Citric Acid Cycle

Overview of metabolic fuel metabolism

Citric acid cycle (CAC)

Not merely an oxidation of pyruvate to CO2

A central pathway for recovering energy from several metabolic fuels

Chapter 16 Opener Fundamentals of Biochemistry, 2/e

Citric acid cycle: metabolic water wheel

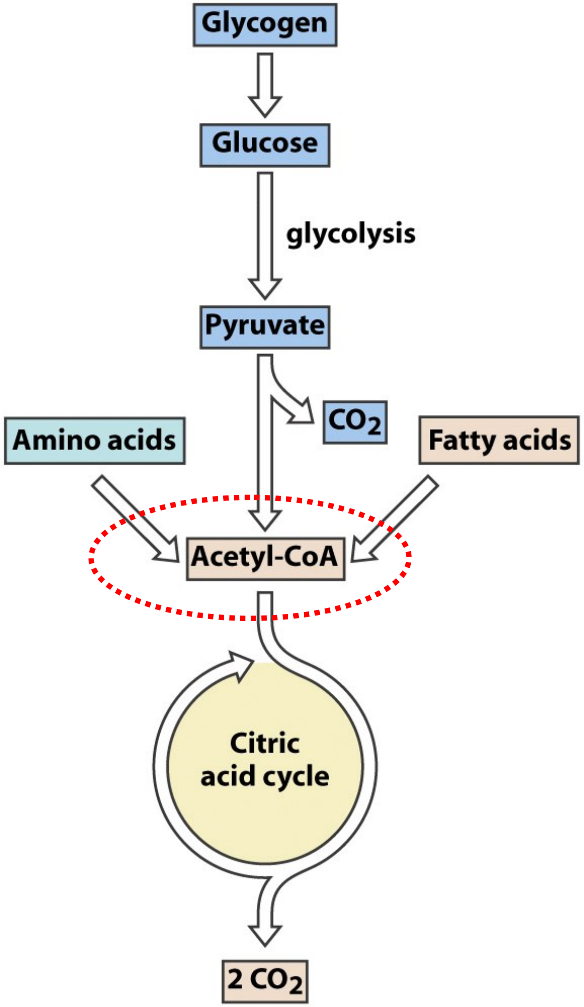


Figure 16-1 Fundamentals of Biochemistry, 2/e

Overview of CAC

8 reactions oxidizing acetyl-CoA to 2 CO_2
Generation of 3 NADH, 1 FADH2, 1 ATP(GTP)

1930s Hans Krebs linked the already known compounds

<u>Plant products</u>
Citric acid: citrus fruit
Aconitate: monkshood
Succinate: amber
Fumarate: Fumaria
Malate: apple

<u>General features</u>

Circular pathway: TCA cycle
Net reaction
Mitochondrial location
Amphibolic pathway: provides biosynthetic intermediates

