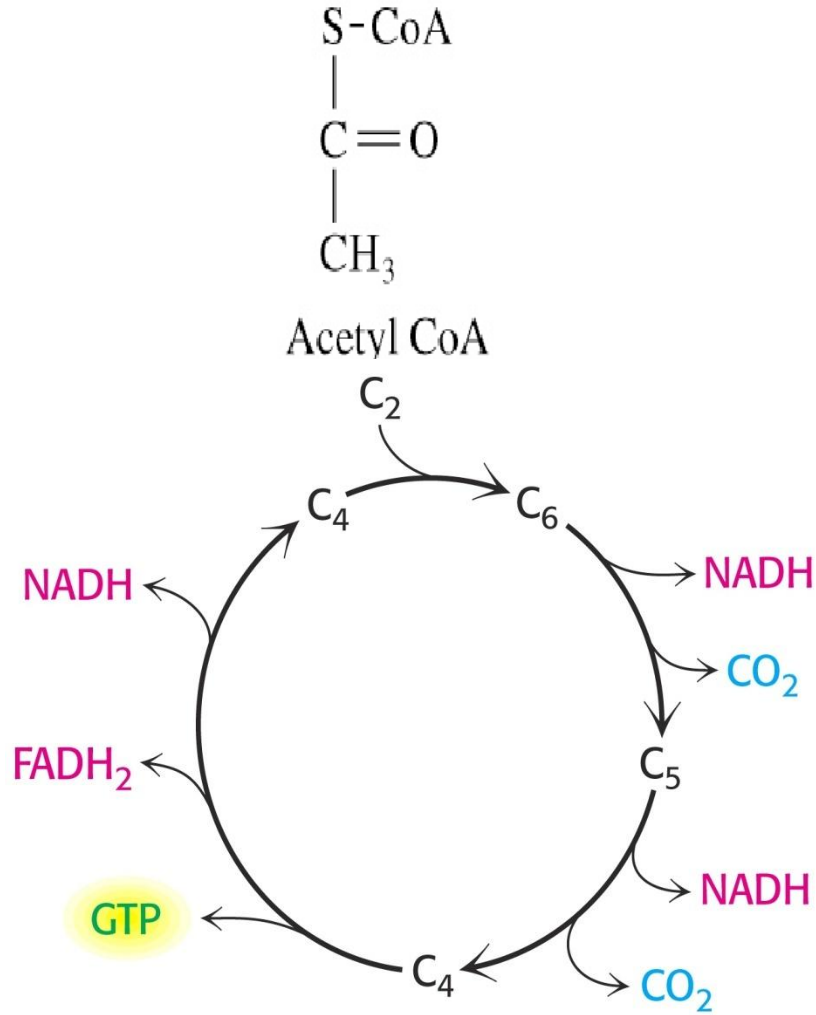
An isomer of citrate is oxidatively decarboxylated and **five-carbon α-ketoglutarate** is formed.

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**.

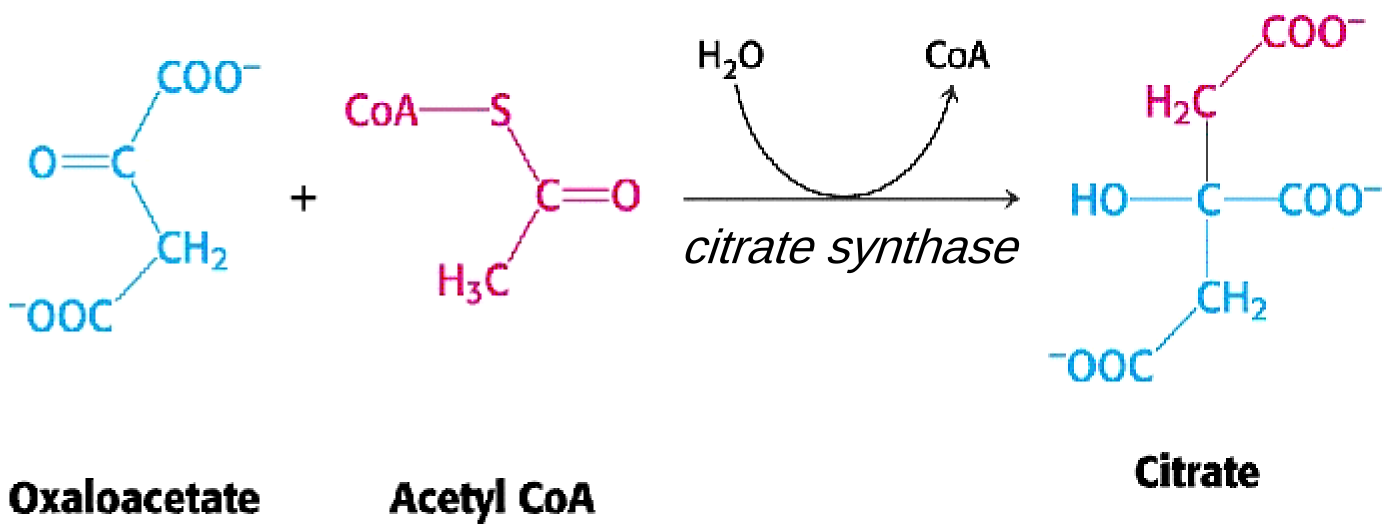
Three hydride ions (**six electrons**) are transferred to three molecules of **NAD^+**, **one pair of hydrogen atoms** (**two electrons**) is transferred to one molecule of **FAD**.



