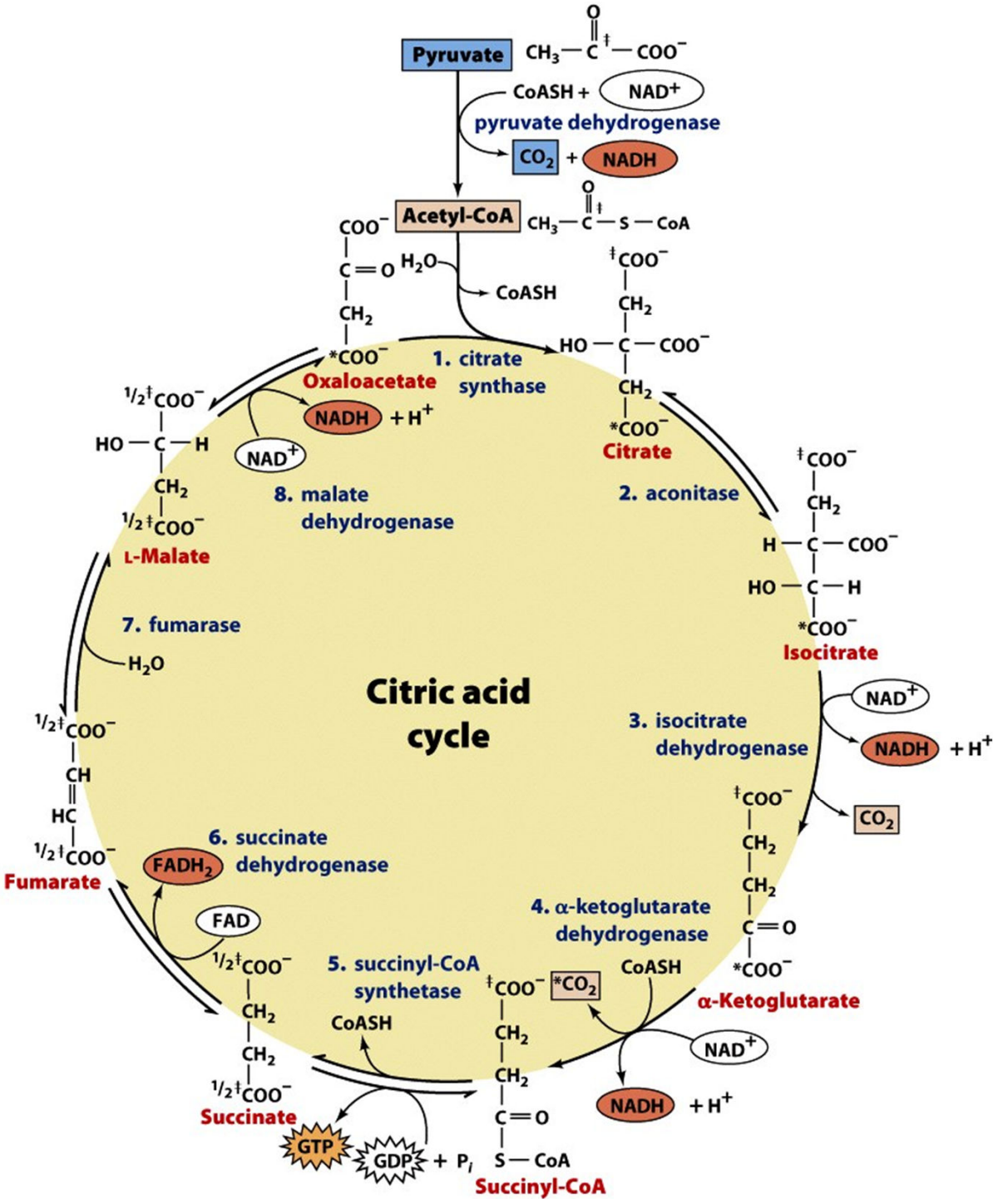
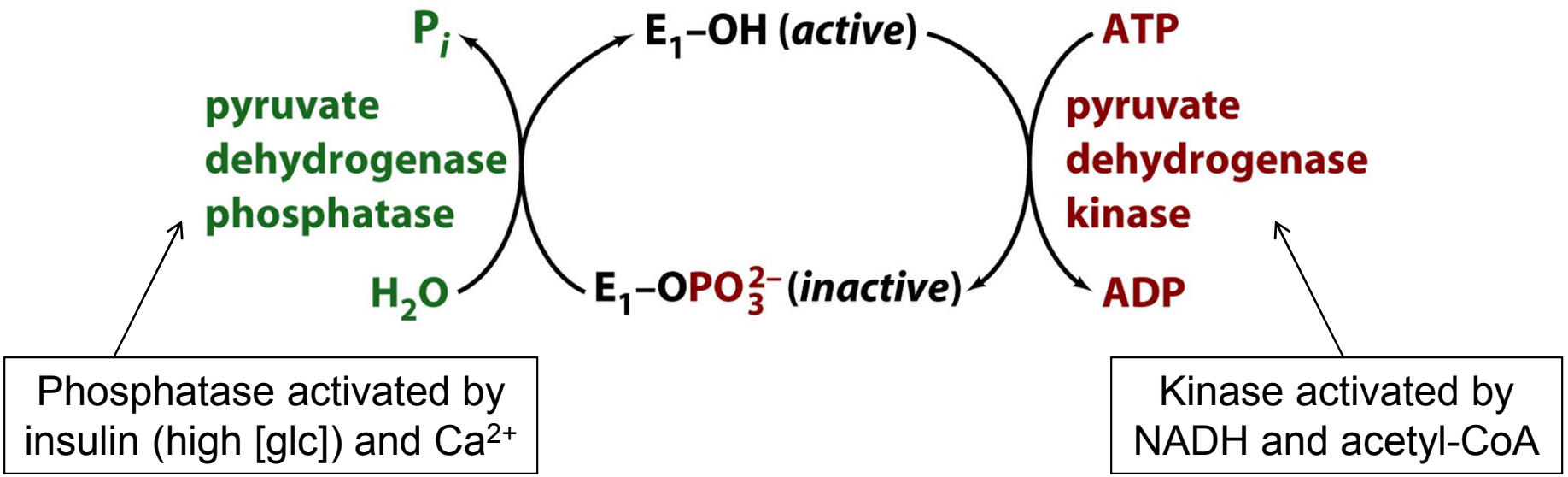