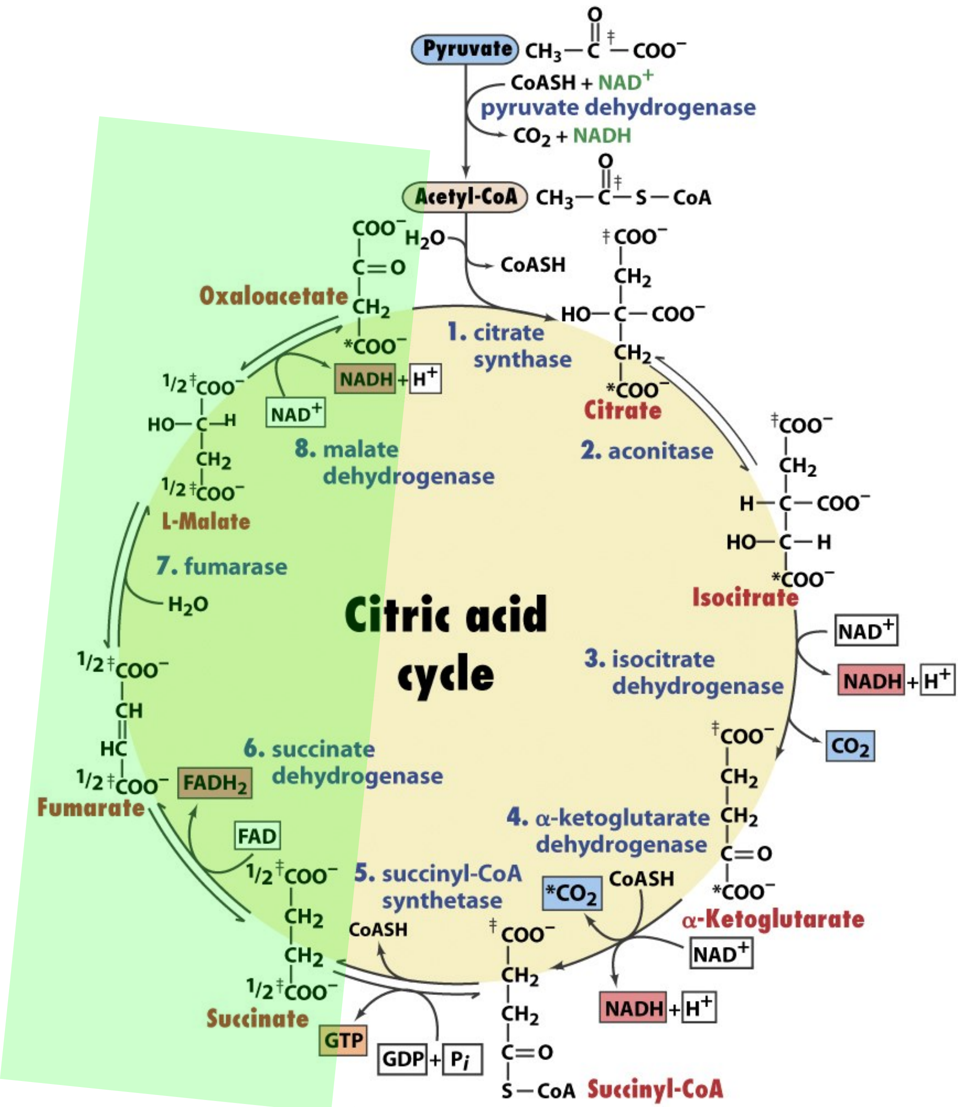


Figure 16-2 Fundamentals of Biochemistry, 2/e

Synthesis of Acetyl-CoA

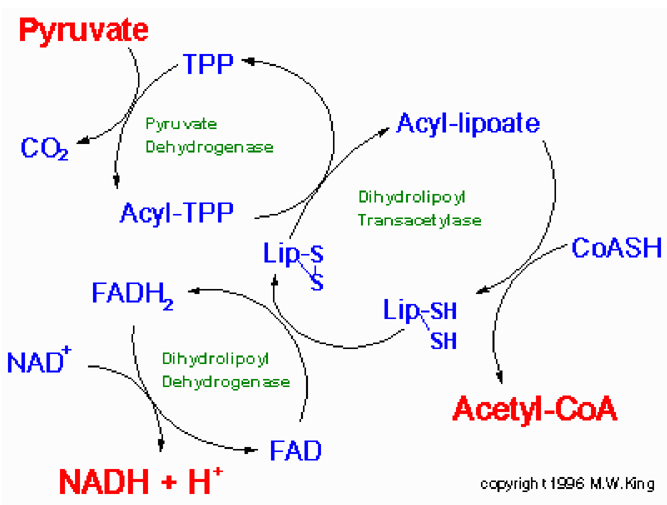
Pyruvate to acetyl-CoA (high-E compound)
Transport to mitochondria via pyruvate-H^+ symport

Pyruvate dehydrogenase multienzyme complex (PDH)
Noncovalently associated enzymes
E. coli enzyme

- Pyruvae dehydrogenase (E1): 24 subunits
- Dihydrolipoyl transacetylase (E2): 24 subunits
- Dihydrolipoyl dehydrogenase (E3): 12 subunits

