

**Nafith Abu Tarboush**  
**DDS, MSc, PhD**  
**natarboush@ju.edu.jo**  
**[www.facebook.com/natarboush](http://www.facebook.com/natarboush)**

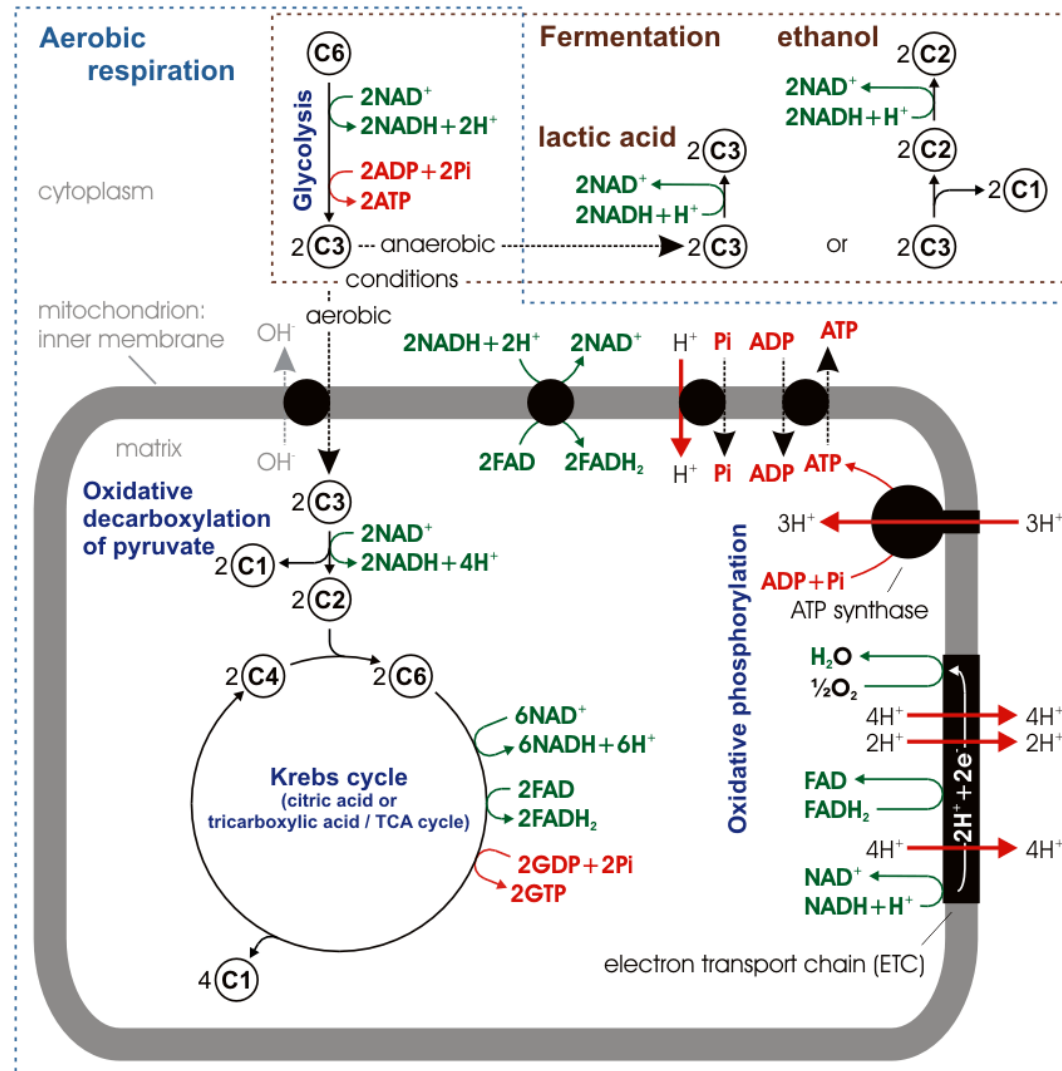
# **(Kreb's, Citric Acid, TCA) Cycle**

# Objectives

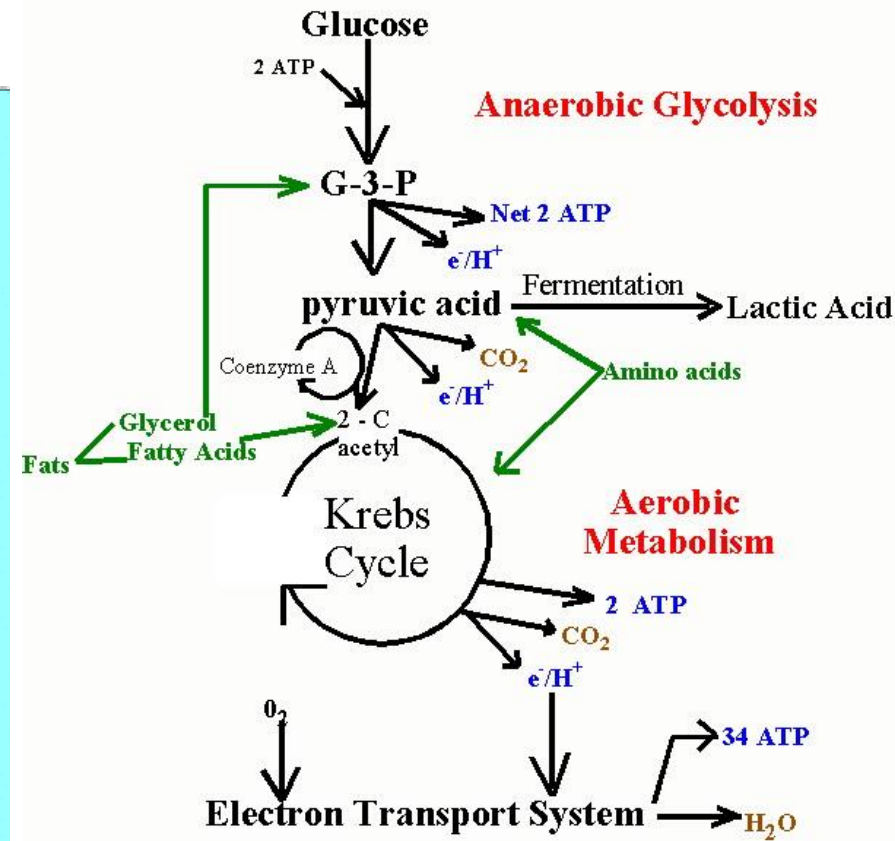
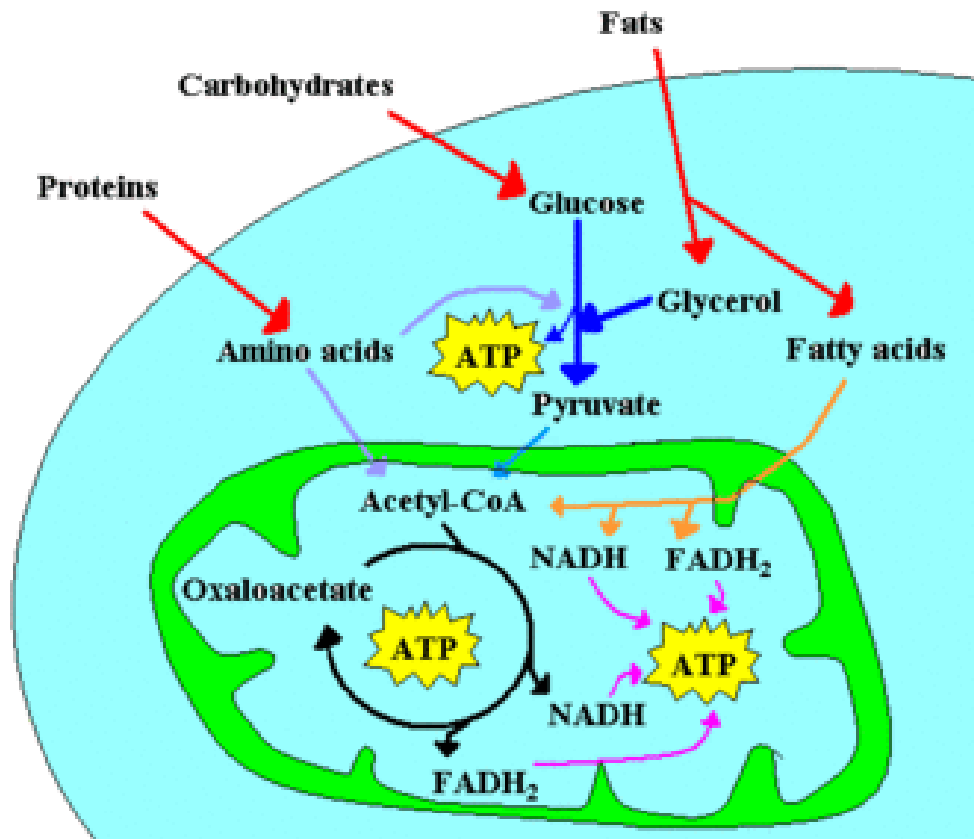
- Why do we need it?
- Location & where is it in the picture?
- Electron (energy) carrying molecules
- Components
- Enzymes & cofactors
- Regulation
- Intermediates & anaplerotic reactions

# Why do we need it?

- A route to make ATP eventually (most ATP is generated through oxidative phosphorylation)
- There is no life without TCA cycle!



