CHAPTER 16

The Citric Acid Cycle

• The Citric Acid Cycle

• Hans Krebs

Hans Krebs, 1900–1981

Unnumbered 16 p633
Lehninger Principles of Biochemistry, Sixth Edition

Citric acid cycle
earned him a Nobel Prize in Physiology or Medicine in 1953.

Urea cycle

Glyoxylate cycle

Catabolism of proteins, fats, and carbohydrates in the three stages of cellular respiration.

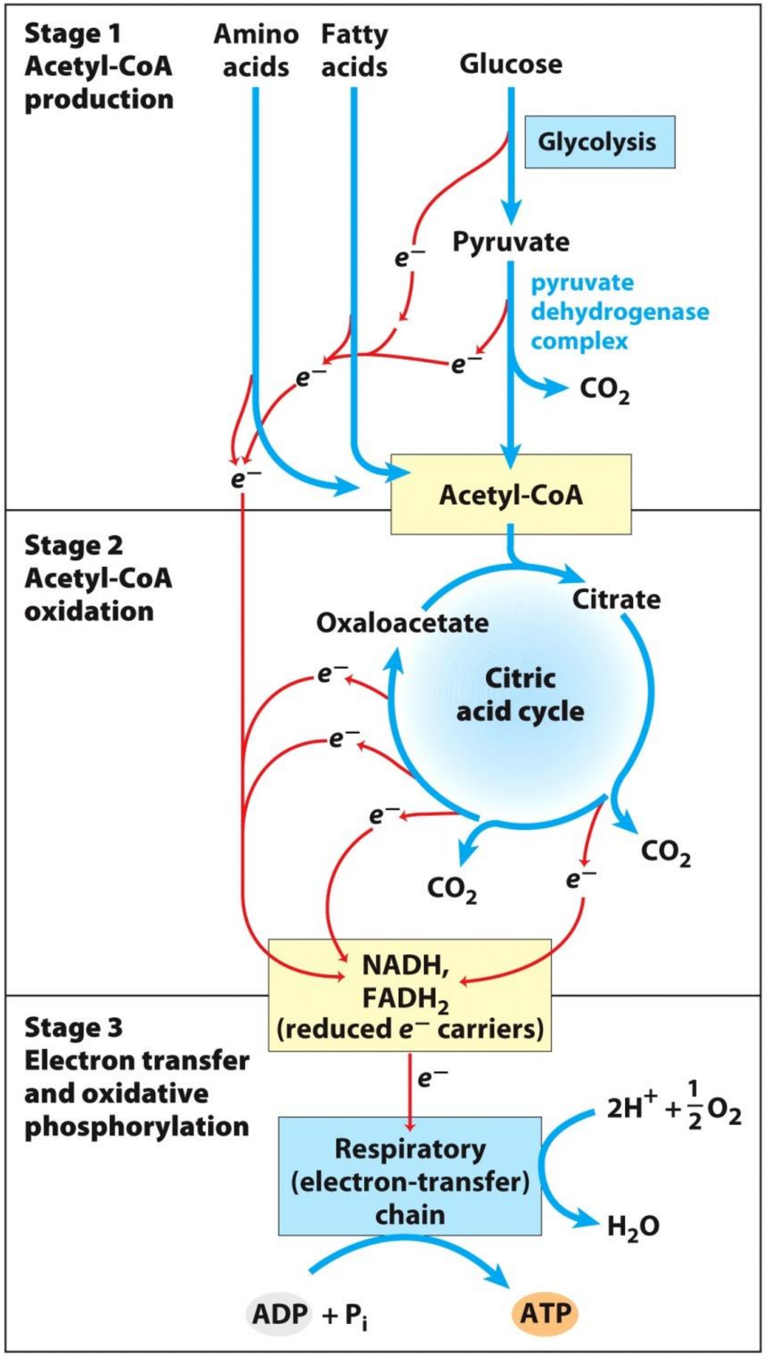

Figure 16-1

- Three stages of cellular respiration

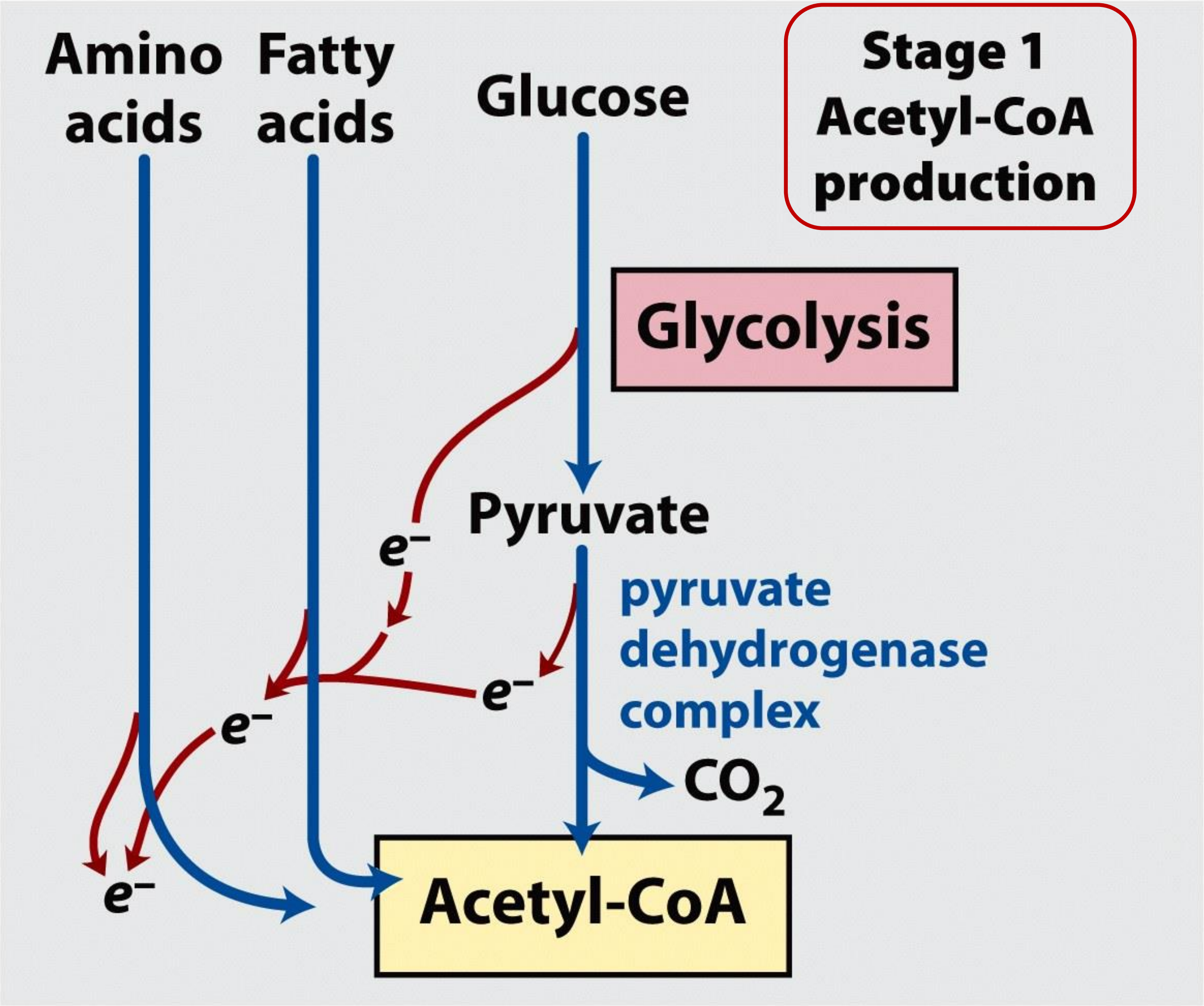

Figure 16-1 part 1
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• Three stages of cellular respiration

