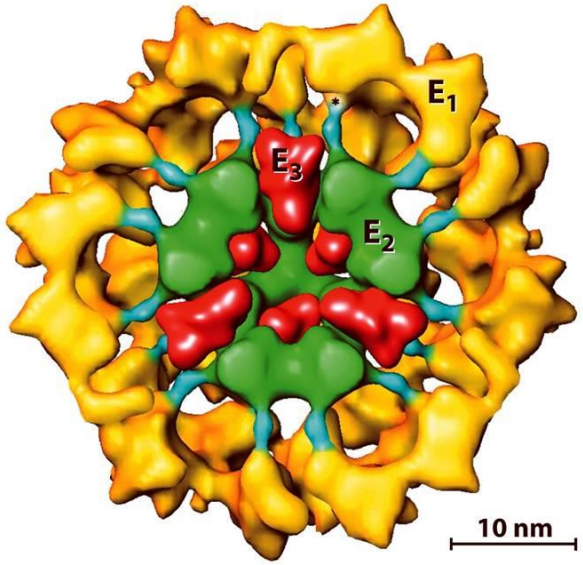
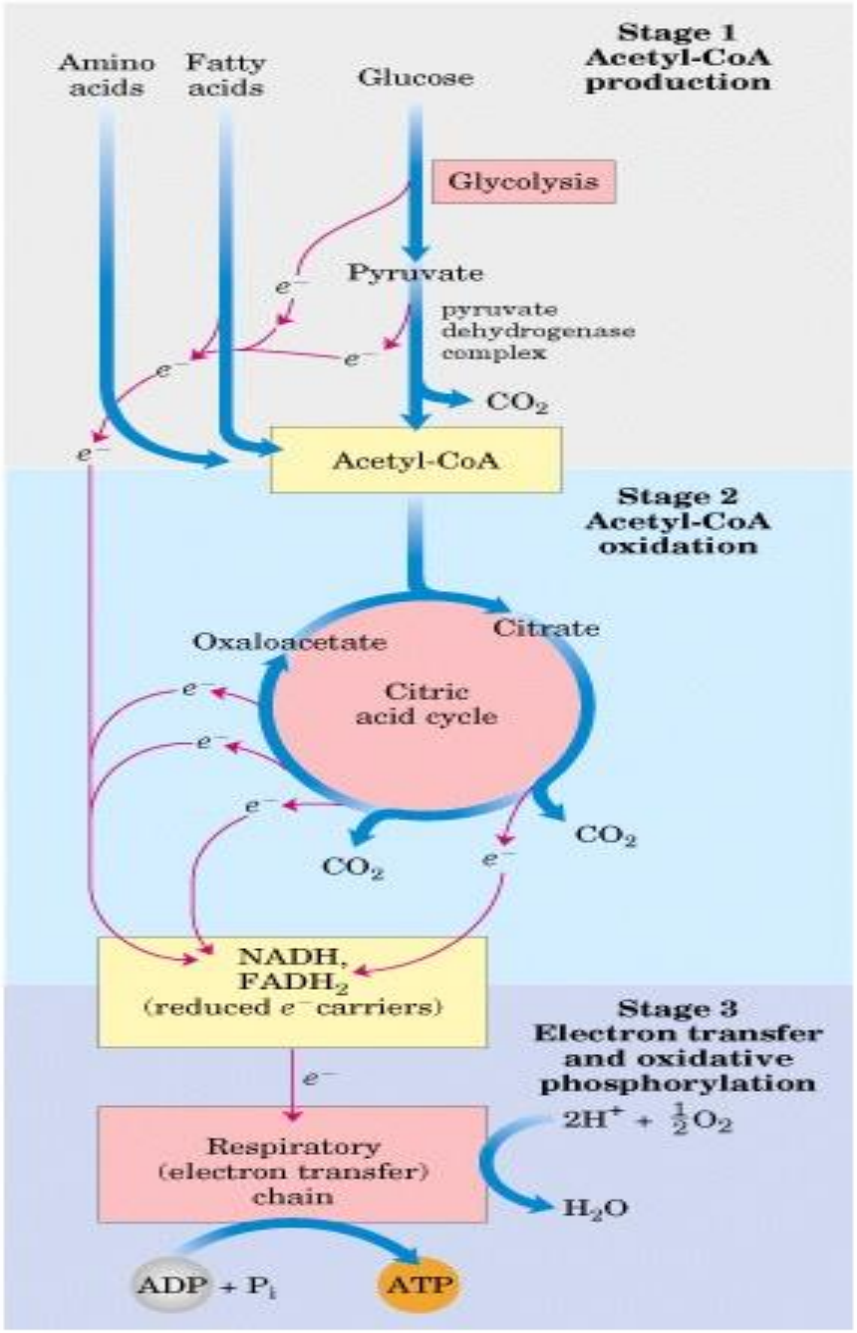
The Citric Acid Cycle