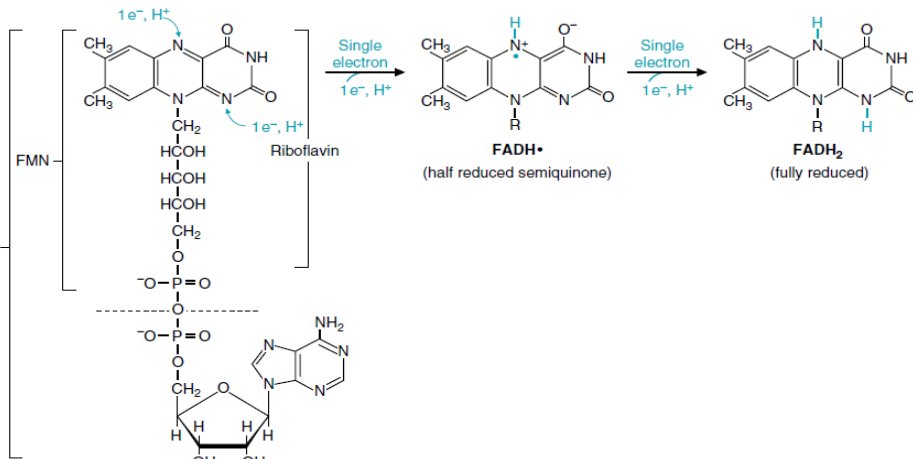
# How does it fit?



# Electron (energy) Carrying Molecules (NAD<sup>+</sup>, FAD)

## ➤ FAD

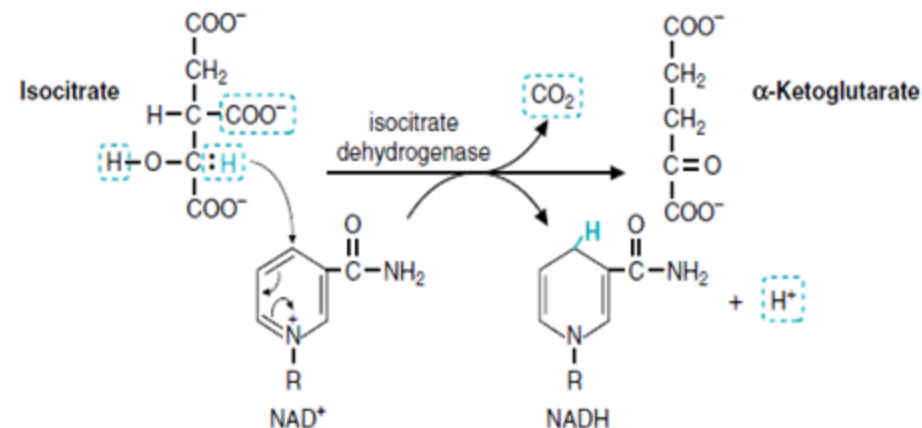
- Single electrons (H•), different sources
- Succinate to fumarate, lipoate to lipoate disulfide in  $\alpha$ -KG
- FAD must remain tightly, sometimes covalently, attached to its enzyme
- $E^\circ$  for enzyme-bound FAD varies



Flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN)