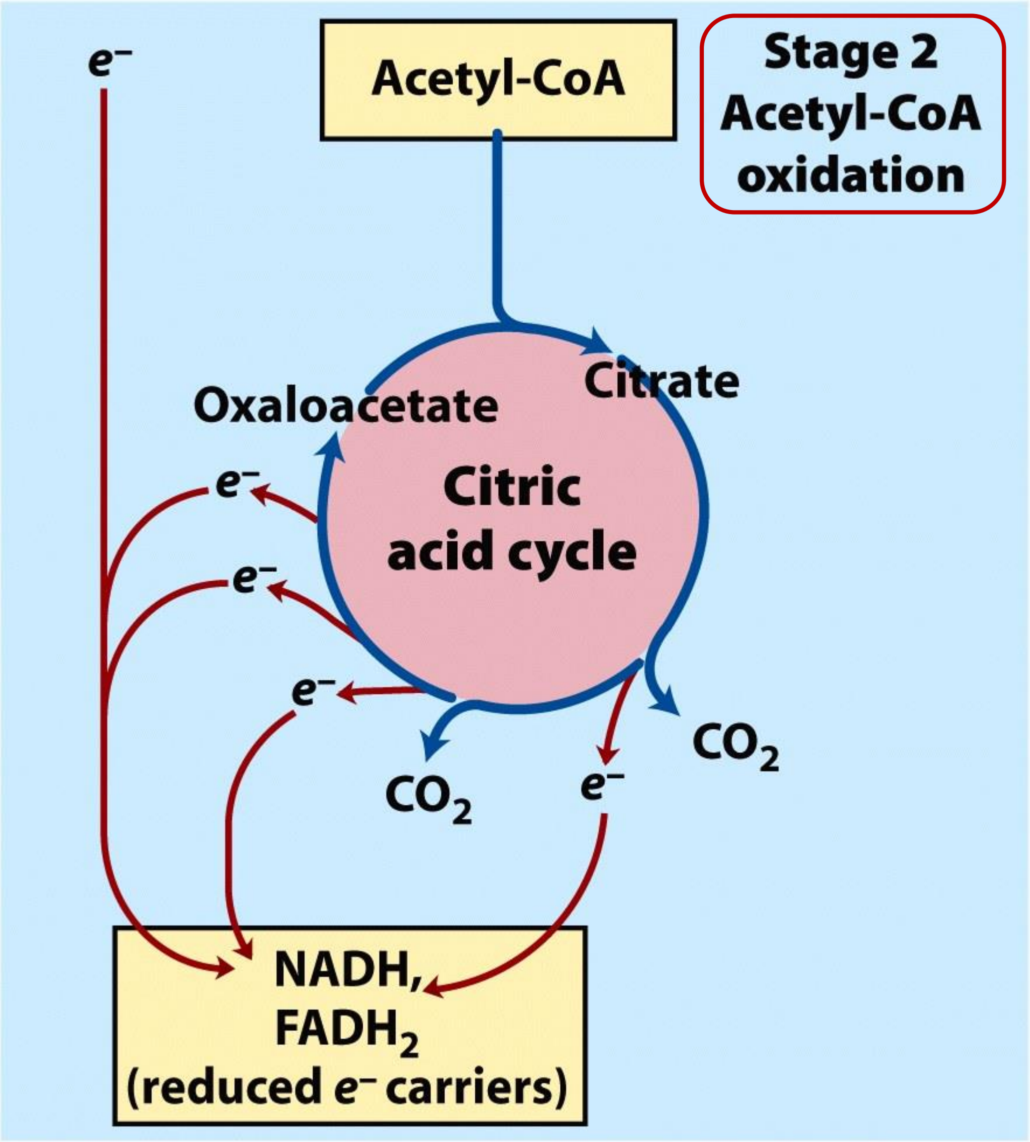

Figure 16-1 part 2
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- **Three stages of cellular respiration**

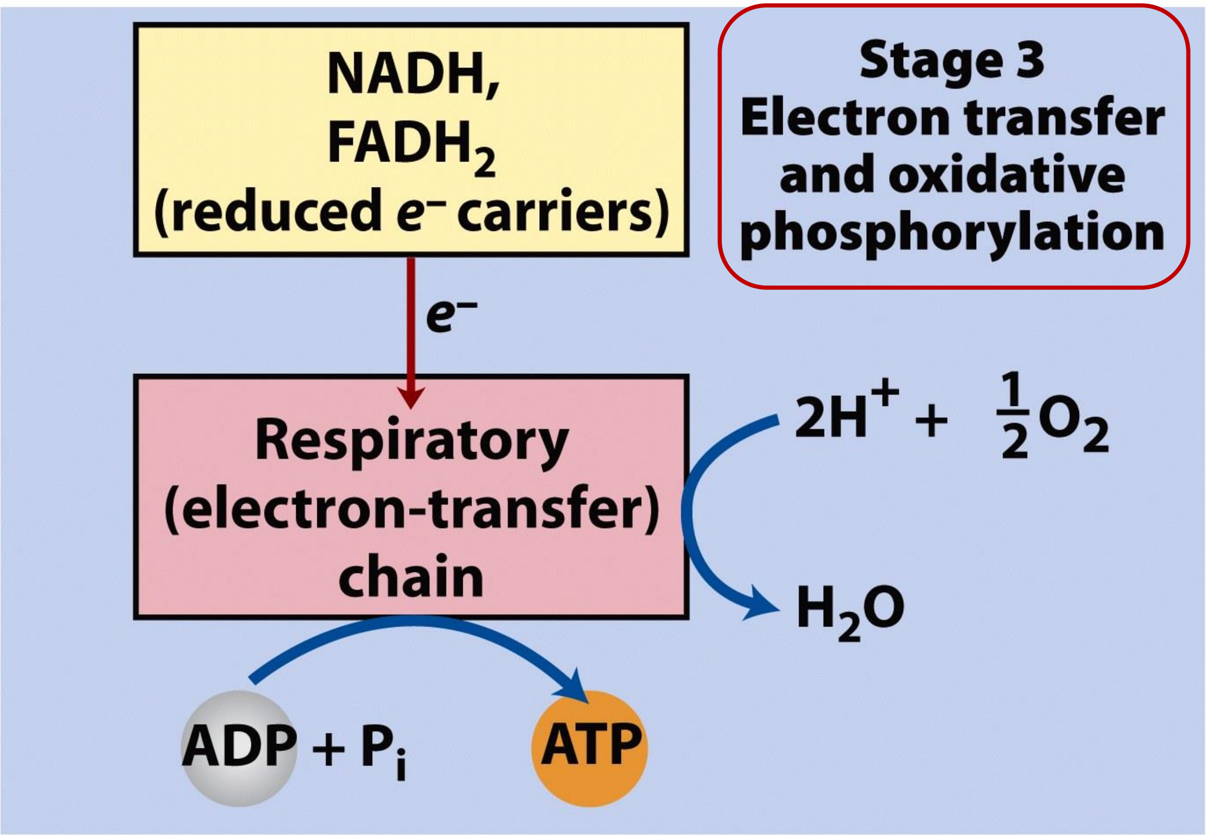

Figure 16-1 part 3
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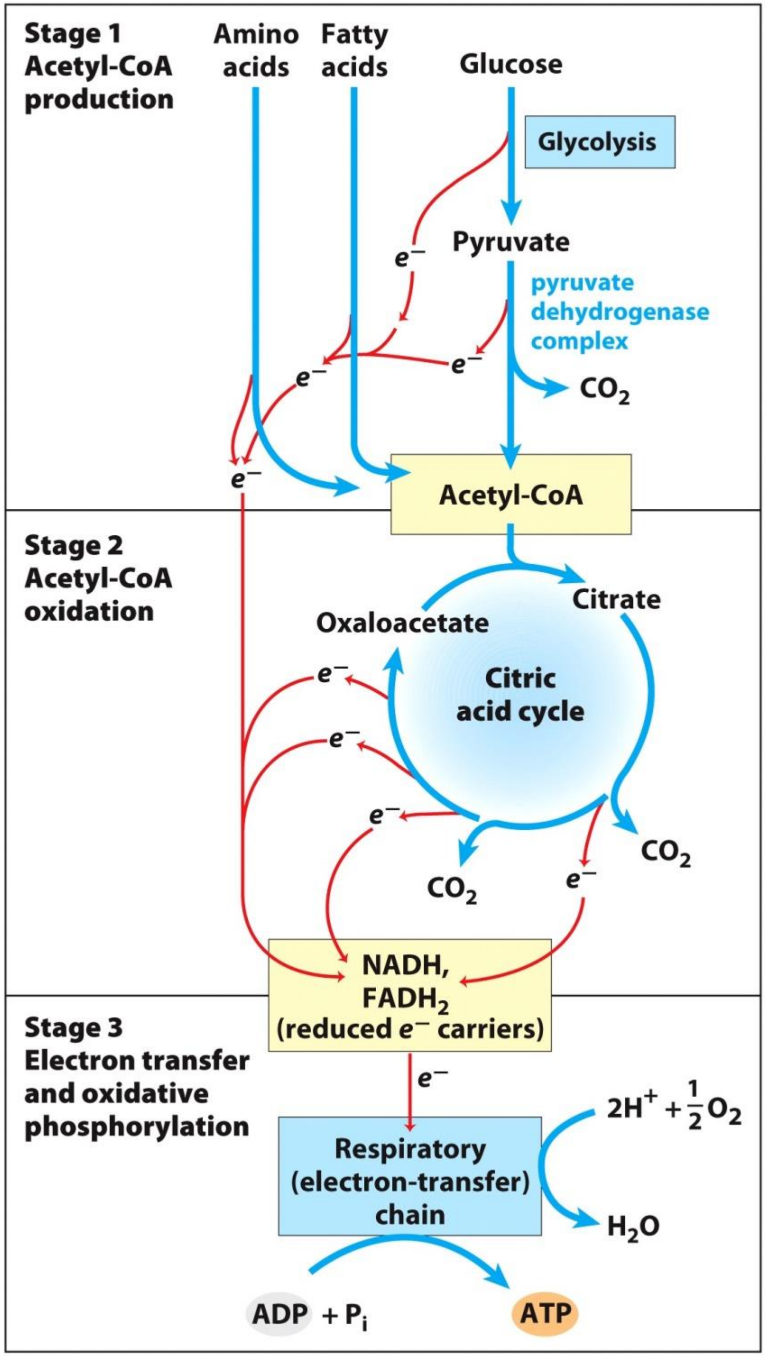
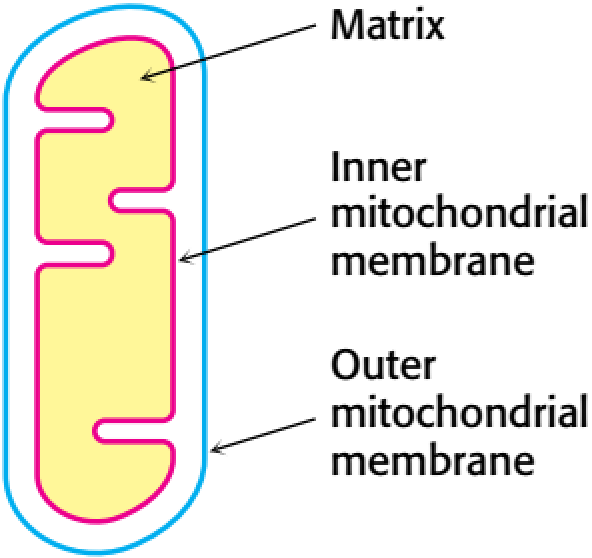