Tricarboxylic Acid cycle(TCA)
Krebs Cycle

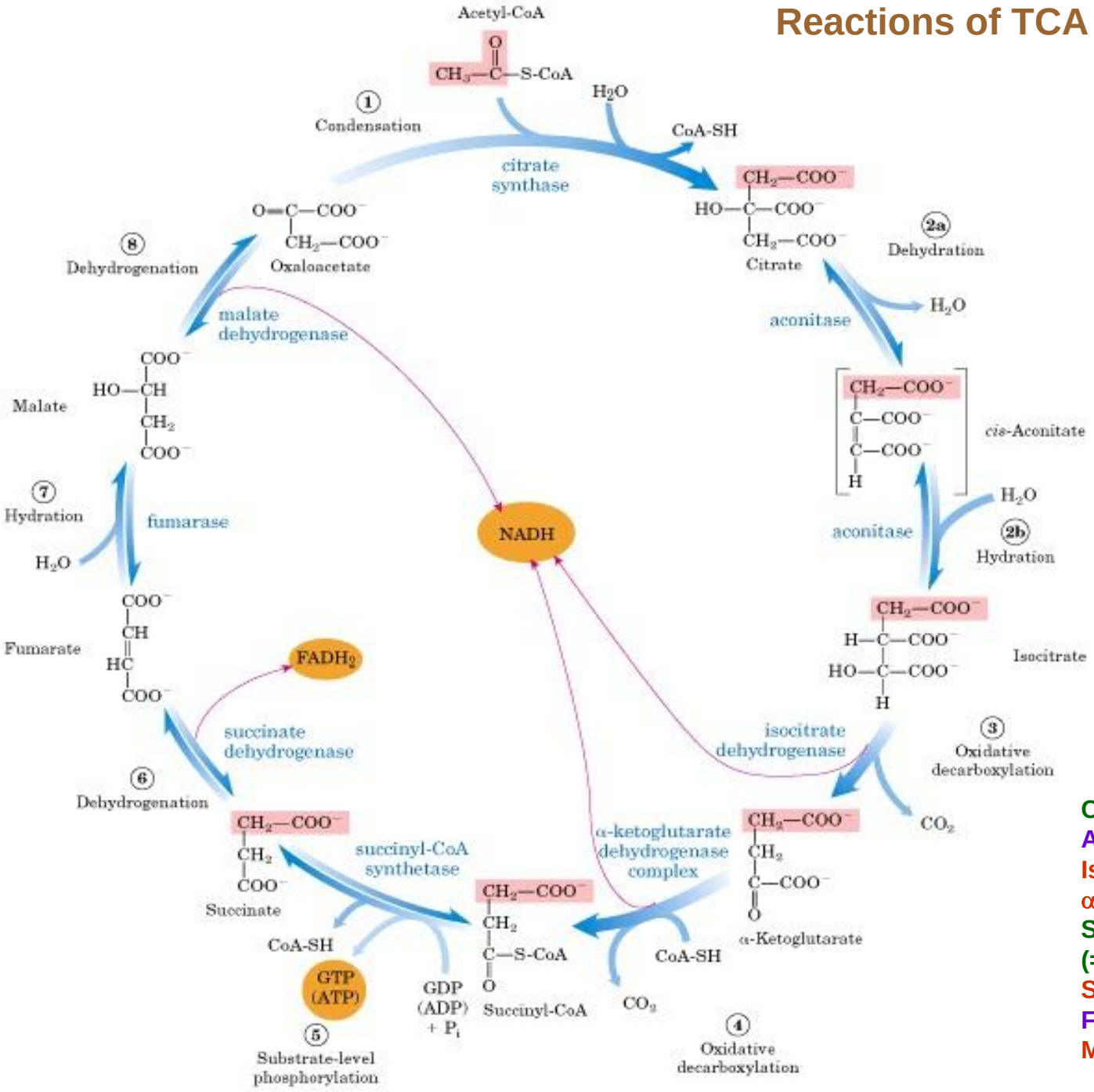




In Cytosol

In Mitochondria

Reactions of TCA cycle (8 reactions)