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

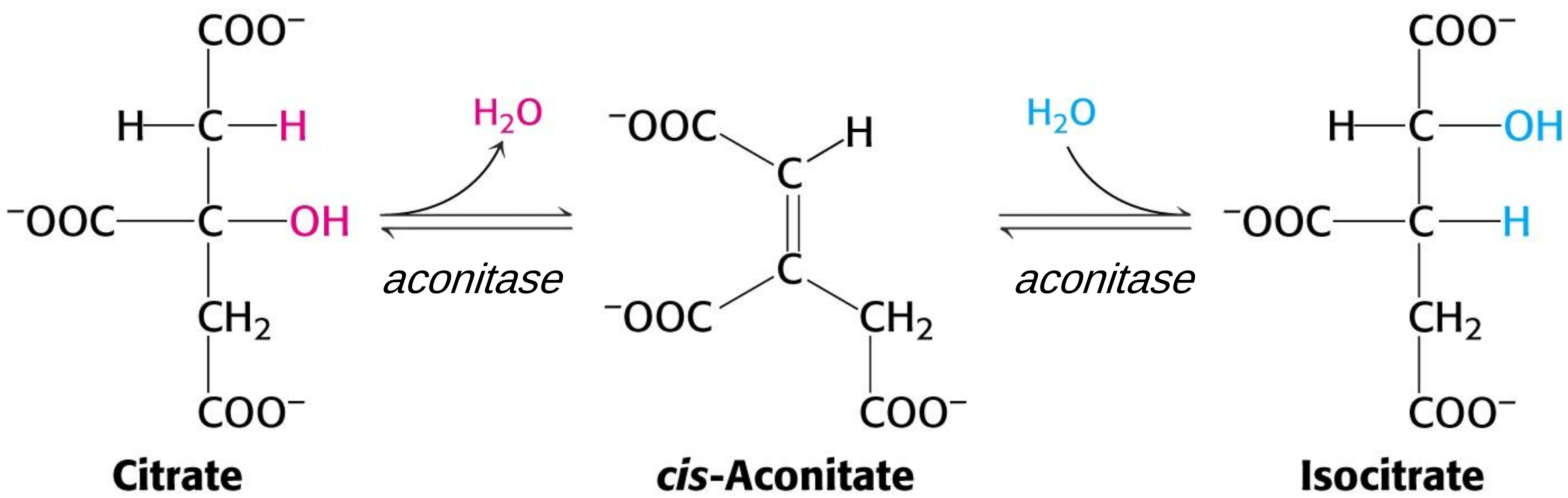
1. Citrate Synthase

- **Citrate** formed from **acetyl CoA** and **oxaloacetate**
- Only cycle reaction with C-C bond formation
- Addition of C_2 **unit** (acetyl) to the keto double bond of C_4 acid, oxaloacetate, to produce C_6 compound, citrate