Stage 1
Acetyl-CoA
production
Amino acids
Fatty acids
Glucose
Glycolysis
Pyruvate
pyruvate dehydrogenase complex
CO_2
e^-
Acetyl-CoA
Stage 2
Acetyl-CoA
oxidation
Oxaloacetate
Citrate
Citric acid cycle
CO_2
CO_2
e^-
NADH, $FADH_2$ (reduced e^- carriers)
Stage 3
Electron transfer
and oxidative
phosphorylation
e^-
Respiratory (electron-transfer) chain
$2H^+ + \frac{1}{2}O_2$
H_2O
ADP + P_i
ATP

Figure 16-1


Matrix
Inner mitochondrial membrane
Outer mitochondrial membrane

16.1 Production of Acetyl-CoA (Activated Acetate)

- **Pyruvate is oxidized to acetyl-CoA and CO_2 by PDH**

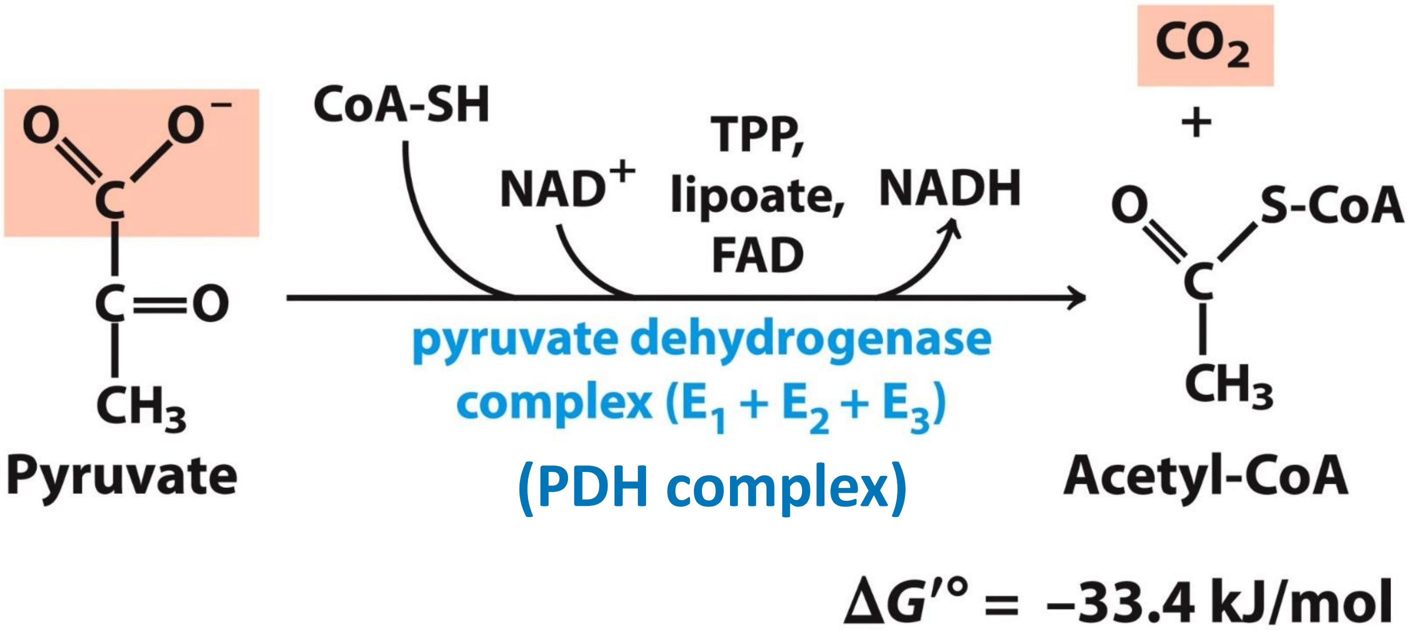


Figure 16-2
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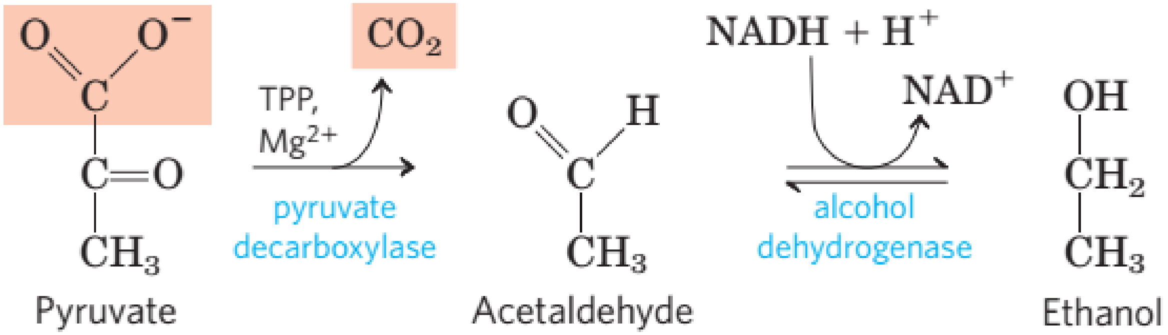
• The PDH complex require 5 coenzymes

- thiamine pyrophosphate (TPP)



- flavin adenine dinucleotide(FAD)
- nicotinamide adenine dinucleotide (NAD)
- coenzyme A (CoA, CoA-SH)
- lipoate

- **The PDH complex require 5 coenzymes**

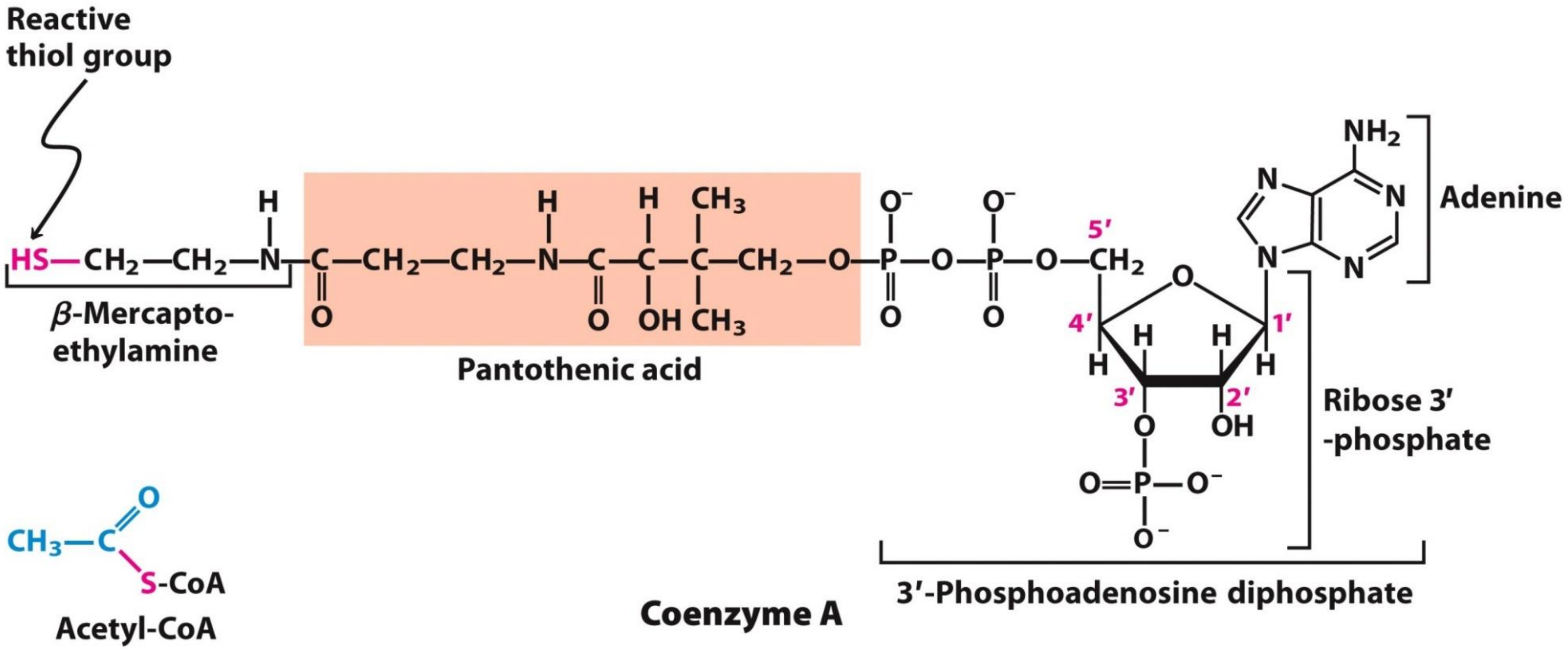


Figure 16-3
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coenzyme A (CoA, CoA-SH)