## ➤ NAD

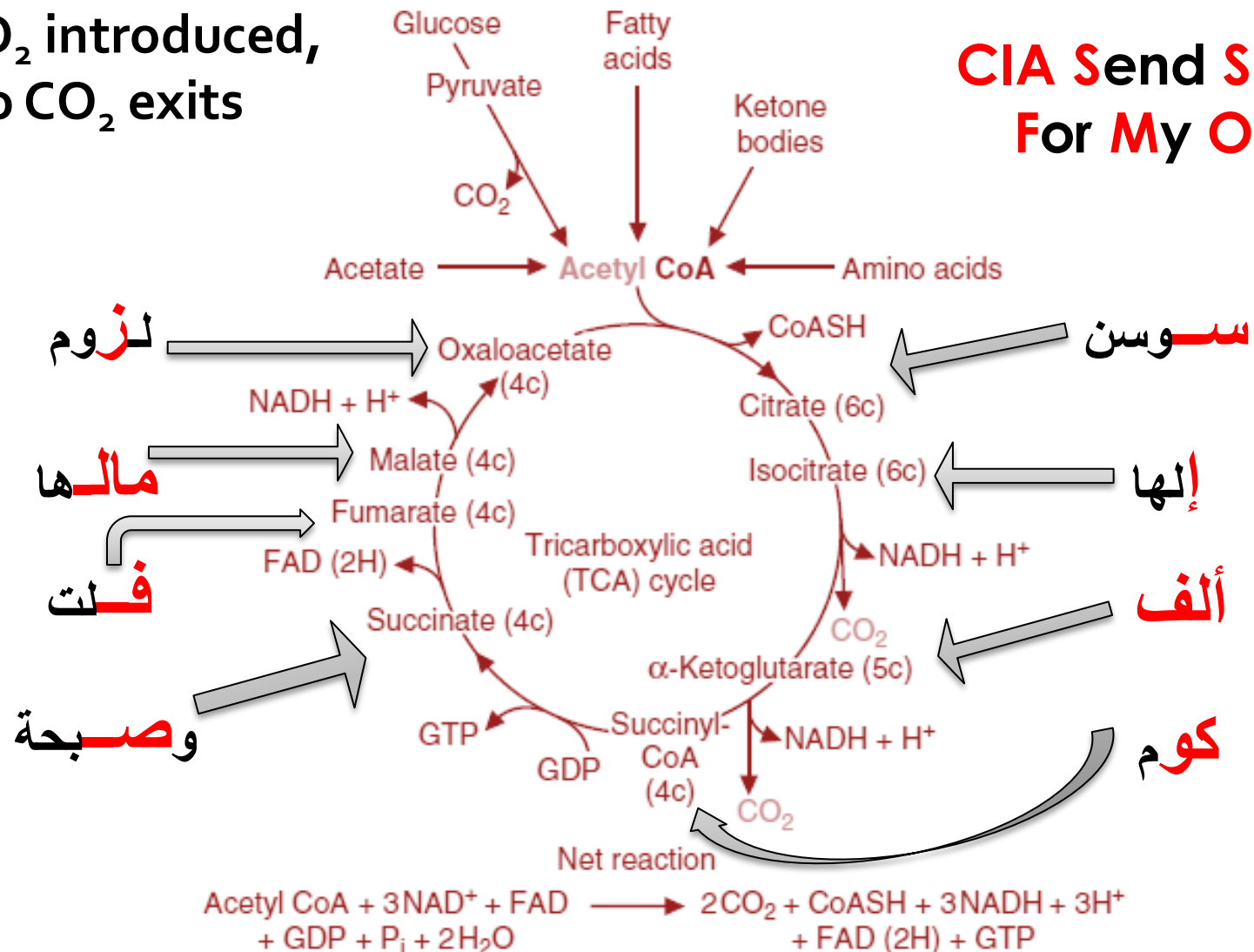
- Pair of electrons (H<sup>-</sup>), same source
- Alcohols to ketones by malate dehydrogenase & isocitrate dehydrogenase
- NADH plays a regulatory role in balancing energy metabolism