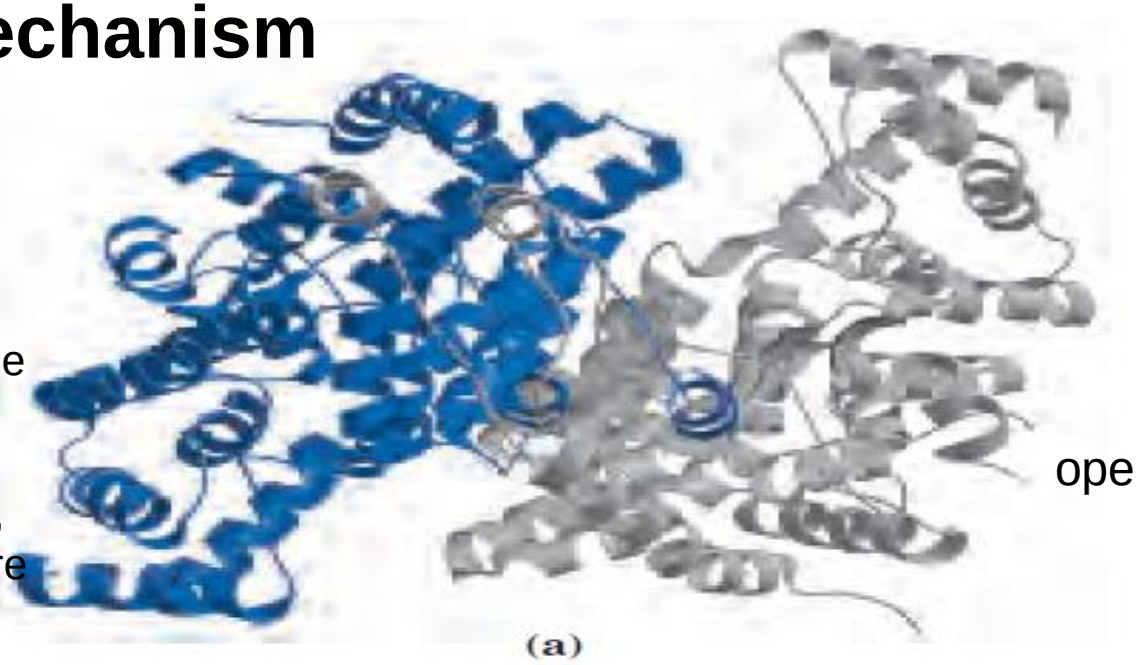


Citrate synthase
Aconitase
Iso-citrate dehydrogenase
α ketoglutarate dehydrogenase
Succinyl-CoA synthetase
(=succinate thiokinase)
Succinate dehydrogenase
Fumerase
Malate dehydrogenase

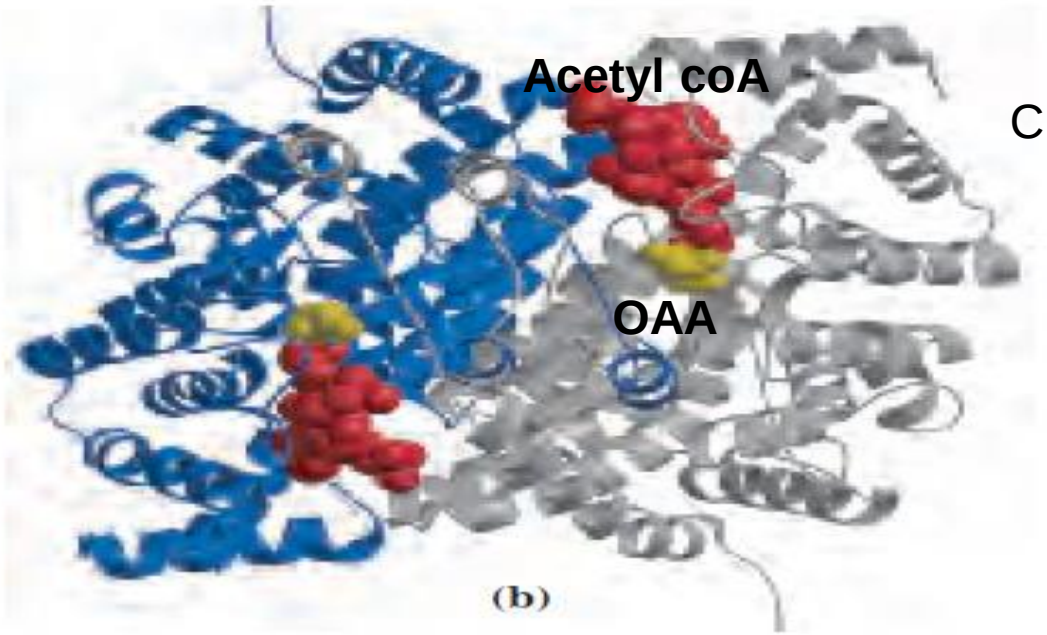
induced fit mechanism

Citrate synthase

Binding of OAA to the enzyme results in conformational change which facilitates the binding of the next substrate, the acetyl Coenzyme A. There is a further conformational change which leads to formation of products.