Pyruvate
CoASH +
NAD+
pyruvate dehydrogenase
CO2 +
NADH
Acetyl-CoA
CoASH
1. citrate synthase
Oxaloacetate
Citrate
2. aconitase
Isocitrate
3. isocitrate dehydrogenase
NAD+
NADH + H+
CO2
4. α-ketoglutarate dehydrogenase
α-Ketoglutarate
CoASH
NAD+
NADH + H+
5. succinyl-CoA synthetase
Succinyl-CoA
GTP
GDP + Pi
CoASH
Succinate
6. succinate dehydrogenase
FADH2
FAD
Fumarate
7. fumarase
H2O
8. malate dehydrogenase
NADH + H+
NAD+
L-Malate
Citric acid cycle

How is the oxidation of pyruvate regulated?

PDH complex is regulated by product inhibition and covalent modification

- Product inhibition:
  - Acetyl-CoA binds and inhibits E_2
  - NADH binds and inhibits E_3
- Covalent modification (eukaryotes only): reversible phosphorylation of E_1 Ser

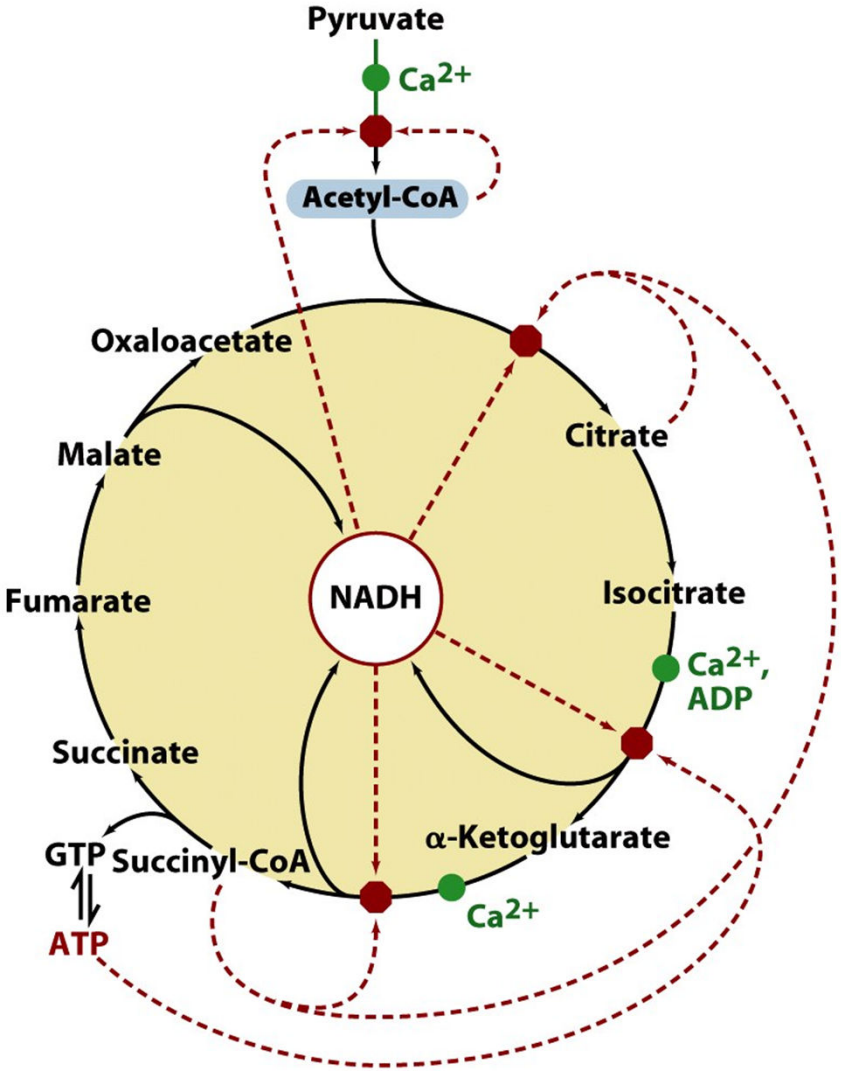


The slowest steps of the citric acid cycle have negative ΔG's, and are regulated

Table 17-2 Standard Free Energy Changes ($\Delta G^{\circ\prime}$) and Physiological Free Energy Changes (ΔG) of Citric Acid Cycle Reactions

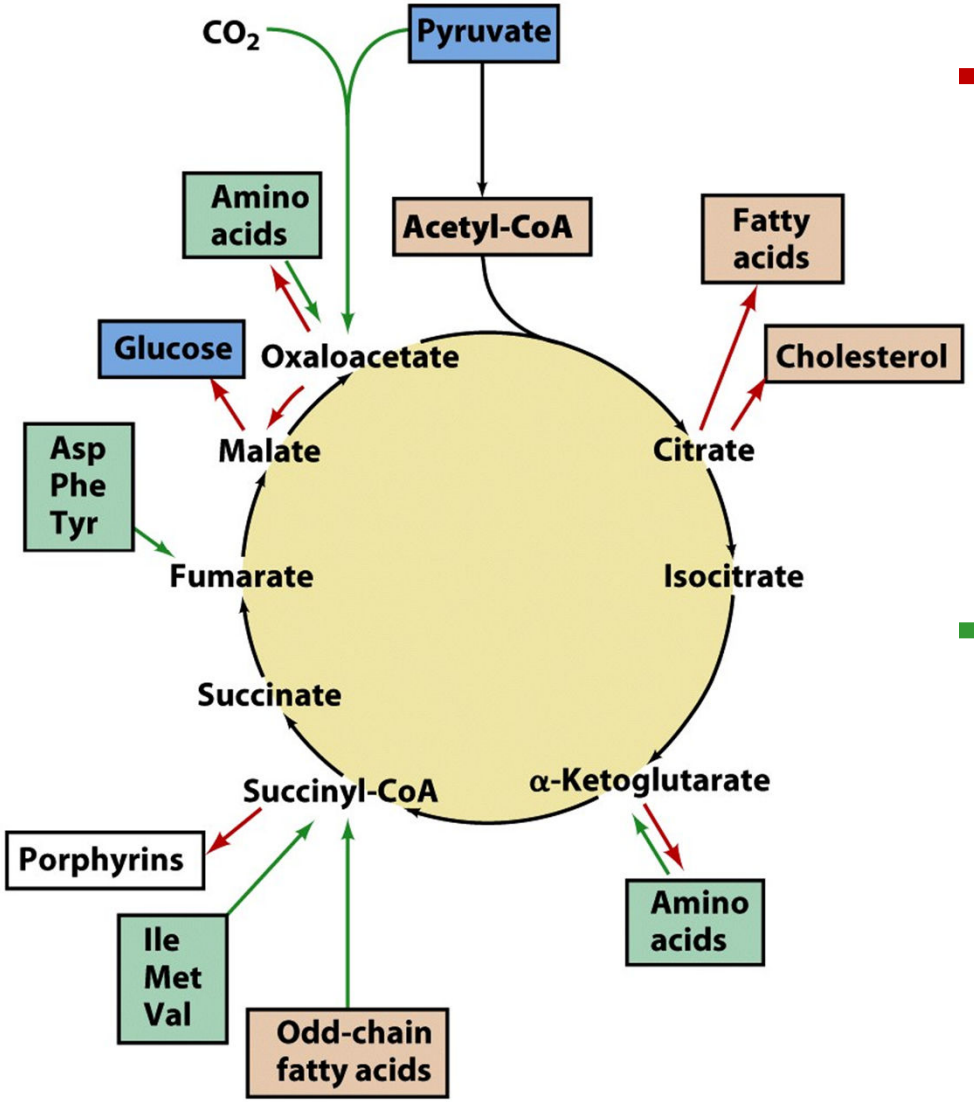
Reaction	Enzyme	$\Delta G^{\circ\prime}$ ($kJ \cdot mol^{-1}$)	ΔG ($kJ \cdot mol^{-1}$)
1	Citrate synthase	−31.5	Negative
2	Aconitase	~5	~0
3	Isocitrate dehydrogenase	−21	Negative
4	α-Ketoglutarate dehydrogenase	−33	Negative
5	Succinyl-CoA synthetase	−2.1	~0
6	Succinate dehydrogenase	+6	~0
7	Fumarase	−3.4	~0
8	Malate dehydrogenase	+29.7	~0