• The PDH complex require 5 coenzymes

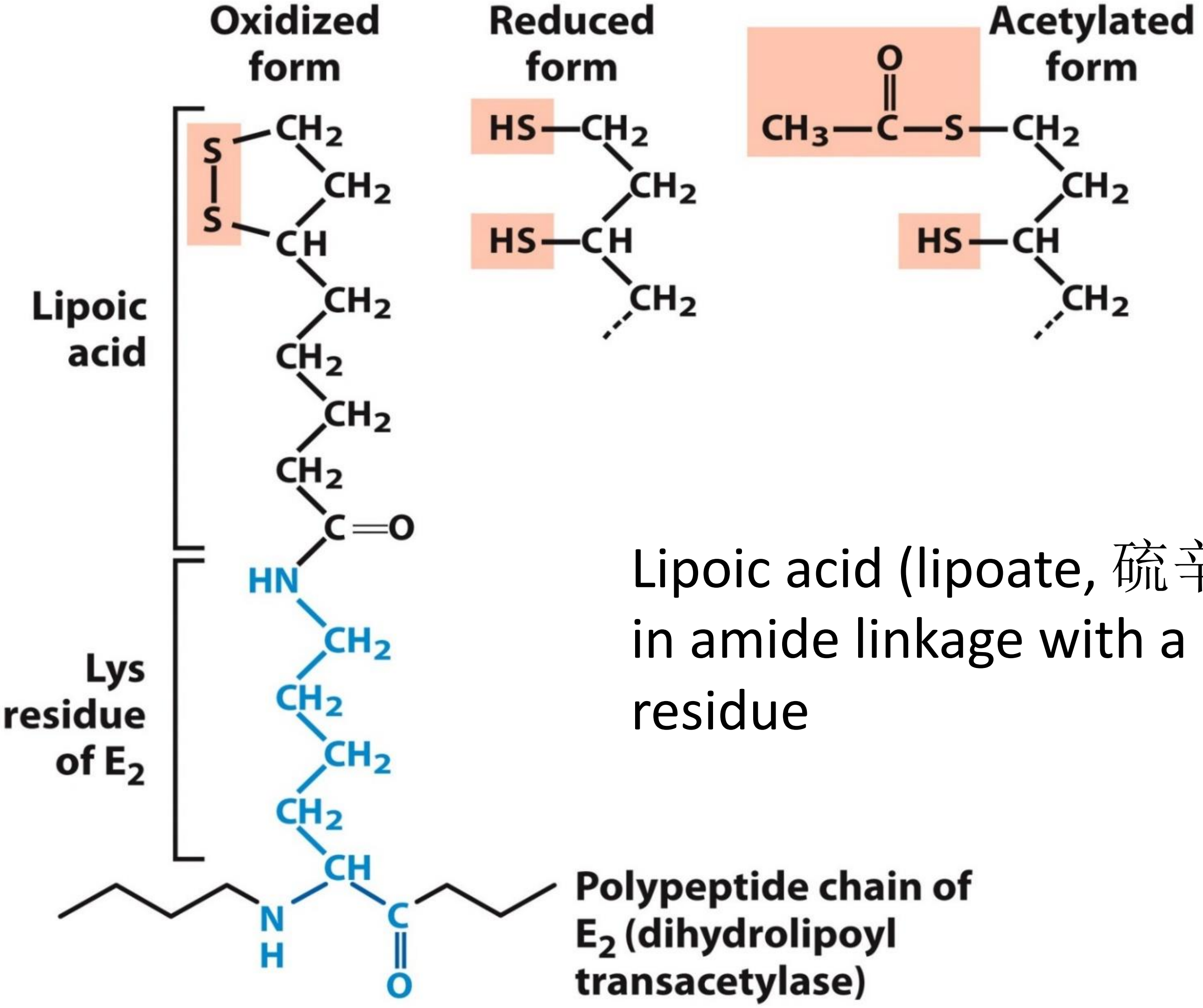
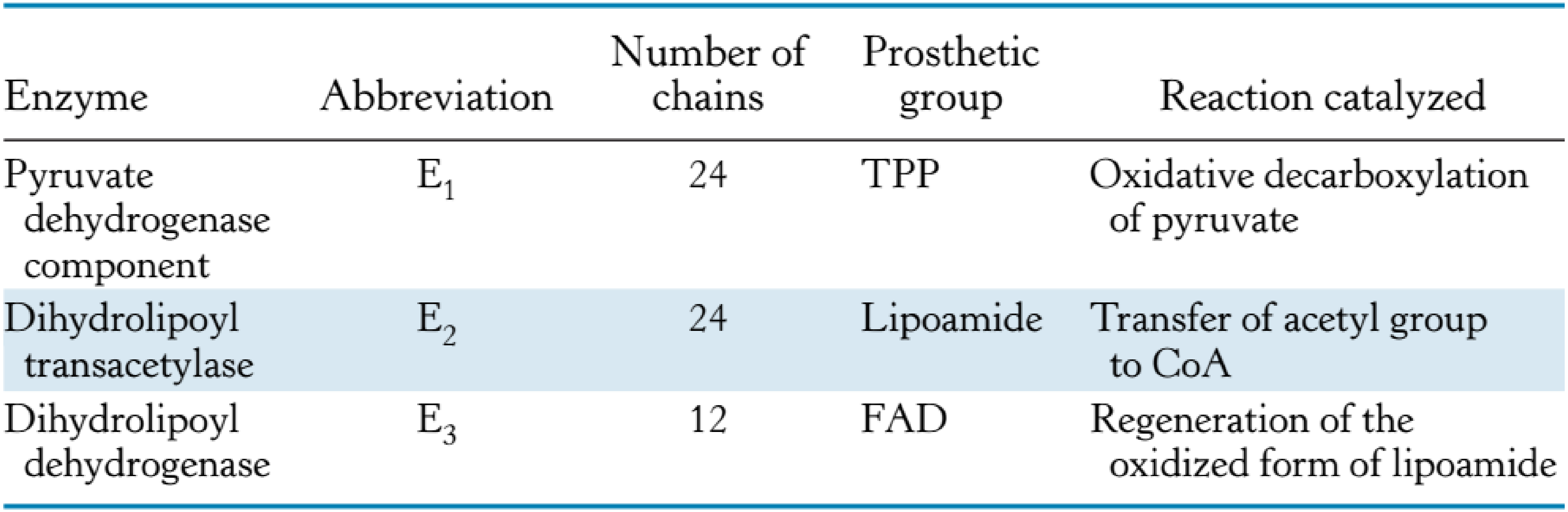