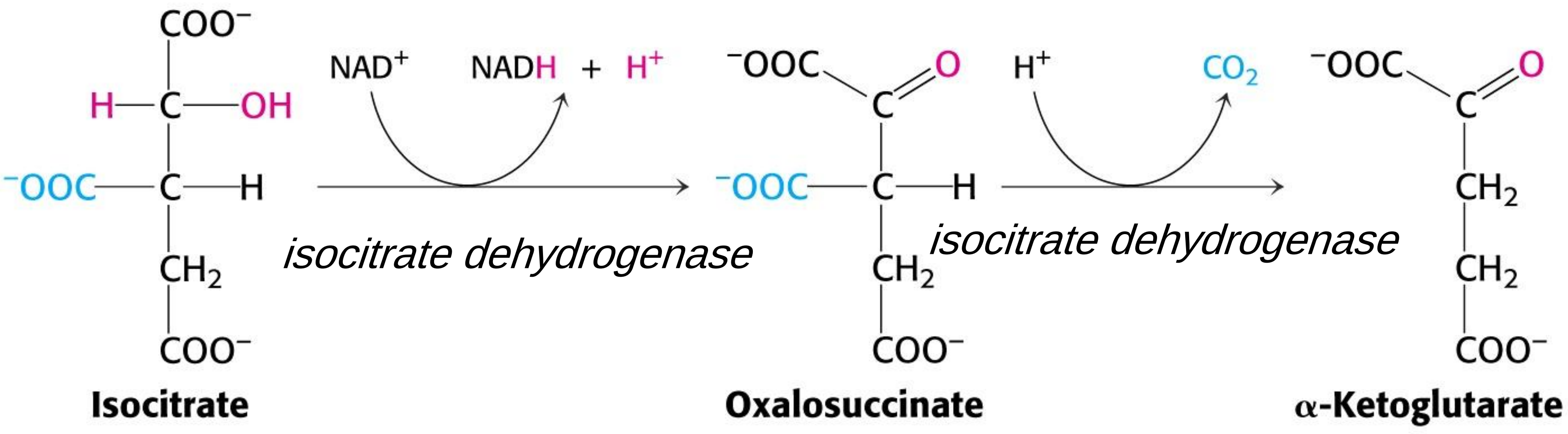
2. Aconitase

- Elimination of H_2O from citrate to form C=C bond of ***cis*-aconitate**
- Stereospecific addition of H_2O to *cis*-aconitate to form **isocitrate**



3. Isocitrate Dehydrogenase

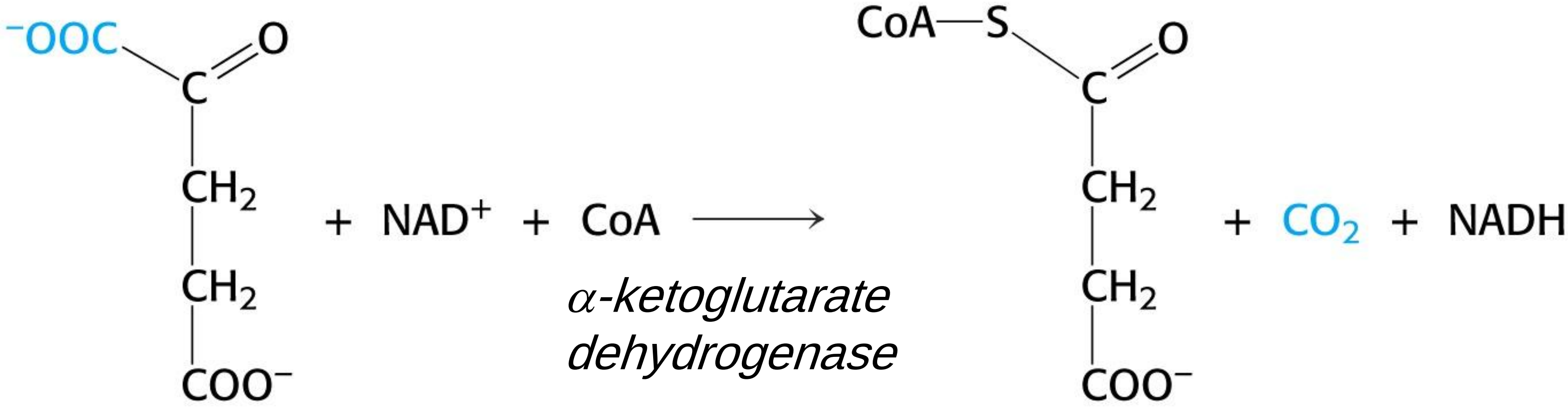
- Oxidative decarboxylation of isocitrate to a-ketoglutarate **(a metabolically irreversible reaction)**
- One of four oxidation-reduction reactions of the cycle
- Hydride ion from the *C*-2 of isocitrate is transferred to NAD^+ to form NADH
- Oxalosuccinate is decarboxylated to a-ketoglutarate



4. The α-Ketoglutarate Dehydrogenase Complex

- Similar to pyruvate dehydrogenase complex
- Same coenzymes, identical mechanisms