# Components & stepwise reactions

➤ No O<sub>2</sub> introduced,  
two CO<sub>2</sub> exits

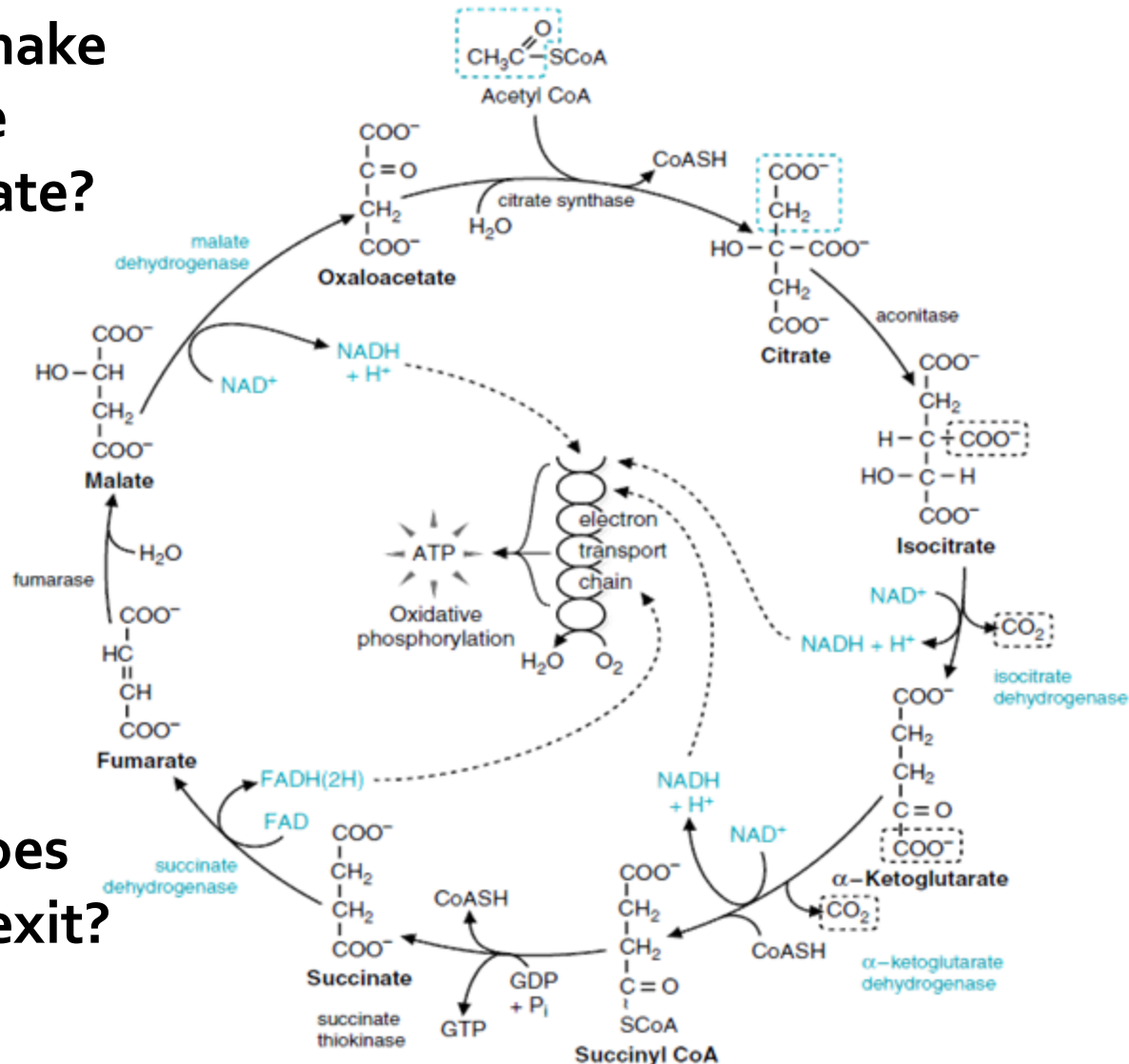
**CIA Send Soldiers  
For My Office**



# Does Acetyl-CoA exit as 2 CO<sub>2</sub>?

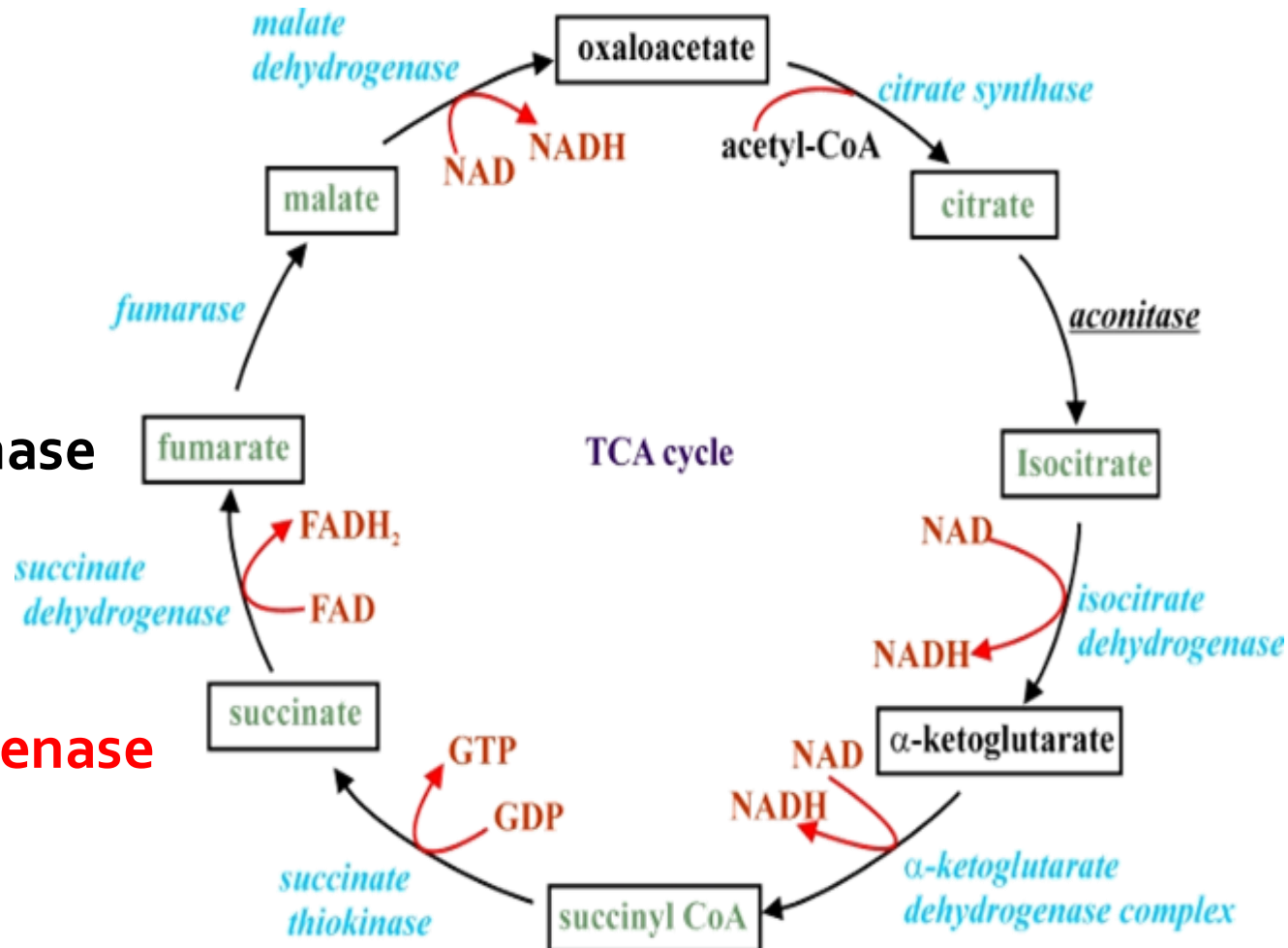
➤ Why to make Isocitrate from citrate?