Multienzyme complex: evolution of catalytic efficiency

1. Overcome diffusion
2. Minimize side reactions
3. Coordinate control



EM of *E. coli* pyruvate dehydrogenase complex

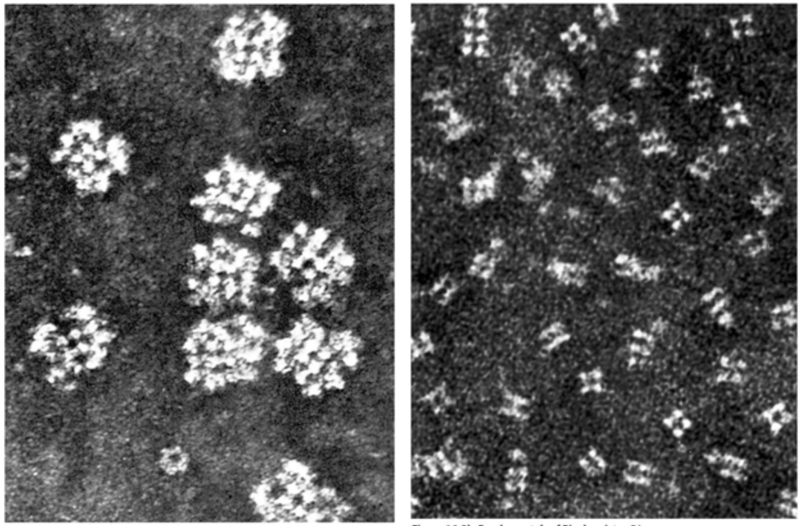


Figure 16-3a Fundamentals of Biochemistry, 2/e

Figure 16-3b Fundamentals of Biochemistry, 2/e

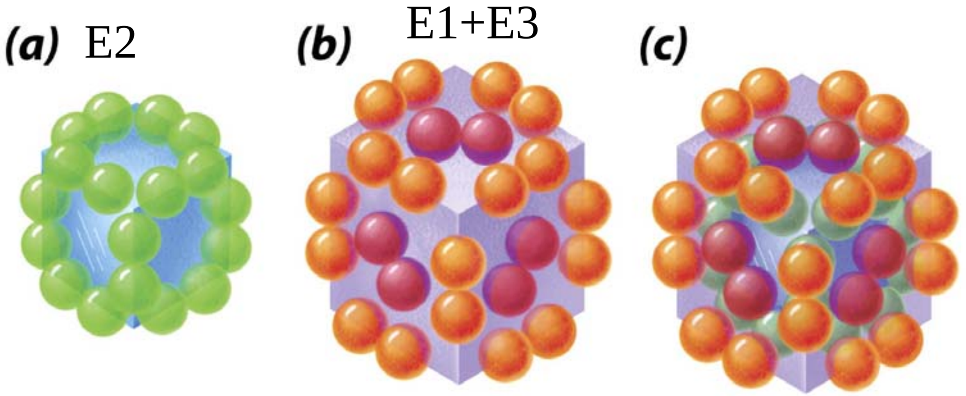
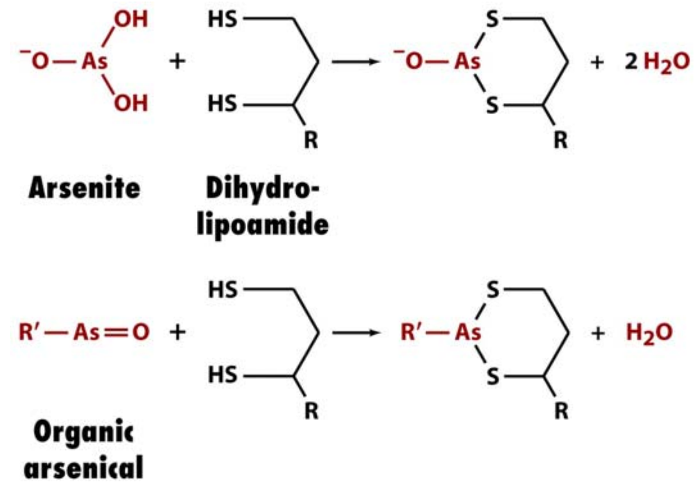


Figure 16-4 Fundamentals of Biochemistry, 2/e

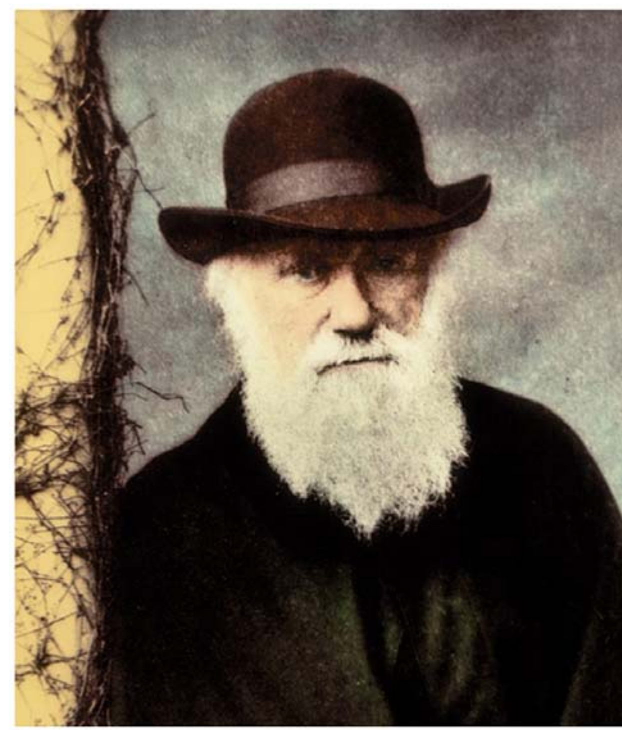
Arsenic poisoning

Arsenite
Organic arsenicals
Binding to -SH of lipoamide
Inactivation of PDH & α-ketoglutarate dehydrogenase