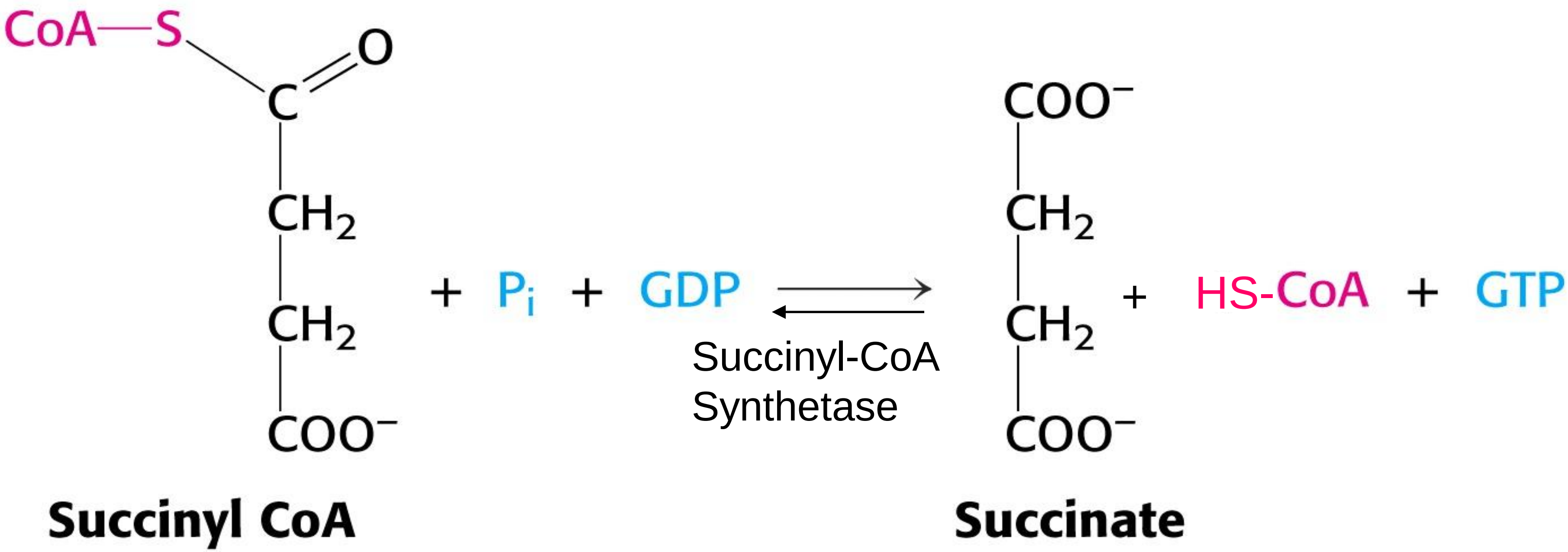
E_1 - ***a-ketoglutarate dehydrogenase*** (with **TPP**)
E_2 – ***dihydrolipoyl succinyltransferase*** (with flexible **lipoamide** prosthetic group)
E_3 - ***dihydrolipoyl dehydrogenase*** (with **FAD**)



α-Ketoglutarate **Succinyl CoA**

5. Succinyl-CoA Synthetase

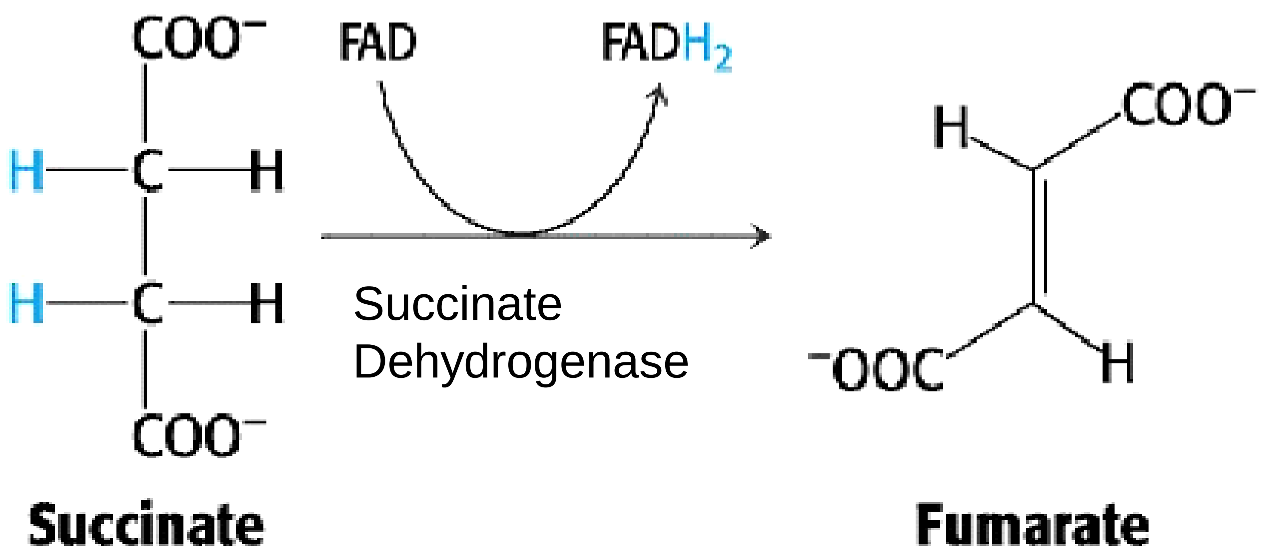
- Free energy in thioester bond of succinyl CoA is conserved as GTP or ATP in higher animals (or ATP in plants, some bacteria)
- **Substrate level phosphorylation** reaction