➤ Where does the CO<sub>2</sub> exit?



# Enzymes of the TCA Cycle

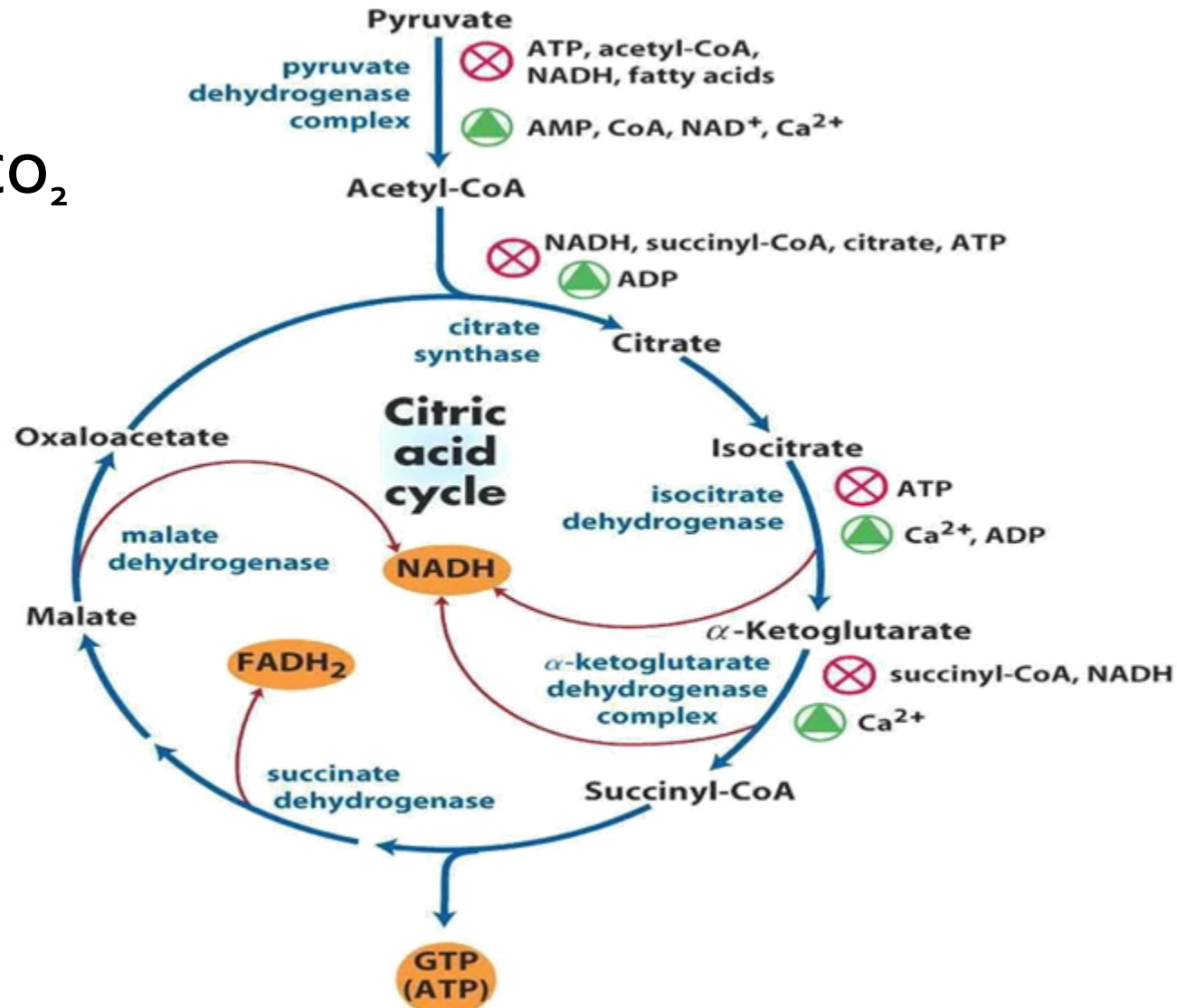
- Citrate synthase
- Aconitase
- Isocitrate dehydrogenase
- $\alpha$ -ketoglutarate dehydrogenase
- Succinate thiokinase
- Succinate dehydrogenase
- Fumarase
- Malate dehydrogenase