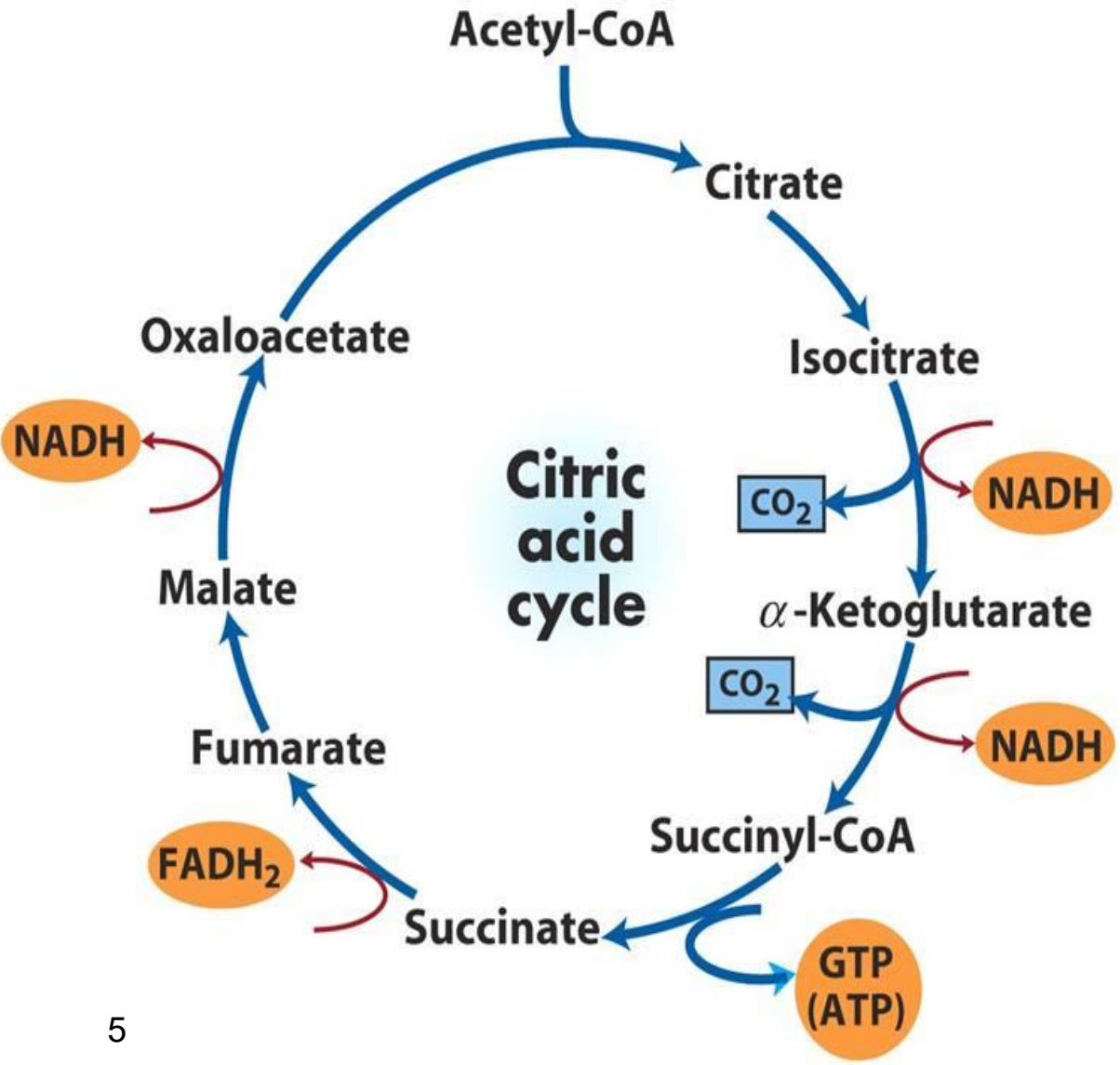


open form



Closed form

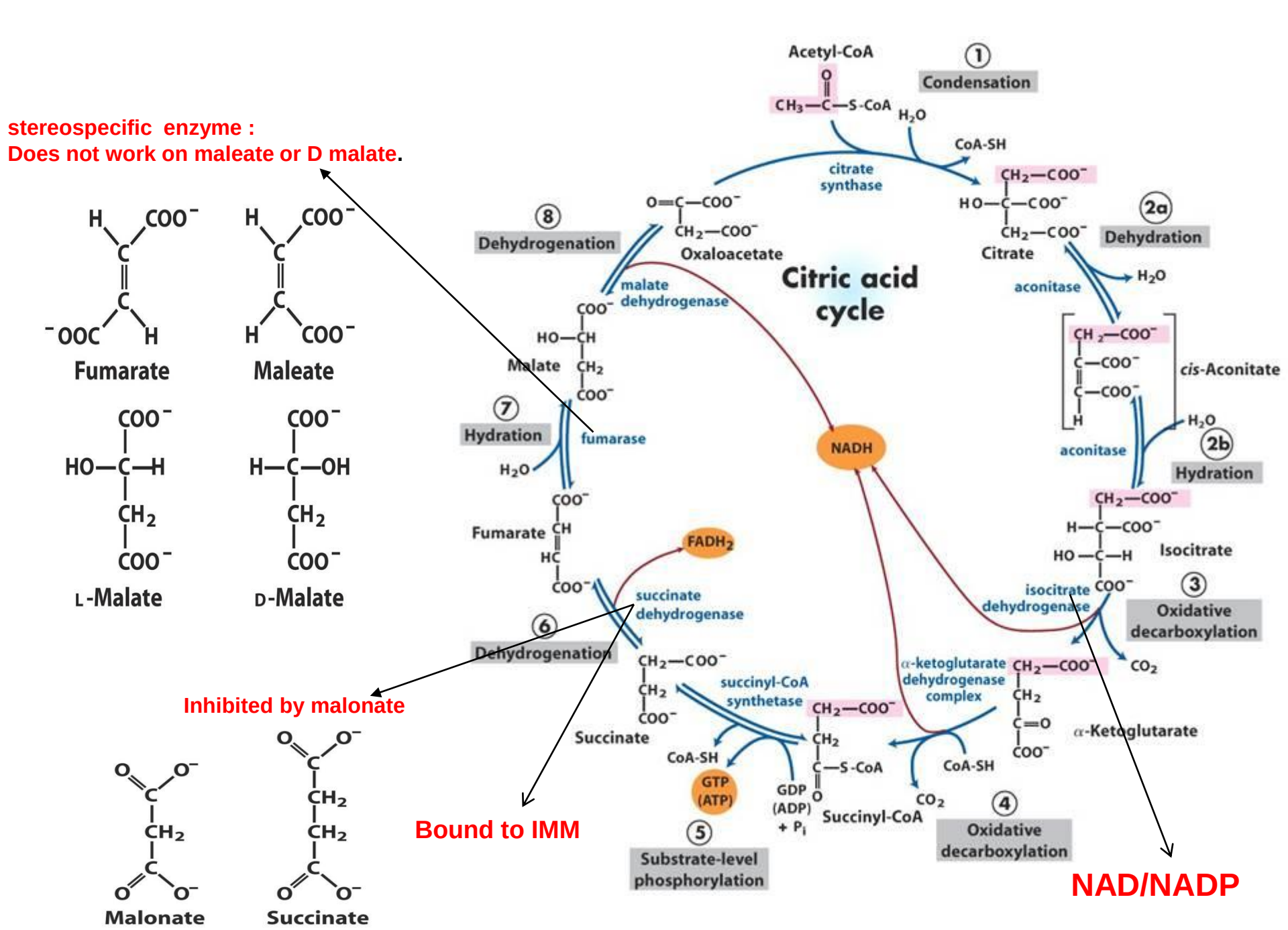
Products of one turn of the TCA cycle



Conservation of energy in the TCA: The two carbon acetyl group generated in PDH reaction enter the TCA, and two molecules of CO2 are released in on cycle. Thus there is complete oxidation of two carbons during one cycle. Although the two carbons which enter the cycle become the part of oxaloacetate, and are released as CO2 only in the third round of the cycle, the energy released due to this oxidation is conserved in the reduction of **3 NAD+, 1 FAD** molecule and synthesis of **1GTP** molecule which is converted to ATP