$$\text{GTP} + \text{ADP} \rightleftharpoons \text{GDP} + \text{ATP}$$

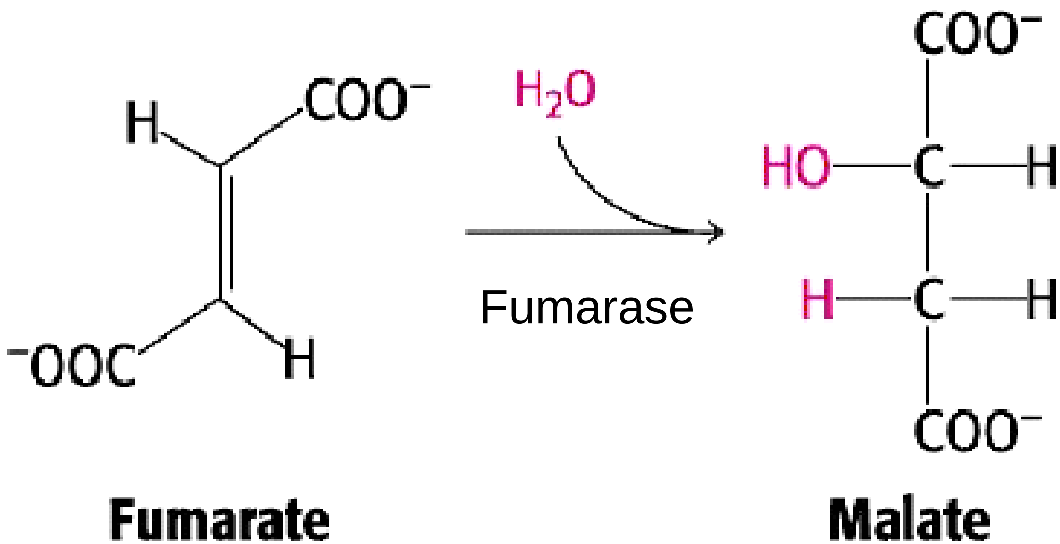
6. The Succinate Dehydrogenase Complex

- Complex of **several polypeptides**, an **FAD** prosthetic group and **iron-sulfur clusters**
- Embedded **in the inner mitochondrial membrane**
- Electrons are transferred **from succinate to FAD and then to ubiquinone (Q)** in electron transport chain
- Dehydrogenation is **stereospecific**; only the ***trans* isomer is formed**



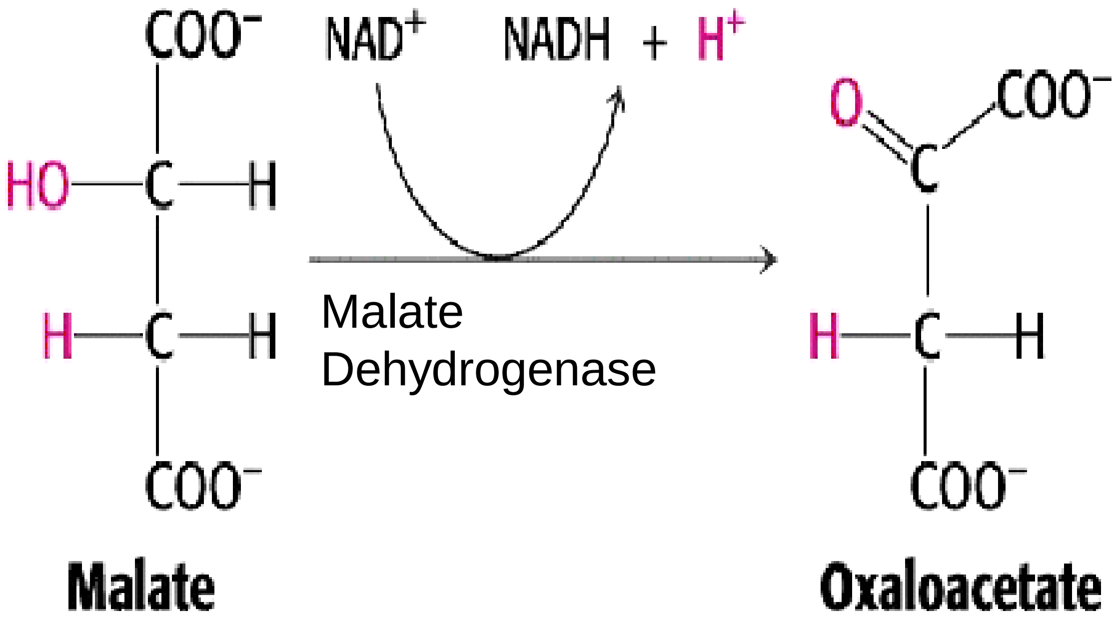
7. Fumarase

- Stereospecific *trans* addition of water to the double bond of **fumarate** to form ***L*-malate**
- Only the **L isomer** of malate is formed