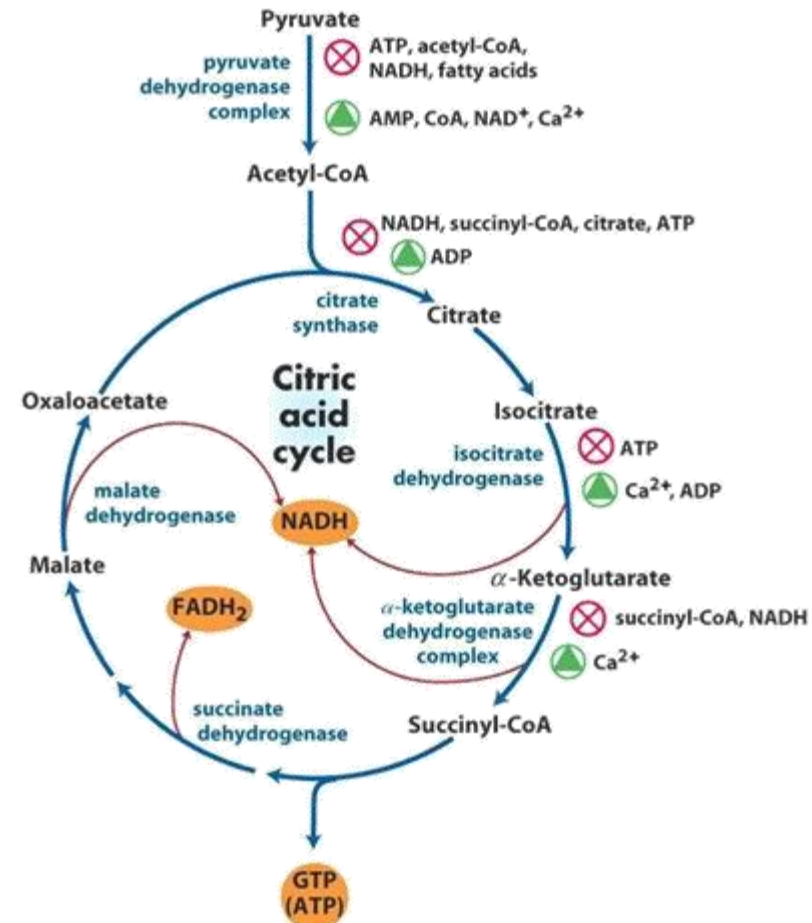
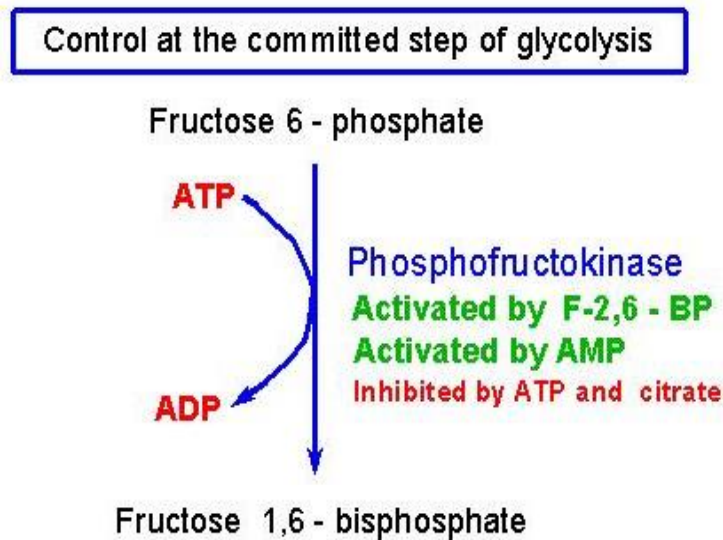
# Formation and Oxidation of Isocitrate

- Oxidative decarboxylation,  $\text{CO}_2$
- $3^\circ$  to  $2^\circ$  alcohol



# Formation and Oxidation of Isocitrate

- Aconitase is inhibited by fluoroacetate (rat poison):  
 $\text{fluoroacetyl CoA} + \text{OA} \rightarrow \text{fluorocitrate}$  (citrate accumulation)