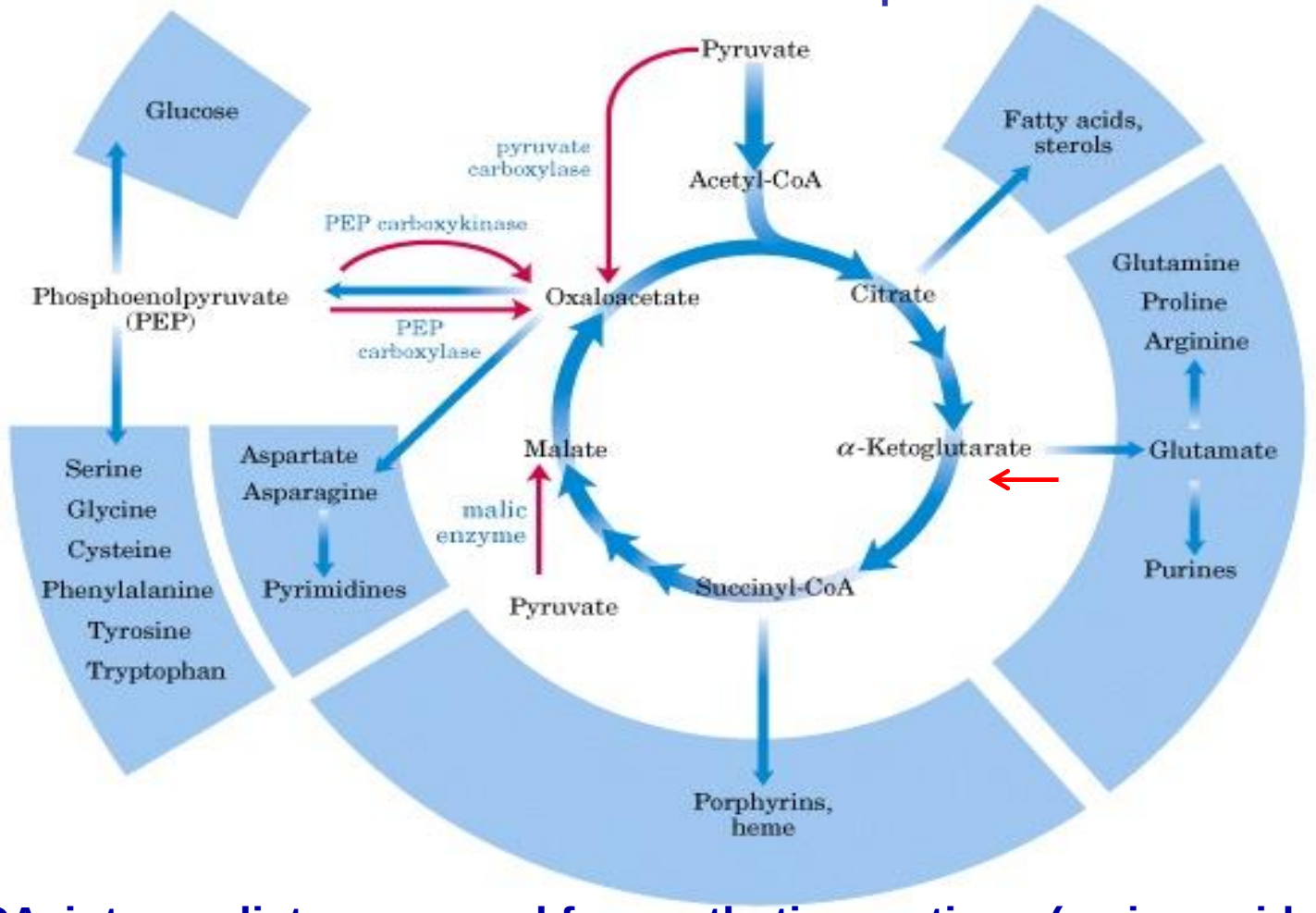
To Summarize…

- To begin a turn of the cycle, acetyl-CoA donates its acetyl group to the four-carbon compound oxaloacetate to form the six-carbon citrate.
- Citrate is then transformed into isocitrate, also a six-carbon molecule, which is dehydrogenated with loss of CO2 to yield the five-carbon compound *ά*-ketoglutarate (also called oxoglutarate).
- *ά* -Ketoglutarate undergoes loss of a second molecule of CO2 and ultimately yields the four-carbon compound succinate.
- Succinate is then enzymatically converted in three steps into the four-carbon oxaloacetate—which is then ready to react with another molecule of acetyl-CoA.
- In each turn of the cycle, one acetyl group (two carbons) enters as acetyl-CoA and two molecules of CO2 leave;
- One molecule of oxaloacetate is used to form citrate and one molecule of oxaloacetate is regenerated. No net removal of oxaloacetate occurs;
  one molecule of oxaloacetate can theoretically bring about oxidation of an infinite
- Number of acetyl groups, and, in fact, oxaloacetate is present in cells in very low concentrations.
- Four of the eight steps in this process are oxidations, in which the energy of oxidation is very efficiently conserved in the form of the reduced coenzymes NADH and FADH2.


stereospecific enzyme :
Does not work on maleate or D malate.
Fumarate
Maleate
L-Malate
D-Malate
Inhibited by malonate
Malonate
Succinate
Bound to IMM
Acetyl-CoA
Condensation
citrate synthase
CoA-SH
Oxaloacetate
Citrate
Dehydration
aconitase
cis-Aconitate
Hydration
Isocitrate
isocitrate dehydrogenase
Oxidative decarboxylation
α-ketoglutarate dehydrogenase complex
α-Ketoglutarate
Succinyl-CoA
Substrate-level phosphorylation
succinyl-CoA synthetase
GTP (ATP)
GDP (ADP) + Pi
succinate dehydrogenase
Dehydrogenation
Fumarate
fumarase
Hydration
Malate
malate dehydrogenase
Dehydrogenation
Citric acid cycle
NADH
FADH2
NAD/NADP

TCA cycle is a source of Biosynthetic Intermediates

Amphibolic nature of the TCA cycle
serves in both catabolic and anabolic processes.