8. Malate Dehydrogenase

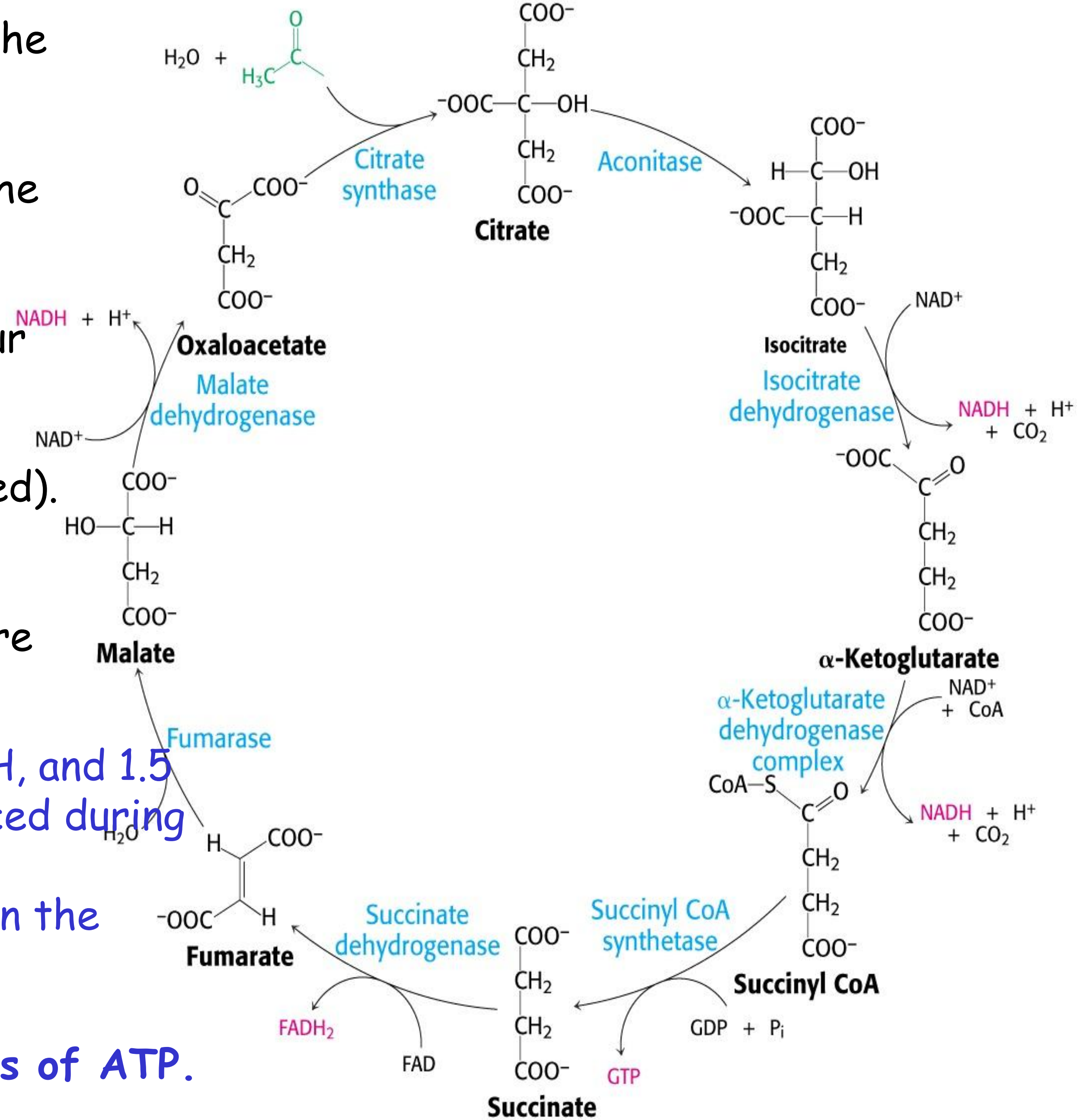
Malate is oxidized to form **oxaloacetate**.



Stoichiometry of the Citric Acid Cycle

- Two carbon atoms enter the cycle in the form of acetyl CoA.
- Two carbon atoms leave the cycle in the form of CO_2 .
- Four pairs of hydrogen atoms leave the cycle in four oxidation reactions (three molecules of NAD^+ one molecule of FAD are reduced).
- One molecule of GTP, is formed.
- Two molecules of water are consumed.