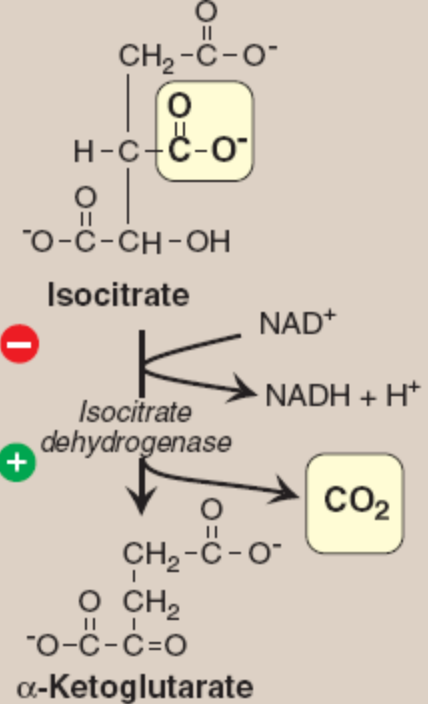
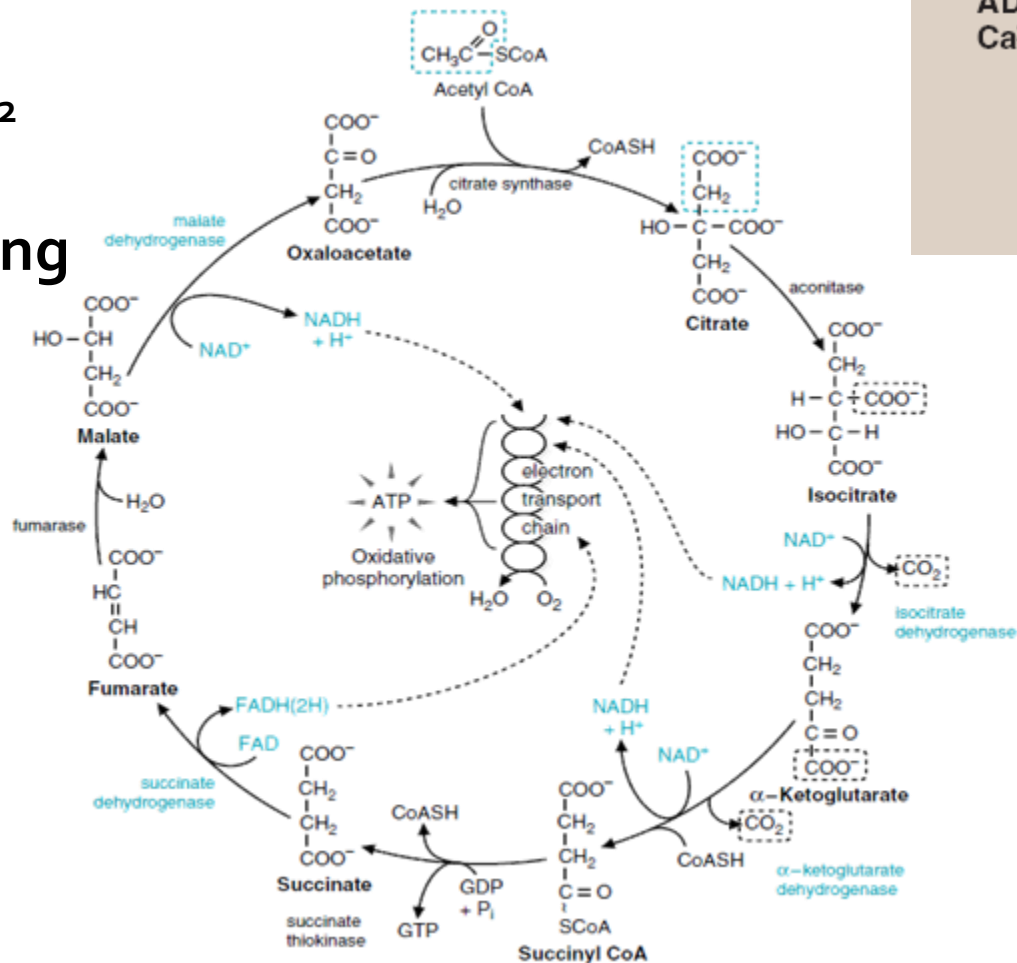
- Activates acetyl CoA carboxylase (the rate-limiting enzyme of fatty acid synthesis)

# Isocitrate to $\alpha$ -Ketoglutarate

➤ ATP & NADH

➤ ADP &  $\text{Ca}^{+2}$

➤ Rate limiting



# $\alpha$ -Ketoglutarate to Succinyl CoA

- Oxidative decarboxylation
- Thiamine pyrophosphate, lipoic acid, and FAD
- Keto group oxidized to acid, CoA-SH, succinyl CoA
- Energy conserved as NADH, thioester bond