Box 16-2 figure 1 Fundamentals of Biochemistry, 2/e

Box 16-2 figure 2 Fundamentals of Biochemistry, 2/e



Box 16-2 figure 3 Fundamentals of Biochemistry, 2/e

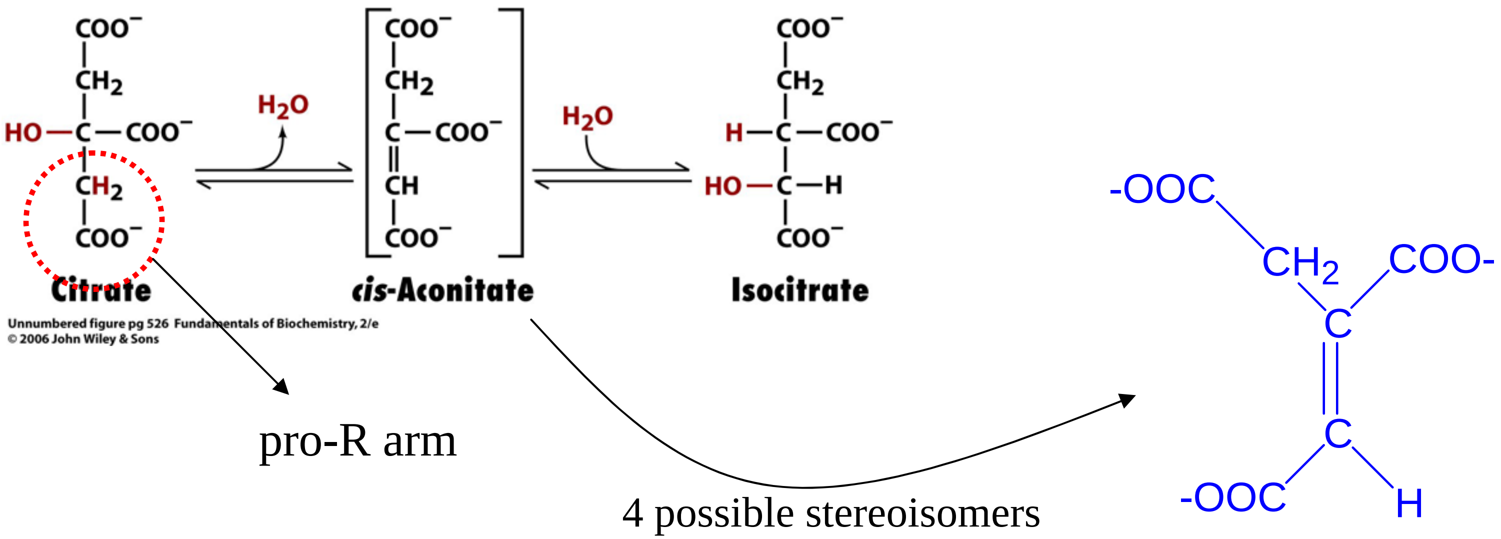
Aconitase

Reversible isomerization of citrate and isocitrate with cis-aconitate as an intermediate