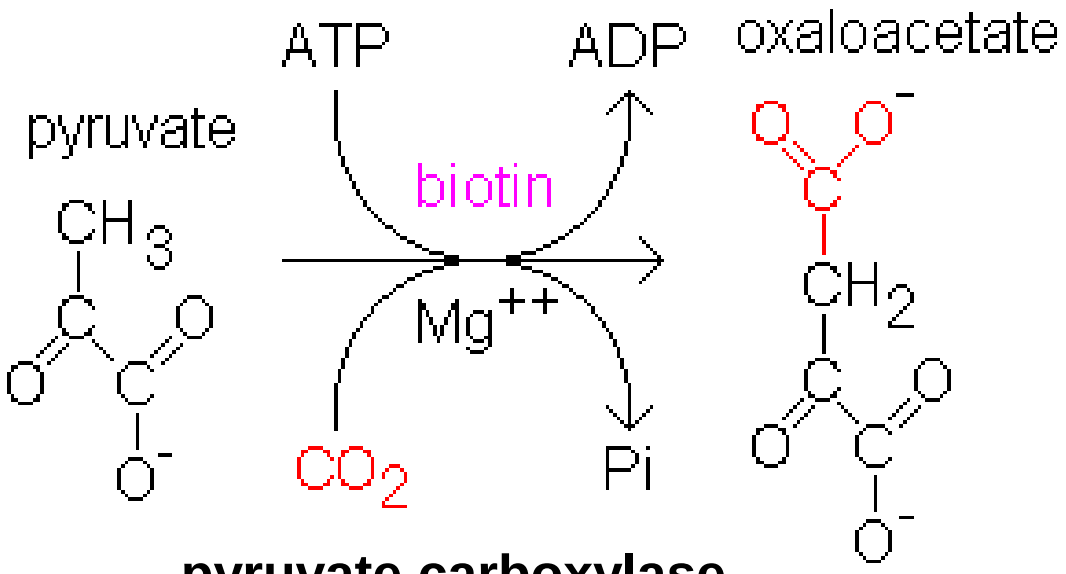
If the TCA intermediates are used for synthetic reactions (amino acids, Fatty acids, Glucose), they are replenished by anaplerotic reactions in the cells (indicated by red colours).

Filling up Reactions

TABLE 16-2 Anaplerotic Reactions

Reaction	*Tissue(s)/organism(s)*
Pyruvate + HCO_3^- + ATP $\xrightleftharpoons{\text{pyruvate carboxylase}}$ oxaloacetate + ADP + P_i	Liver, kidney and nervous tissues
Phosphoenolpyruvate + CO_2 + GDP $\xrightleftharpoons{\text{PEP carboxykinase}}$ oxaloacetate + GTP	Heart, skeletal muscle
~~Phosphoenolpyruvate + HCO_3^- $\xrightleftharpoons{\text{PEP carboxylase}}$ oxaloacetate + P_i~~	~~Higher plants, yeast, bacteria~~
Pyruvate + HCO_3^- + NAD(P)H $\xrightleftharpoons{\text{malic enzyme}}$ malate + $NAD(P)^+$	Widely distributed in eukaryotes and prokaryotes

The most important anaplerotic reaction:



pyruvate carboxylase

TCA Cycle is carefully Regulated

Rate controlling enzymes: Key regulatory

Citrate synthase

Isocitrate dehydrogenase

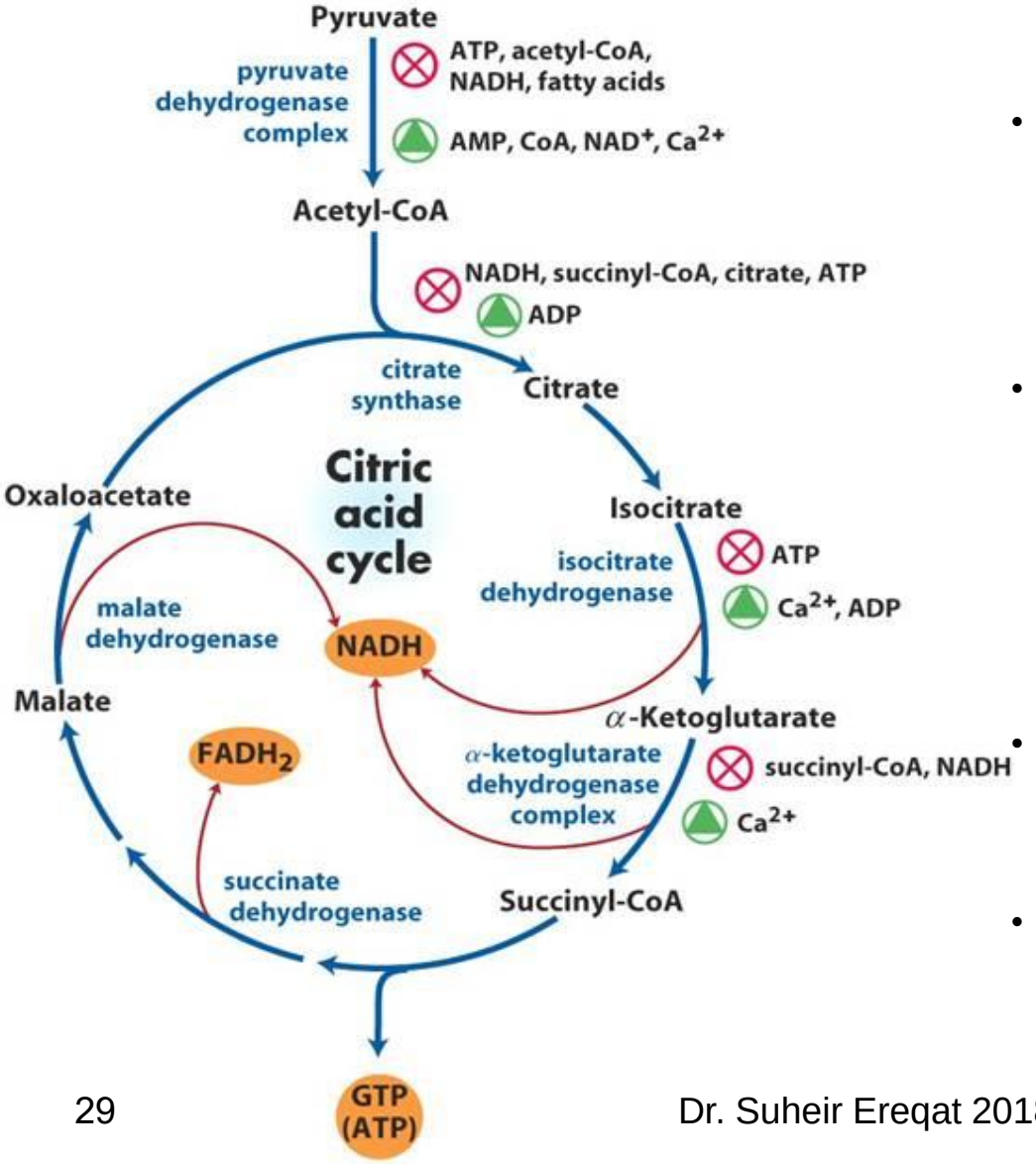
a-keoglutarate dehydrogenase

Regulation of the TCA cycle

= by availability of substrates and consumption of produts

regulatory enzyme	activation	inhibition
citrate synthase	ADP	• ↑ NADH / NAD^{+},ATP • succinyl-CoA • long chain F.A, citrate
isocitrate dehydrogenase	• ↓ ATP / ADP • Ca^{2+}	• ↑ NADH / NAD^{+} • ↑ ATP / ADP
a-ketoglutarate dehydrogenase	• Ca^{2+}	• ↑ NADH / NAD^{+} • ↑ ATP / ADP • GTP • succinyl-CoA

Summary: Regulation of metabolite flow from the PDH complex through the citric acid cycle



- **The PDH complex is allosterically inhibited when [ATP]/[ADP], [NADH]/[NAD], and [acetyl-CoA]/[CoA] ratios are high, indicating an energy-sufficient metabolic state.**
- **The rate of flow through the citric acid cycle can be limited by the availability of the citrate synthase substrates, oxaloacetate and acetyl-CoA, or of NAD, which is depleted by its conversion to NADH, slowing the three NAD-dependent oxidation steps.**
- **Feedback inhibition by succinyl-CoA, citrate, and ATP also slows the cycle by inhibiting early steps.**
- **In muscle tissue, Ca2 signals contraction and, as shown here, stimulates energy-yielding metabolism to replace the ATP consumed by contraction.**