- 9 ATP (2.5 ATP per NADH, and 1.5 ATP per $FADH_2$) are produced during oxidative phosphorylation.
- 1 ATP is directly formed in the citric acid cycle.
- **1 acetyl CoA generates approximately 10 molecules of ATP.**



Functions of the Citric Acid Cycle

- **Integration of metabolism.** The citric acid cycle is ***amphibolic*** **(both catabolic and anabolic).**

The cycle is involved in the aerobic **catabolism** of carbohydrates, lipids and amino acids.

Intermediates of the cycle are starting points for many **anabolic** reactions.

- Yields **energy** in the form of **GTP (ATP).**

- Yields **reducing power** in the form of **$NADH_2$** and **$FADH_2$.**

Regulation of the Citric Acid Cycle

- **Pathway controlled by:**

  (1) Allosteric modulators

  (2) Covalent modification of cycle enzymes

  (3) Supply of acetyl CoA (pyruvate dehydrogenase complex)

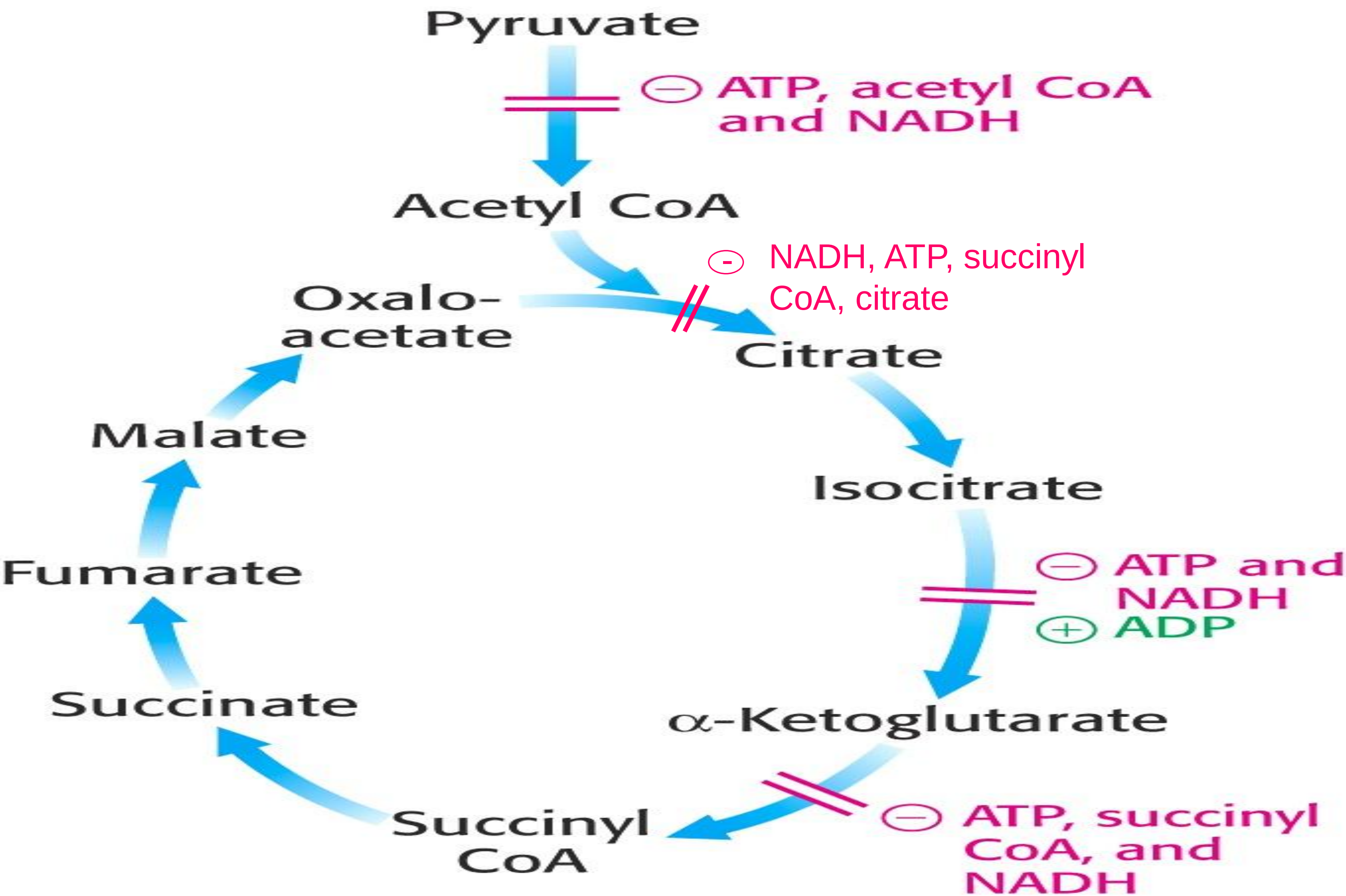
Three enzymes have regulatory properties