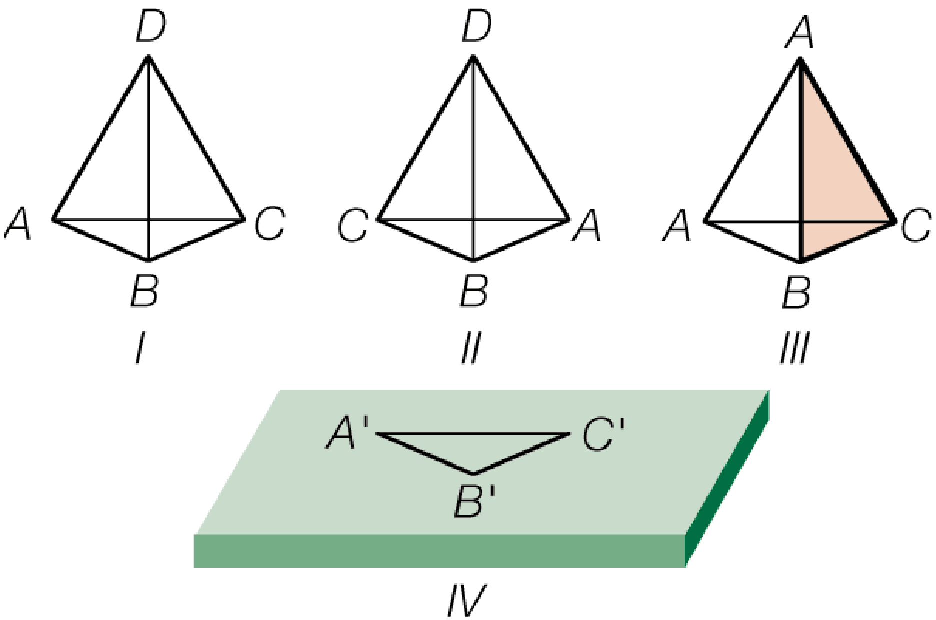
Dehydration and rehydration

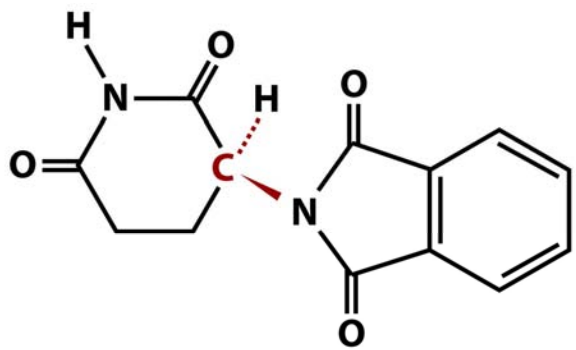
- Citrate: pro-chiral compound
- Isocitrate: chiral compound

[4Fe-4S] iron-sulfur cluster: (normally involve in redox reactions)



Chirality





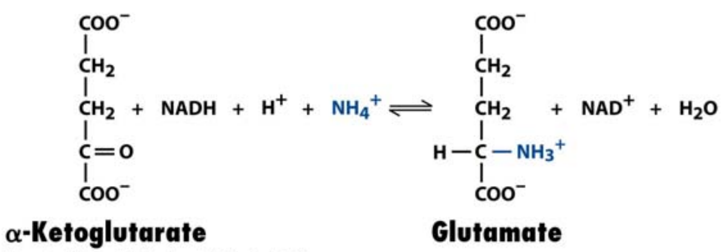
Thalidomide

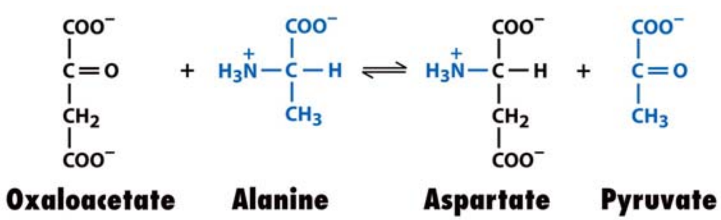
Its enantiomer causes severe birth defects in human

Amphibolic pathway: both anabolic & catabolic

<u>Cataplerotic reactions (emptying): for synthesis /to avoid inappropriate buildup</u>

Glucose synthesis: oxaloacetate
Fatty acid synthesis: acetyl-CoA
Amino acid synthesis: α-ketoglutarate, oxaloacetate