Compounds reflecting energy status and energy use are regulators of the TCA cycle



- NADH
  - Product inhibitor of NAD^+-using dehydrogenases
  - Inhibitor of citrate synthase
- Pathway intermediates
  - Citrate and succinyl-CoA act via product inhibition or competitive feedback inhibition
  - Levels of substrates OAA and acetyl-CoA determine activity of citrate synthase
- Adenylates
  - Allosteric inhibitors (ATP) or activators (ADP) of isocitrate DH
- Ca^{2+} (muscle contraction)
  - Allosteric activator of the dehydrogenases

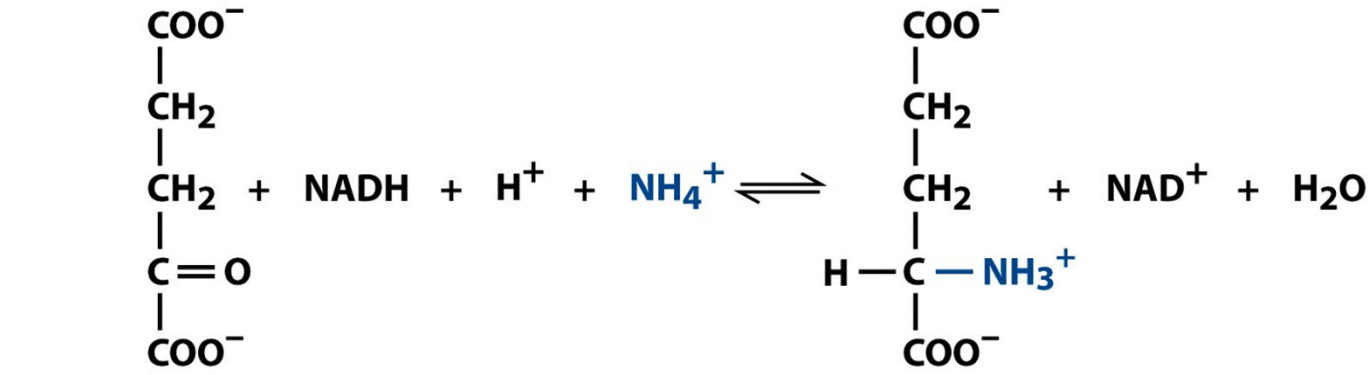
TCA cycle intermediates are made and used in additional metabolic pathways



- *Cata*plerotic reactions *use* cycle intermediates to make:
  - Glucose
  - Amino acids
  - Lipids
  - Cofactors
- *Ana*plerotic reactions *generate* cycle intermediates from:
  - Pyruvate
  - Amino acids
  - Odd-chain fatty acids

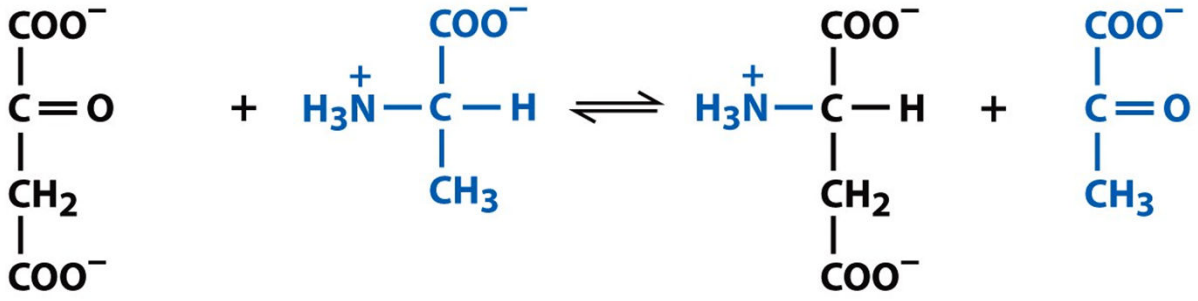
Amino acids and TCA cycle intermediates are readily inter-converted