- ***citrate synthase*** (is allosterically inhibited by NADH, ATP, succinyl CoA, citrate – feedback inhibition)

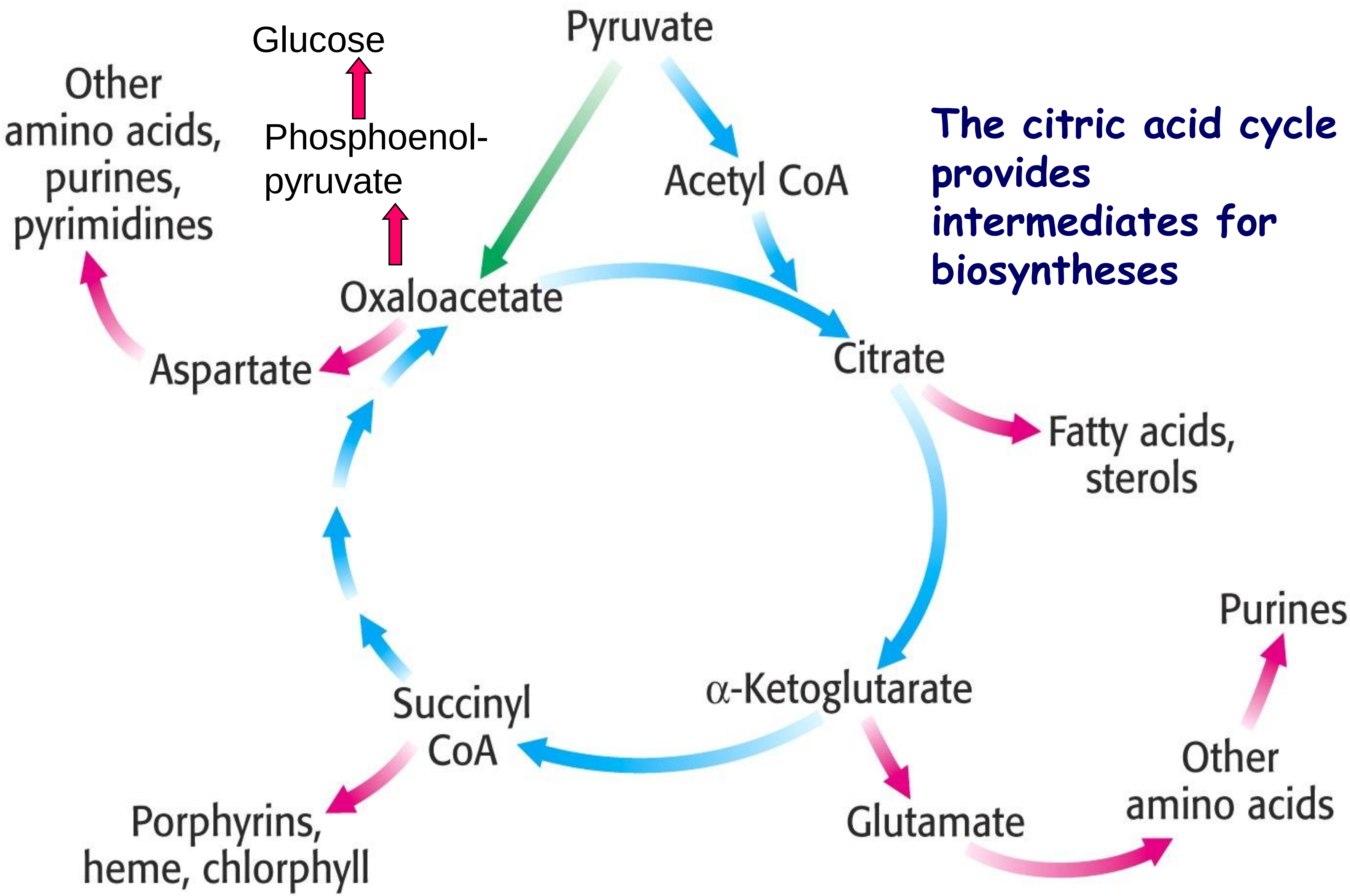
- ***isocitrate dehydrogenase***
(allosteric effectors: (+) ADP; (-) NADH, ATP. Bacterial ICDH can be covalently modified by kinase/phosphatase)

-***α-ketoglutarate dehydrogenase complex*** (inhibition by ATP, succinyl CoA and NADH

Regulation of the citric acid cycle



Krebs Cycle is a Source of Biosynthetic Precursors



The citric acid cycle provides intermediates for biosyntheses