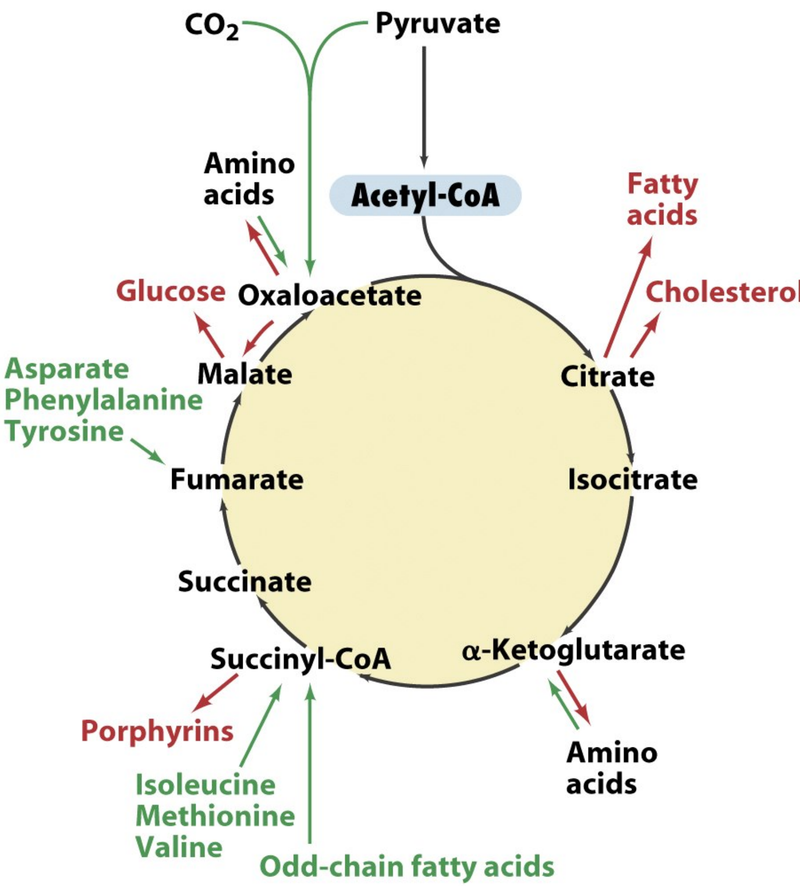


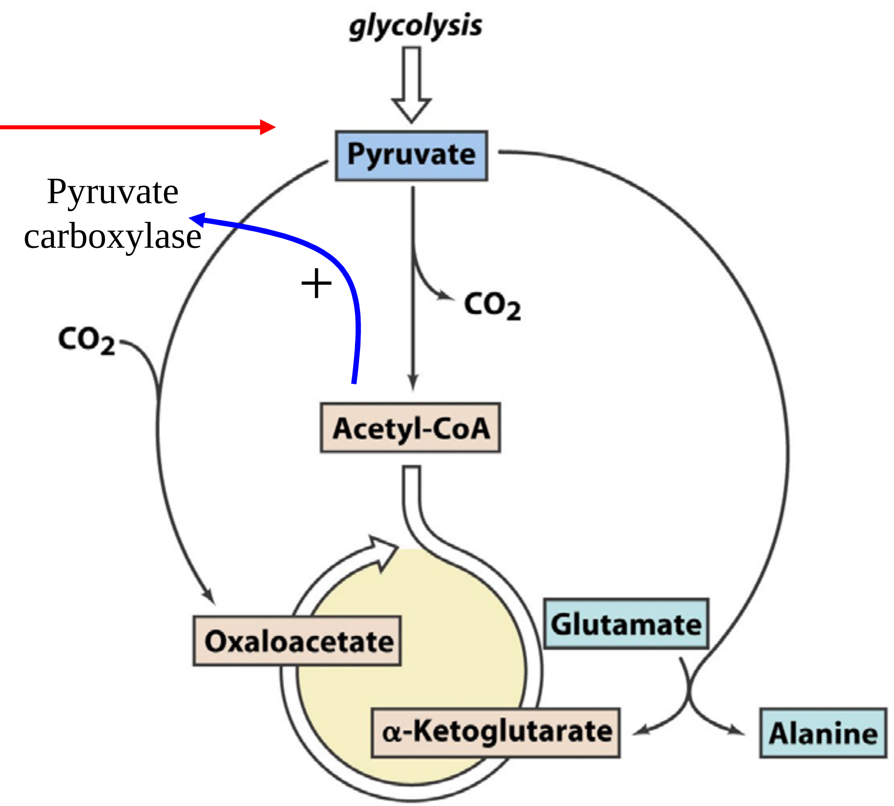
Figure 16-16 Fundamentals of Biochemistry, 2/e

<u>Anaplerotic reactions (filling up)</u>

Pyruvate carboxylase: senses the need of CAC via acetyl-CoA

CAC flux increase during exercise: 60~100 fold in muscle
- increase of intermediates
- upregulation of rate-controlling steps

The fate of pyruvate during exercise
- Acetyl-CoA
- Oxaloacetate
- α-ketoglutarate