Figure 16-4

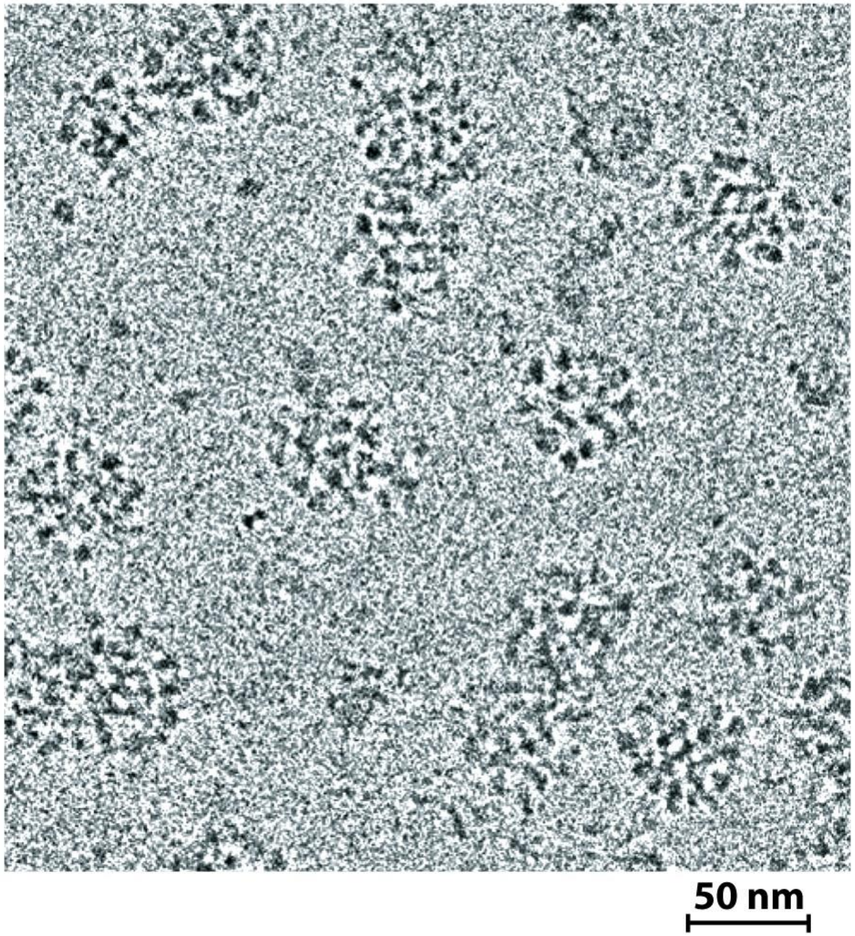
Lipoic acid (lipoate, 硫辛酸) in amide linkage with a Lys residue

PDH complex of *E. coli*



Enzyme	Abbreviation	Number of chains	Prosthetic group	Reaction catalyzed
Pyruvate dehydrogenase component	E_1	24	TPP	Oxidative decarboxylation of pyruvate
Dihydrolipoyl transacetylase	E_2	24	Lipoamide	Transfer of acetyl group to CoA
Dihydrolipoyl dehydrogenase	E_3	12	FAD	Regeneration of the oxidized form of lipoamide

• The PDH complex



Cryoelectron micrograph of PDH complexes isolated from bovine kidney. 50 nm in diameter—more than five times the size of an entire ribosome.