Reductive amination:



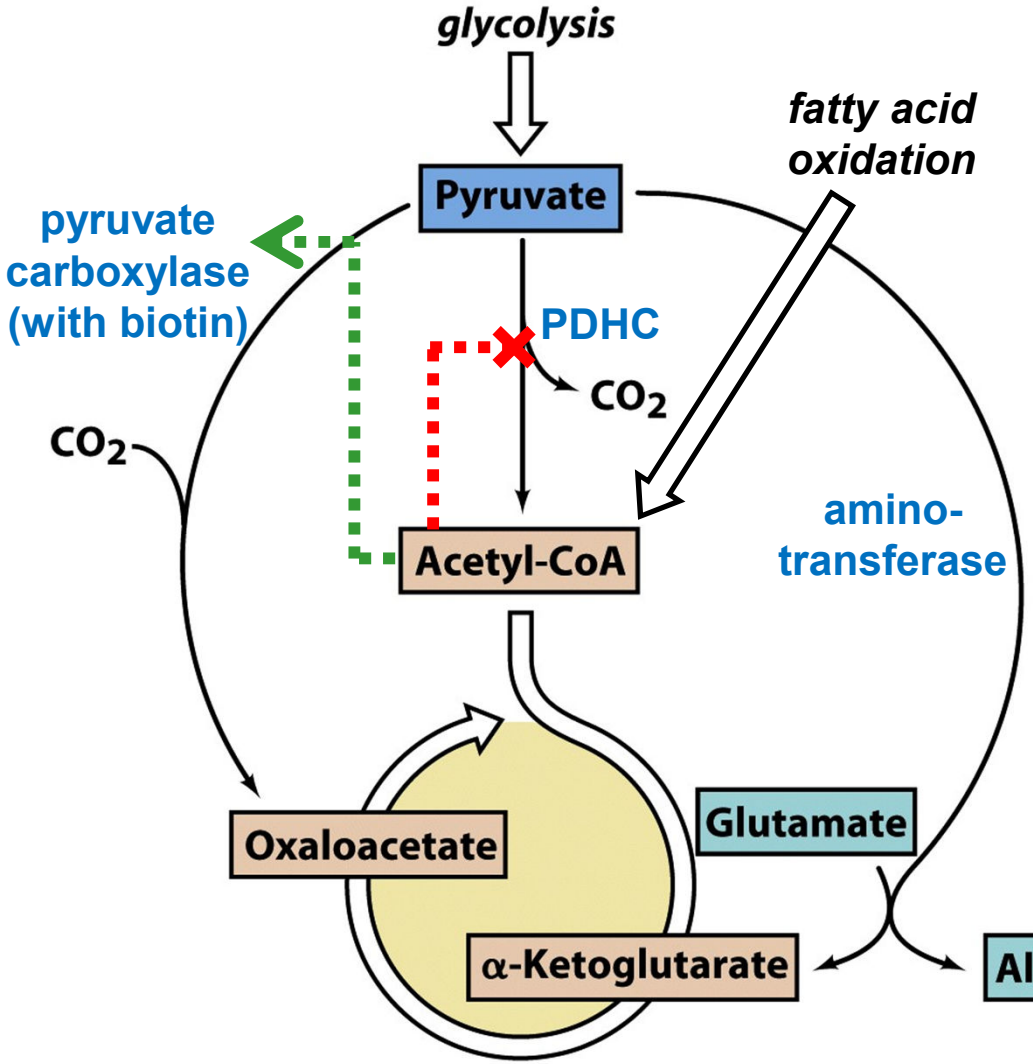
α-Ketoglutarate Glutamate

Transamination:



Oxaloacetate Alanine Aspartate Pyruvate

Production of pyruvate increases flux through TCA cycle by increasing [substrate]



- Action of PDH complex increases [acetyl-CoA] (as does FA oxidation), but [OAA] can limit flux
- Pyruvate carboxylase is activated by acetyl-CoA, and can generate more OAA to enhance flux
- Pyruvate can also act in transamination rxns, yielding α-KG (from Glu) or OAA (from Asp)

The oxidation of acetyl-CoA to CO_2 in the TCA cycle generates energy currencies