Unnumbered figure pg 538 Fundamentals of Biochemistry, 2/e

The glyoxylate cycle: in plant

Acetyl-CoA to oxaloacetate

Two additional enzymes in glyoxysome: isocitrate lyase, malate synthase

Furnishing CAC

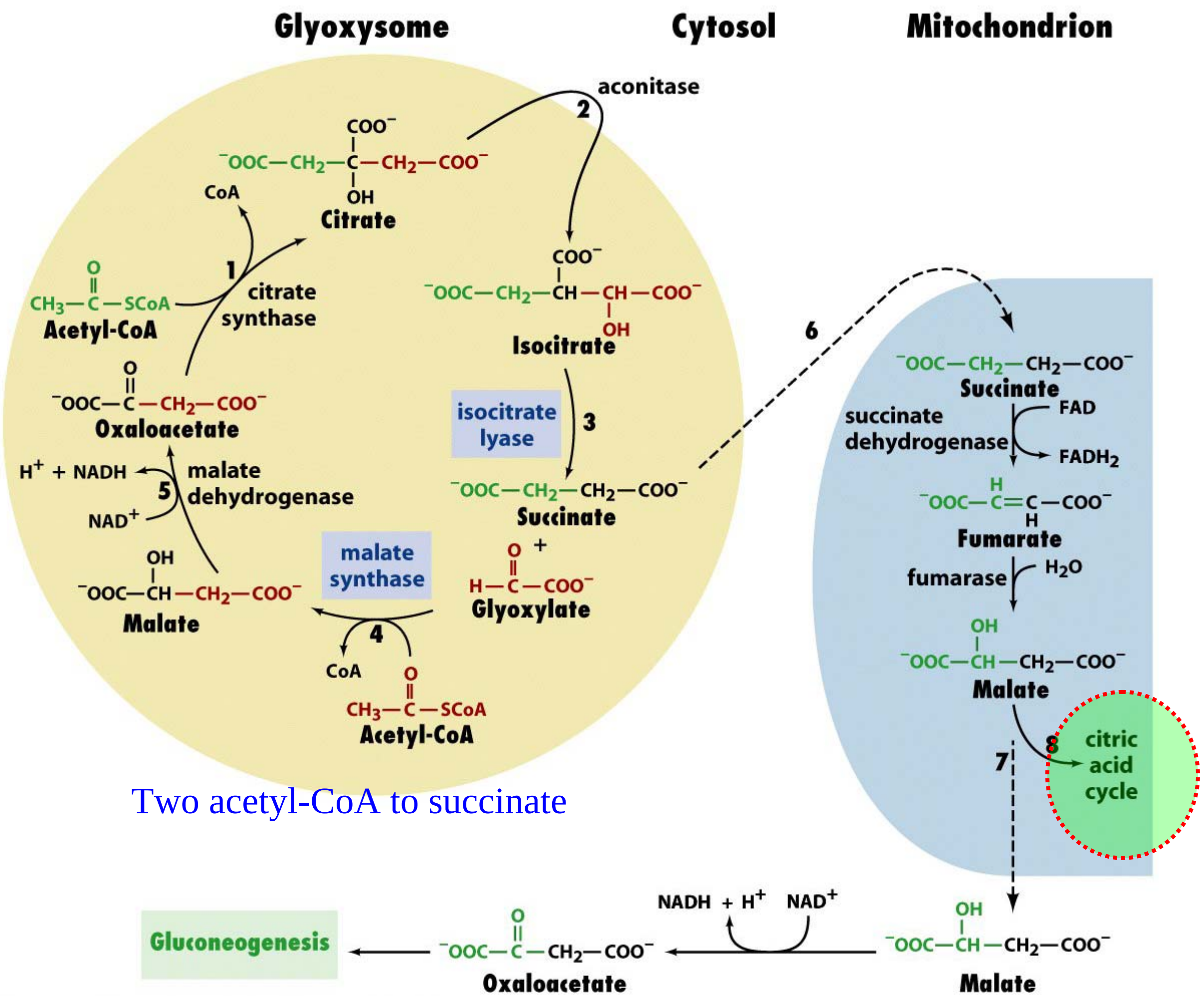
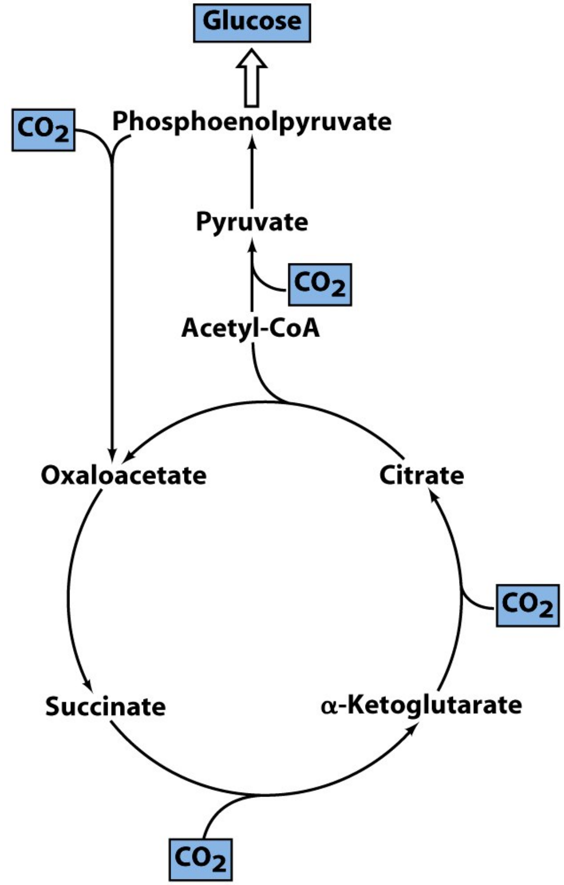