- **The PDH complex**

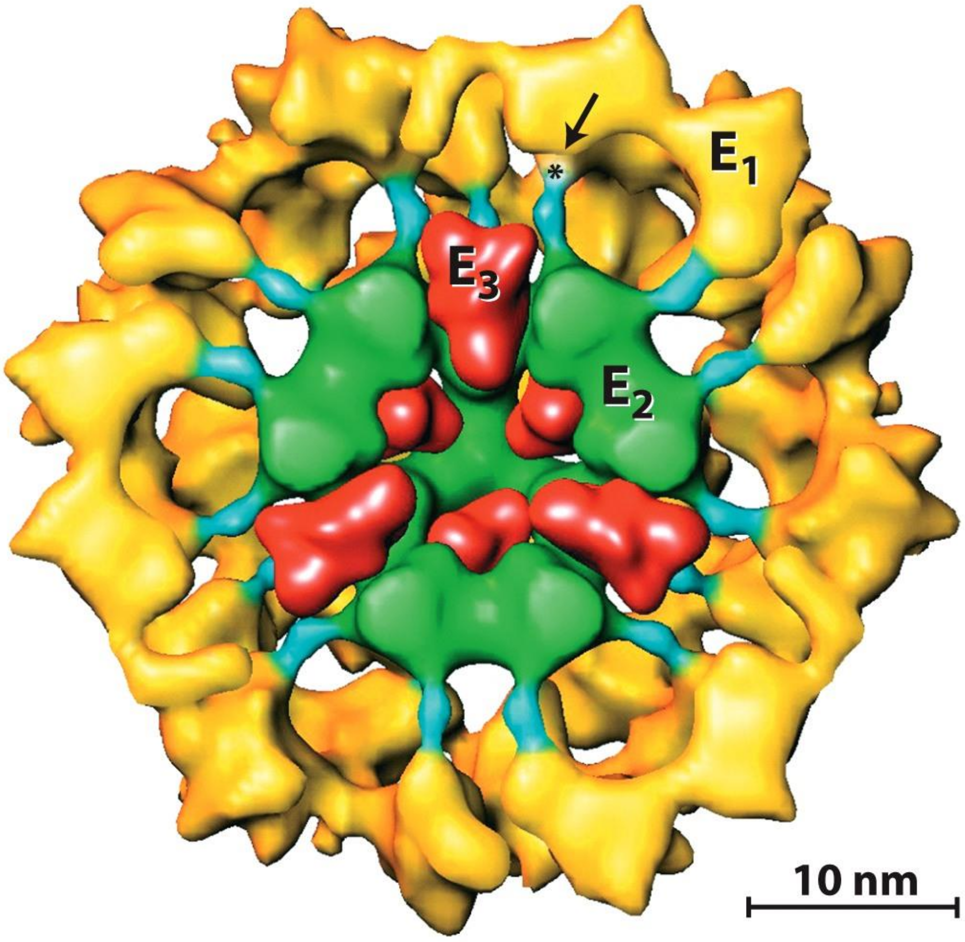


Figure 16-5b

E1:
pyruvate
dehydrogenase

E2:
dihydrolipoyl
transacetylase

E3:
dihydrolipoyl
dehydrogenase

Three-dimensional image of PDH complex

- **E2 has three functionally distinct domains**

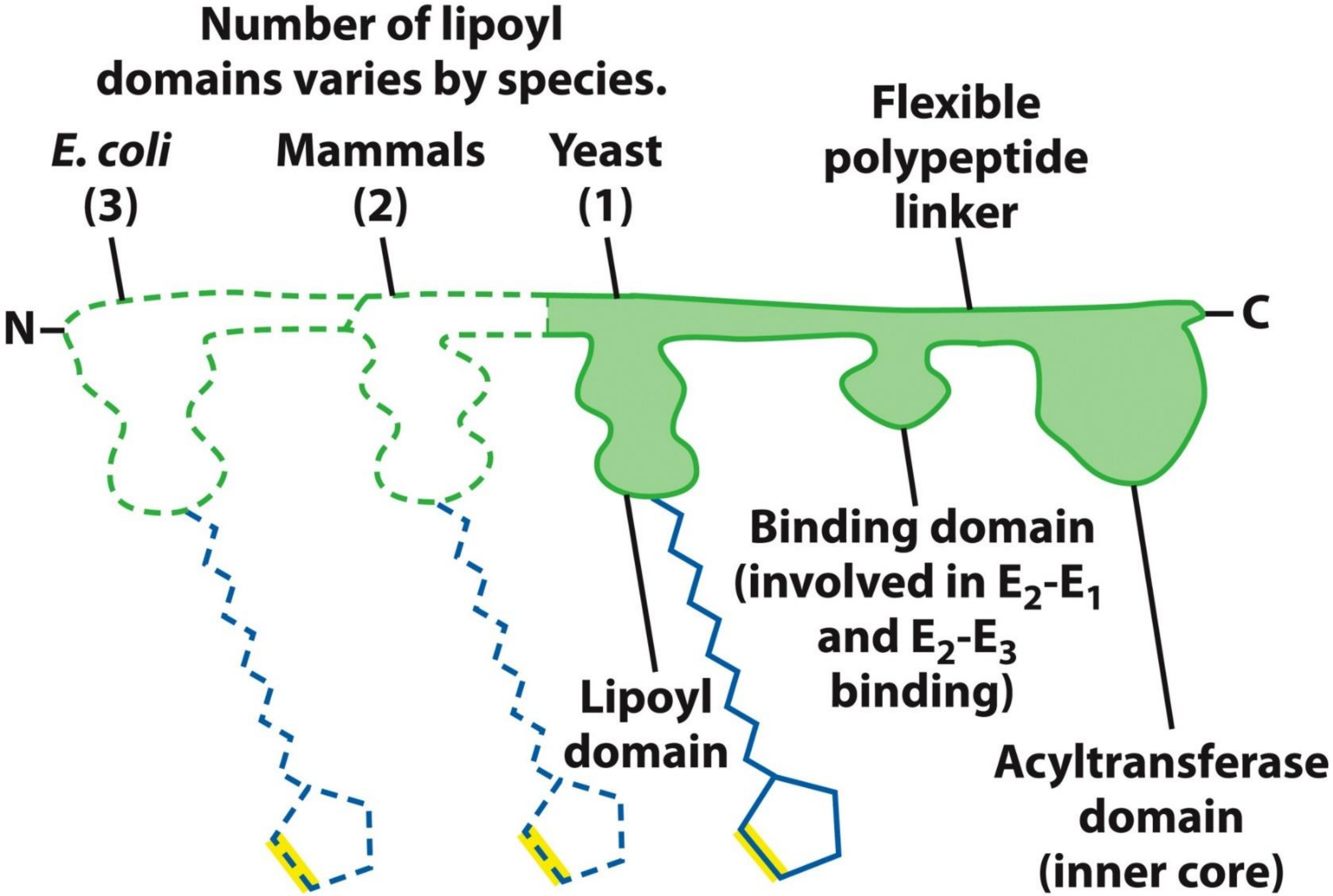
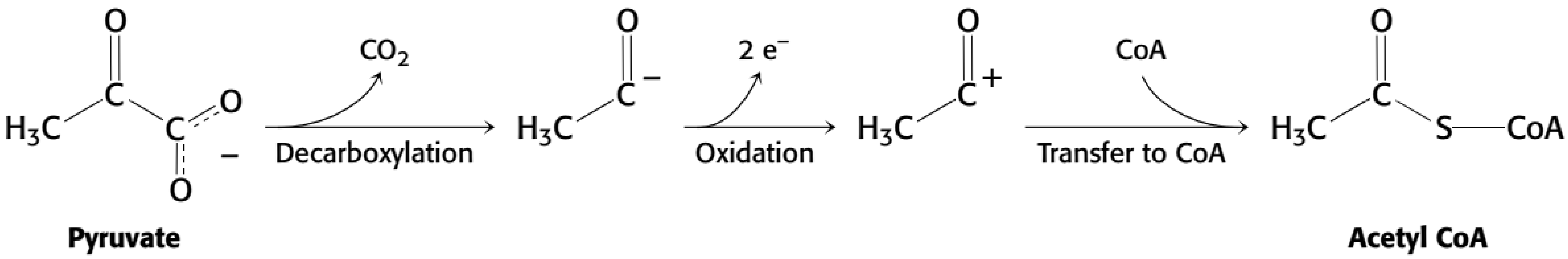
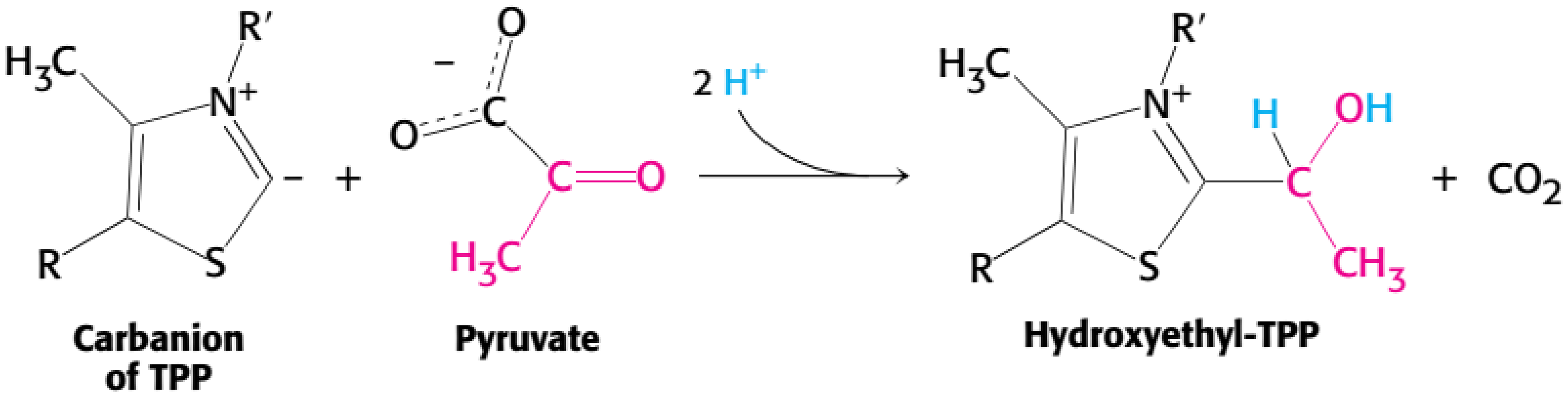


Figure 16-5c

• Reactions of the pyruvate dehydrogenase complex

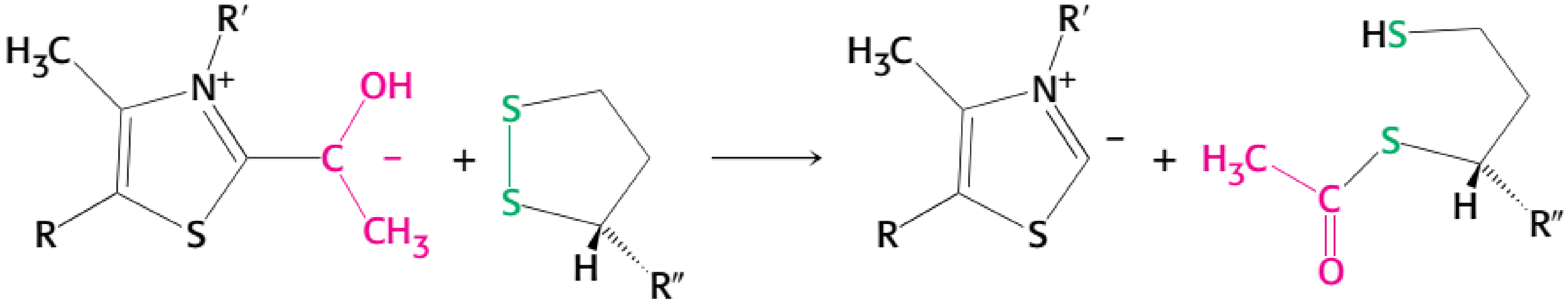


1. Decarboxylation (rate limiting step)



• Reactions of the pyruvate dehydrogenase complex

2. Oxidation



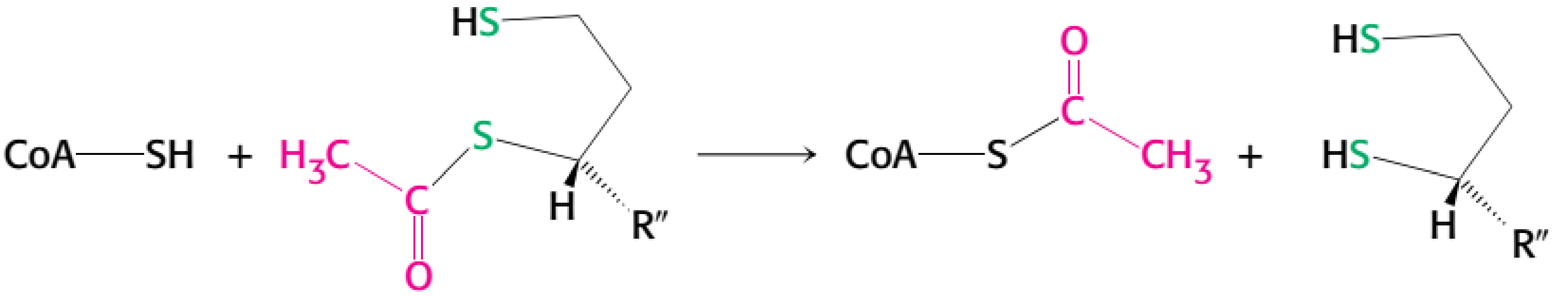
Hydroxyethyl-TPP
(ionized form)

Lipoamide

Carbanion of TPP

Acetyllipoamide

3. Formation of Acetyl CoA



Coenzyme A

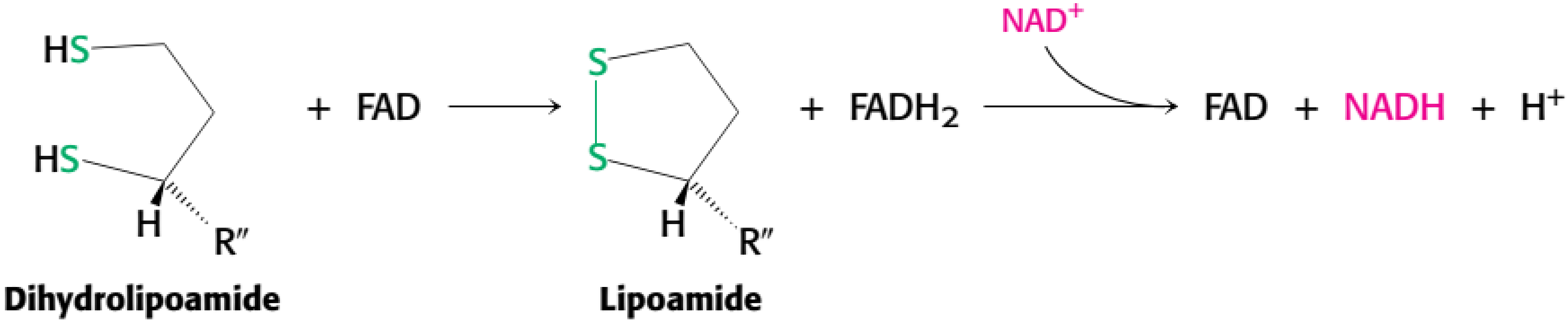
Acetyllipoamide

Acetyl CoA

Dihydrolipoamide

• Reactions of the pyruvate dehydrogenase complex

4-5. Regeneration of oxidized lipoamide



$$\text{Pyruvate} + \text{CoA} + \text{NAD}^+ \longrightarrow \text{acetyl CoA} + \text{CO}_2 + \text{NADH} + \text{H}^+$$