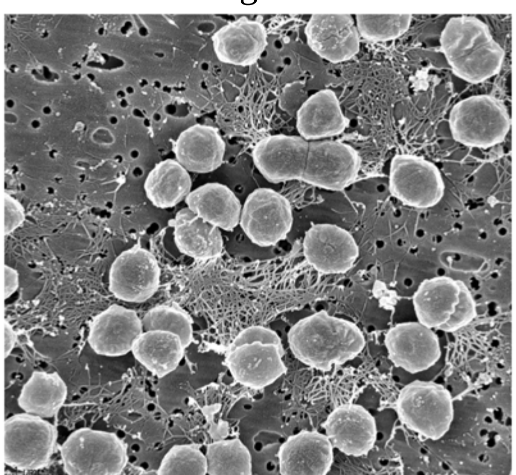
Figure 16-17 Fundamentals of Biochemistry, 2/e

Origin of CAC

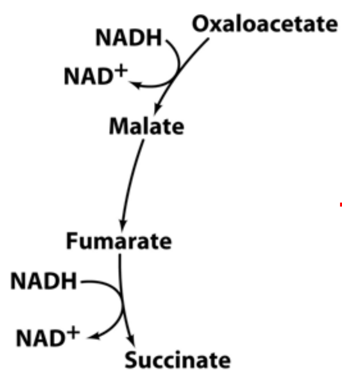


Box 16-3 figure 4 Fundamentals of Biochemistry, 2/e

Methanococcus jannaschii
lacking CAC

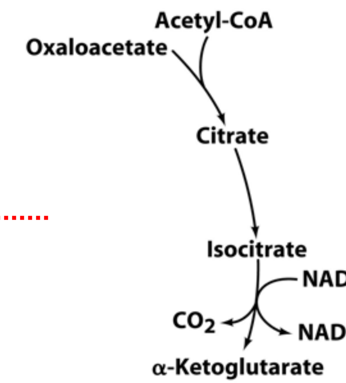


Box 16-3 figure 1 Fundamentals of Biochemistry, 2/e

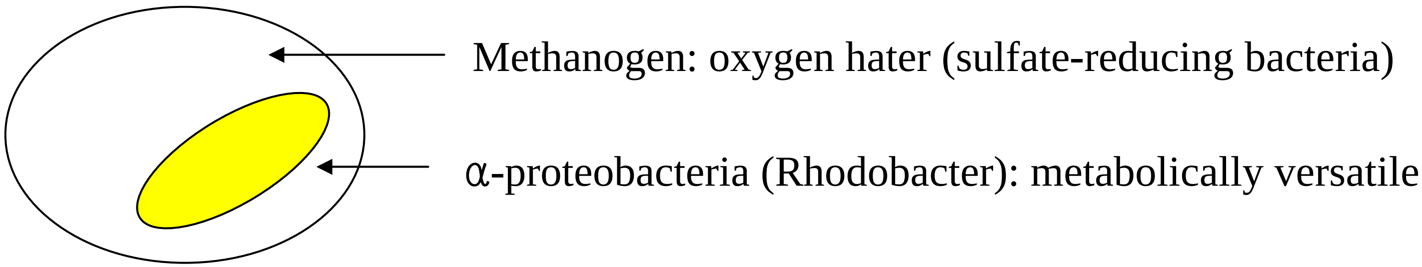


Box 16-3 figure 2 Fundamentals of Biochemistry, 2/e

Merge to reductive pathway?



Box 16-3 figure 3 Fundamentals of Biochemistry, 2/e



Changing chemistry of oceans: Ariel Anbar & Andrew Knoll (Science, 2002)