- **Reactions of the pyruvate dehydrogenase complex**

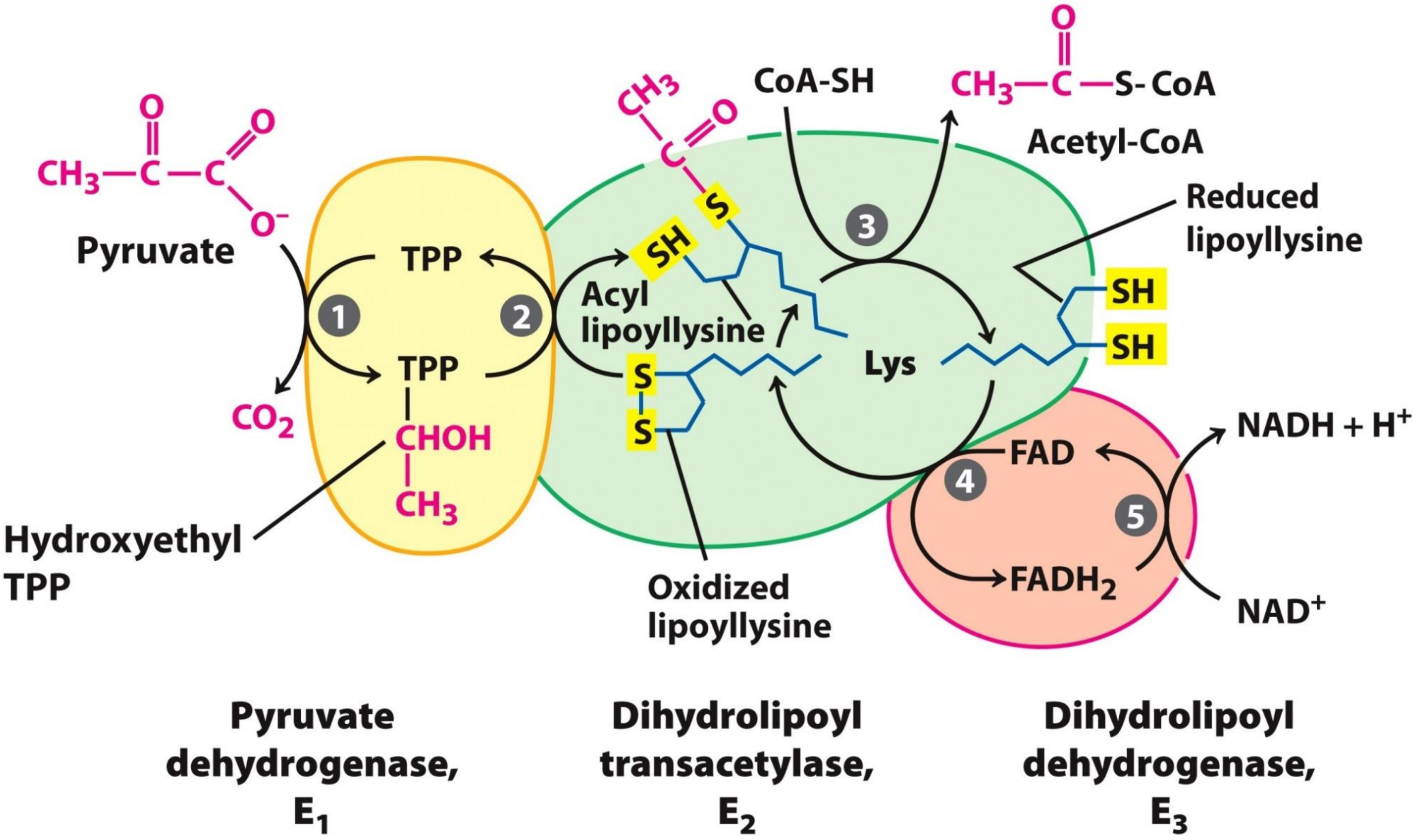


Figure 16-6

Oxidative decarboxylation of pyruvate to acetyl-CoA by the PDH

- The PDH complex

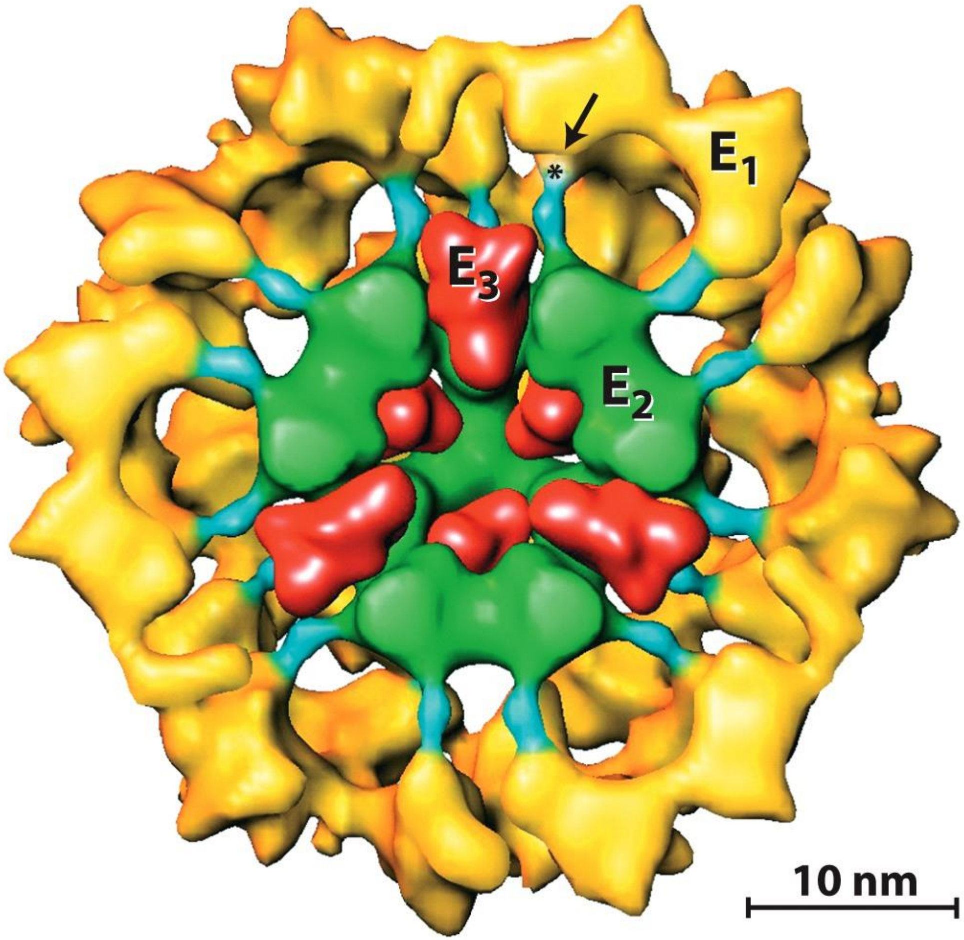


Figure 16-5b

E1:
pyruvate
dehydrogenase

E2:
dihydrolipoyl
transacetylase

E3:
dihydrolipoyl
dehydrogenase

Three-dimensional image of PDH complex

• Reactions of the pyruvate dehydrogenase complex

- Substrate channeling

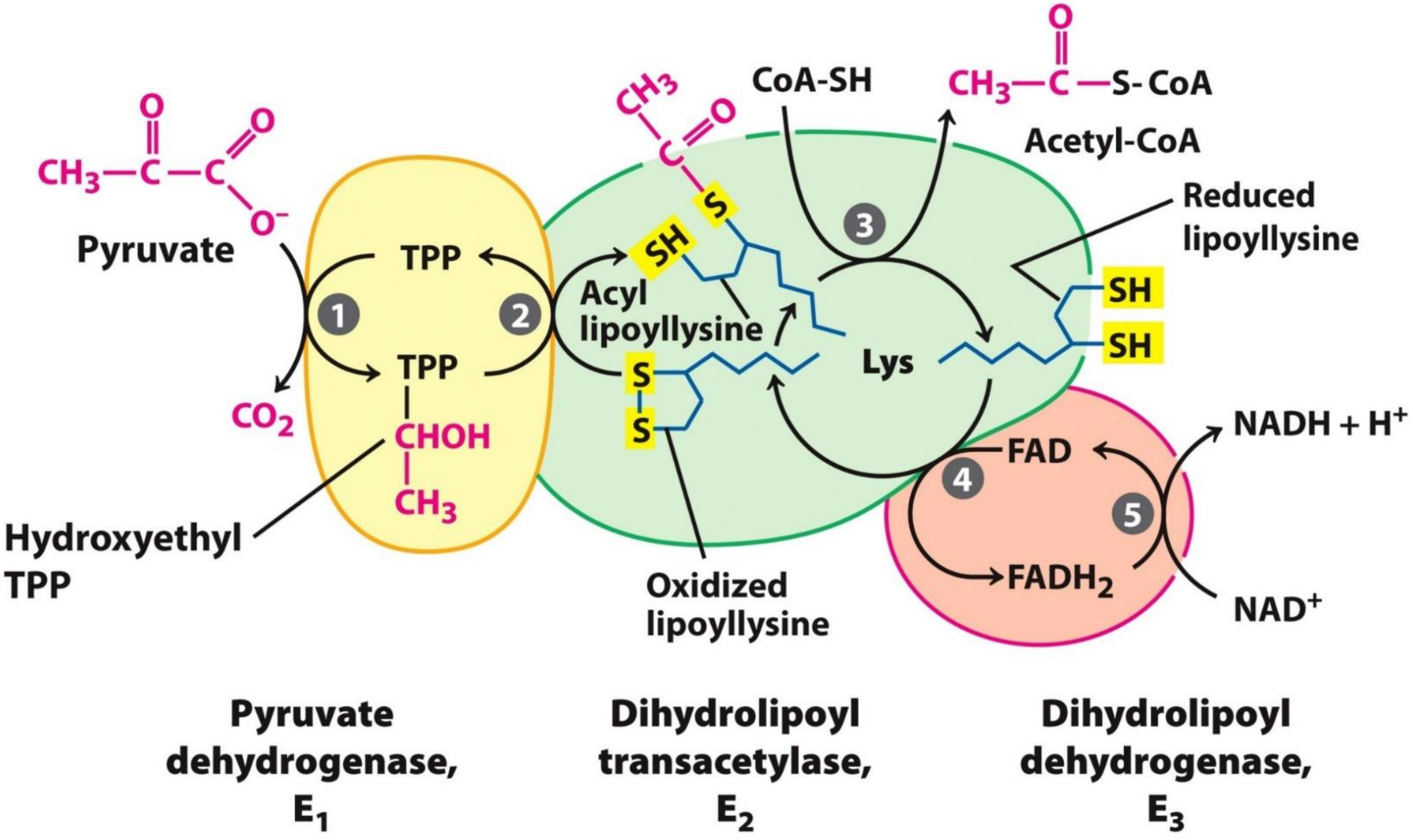
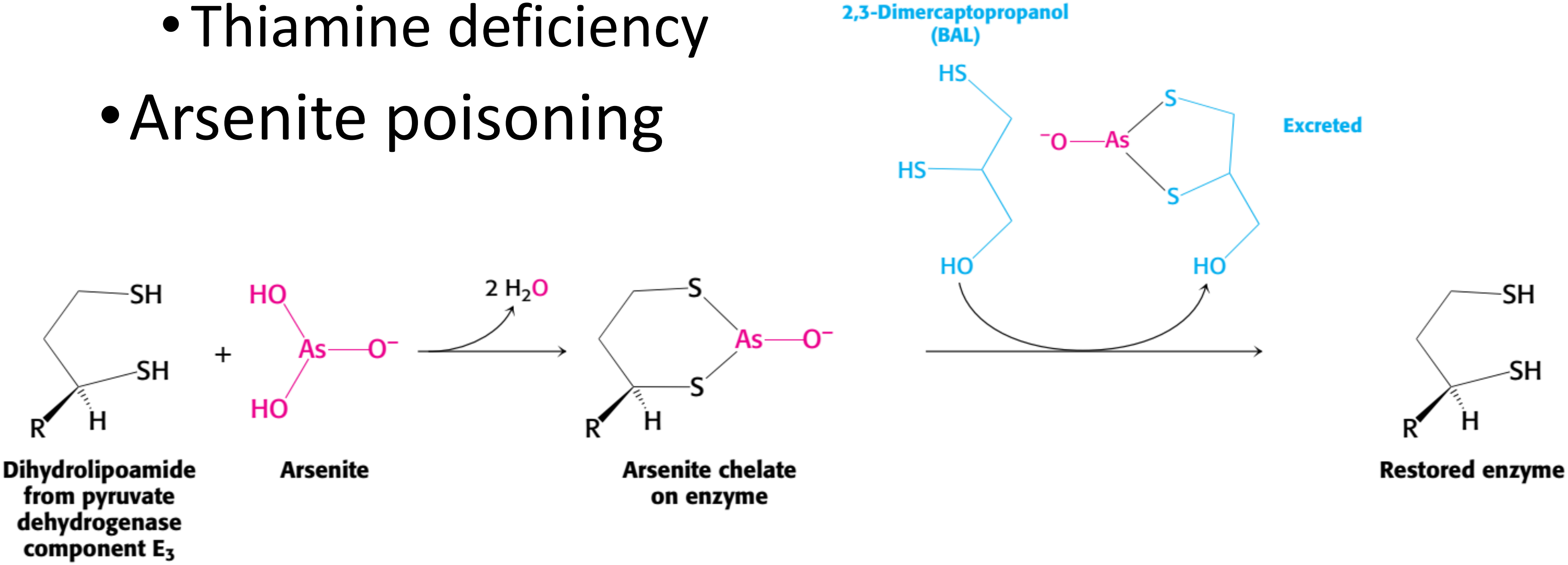


Figure 16-6

Reactions of the pyruvate dehydrogenase complex

- Involvement of Vitamins
  - Thiamine (Vb1) : in TPP
  - riboflavin (Vb2) : in FAD
  - Niacin (Vb3) : in NAD
  - Pantothenate (Vb5): in CoA
- Beriberi (脚气病)
  - Thiamine deficiency
- Arsenite poisoning



• Summary 16.1

- Pyruvate, the product of glycolysis, is converted to acetyl-CoA, the starting material for the citric acid cycle, by the pyruvate dehydrogenase (PDH) complex.

- The PDH complex is composed of multiple copies of three enzymes: pyruvate dehydrogenase, E1 (with its bound cofactor TPP); dihydrolipoyltransacetylase, E2 (with its covalently bound lipoyl group); and dihydrolipoyl dehydrogenase, E3 (with its cofactors FAD and NAD).

- E1 catalyzes first the decarboxylation of pyruvate, producing hydroxyethyl-TPP, and then the oxidation of the hydroxyethyl group to an acetyl group.

Summary 16.1

- E2 catalyzes the transfer of the acetyl group to coenzyme A, forming acetyl-CoA.

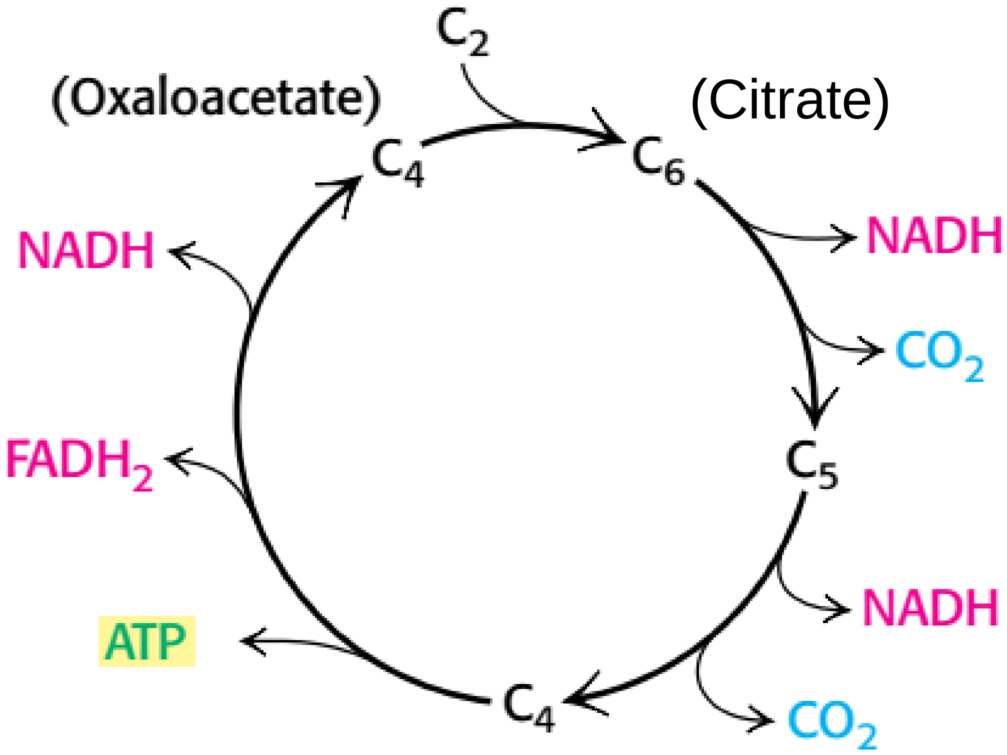
- E3 catalyzes the regeneration of the disulfide (oxidized) form of lipoate; electrons pass first to FAD, then to NAD^+.

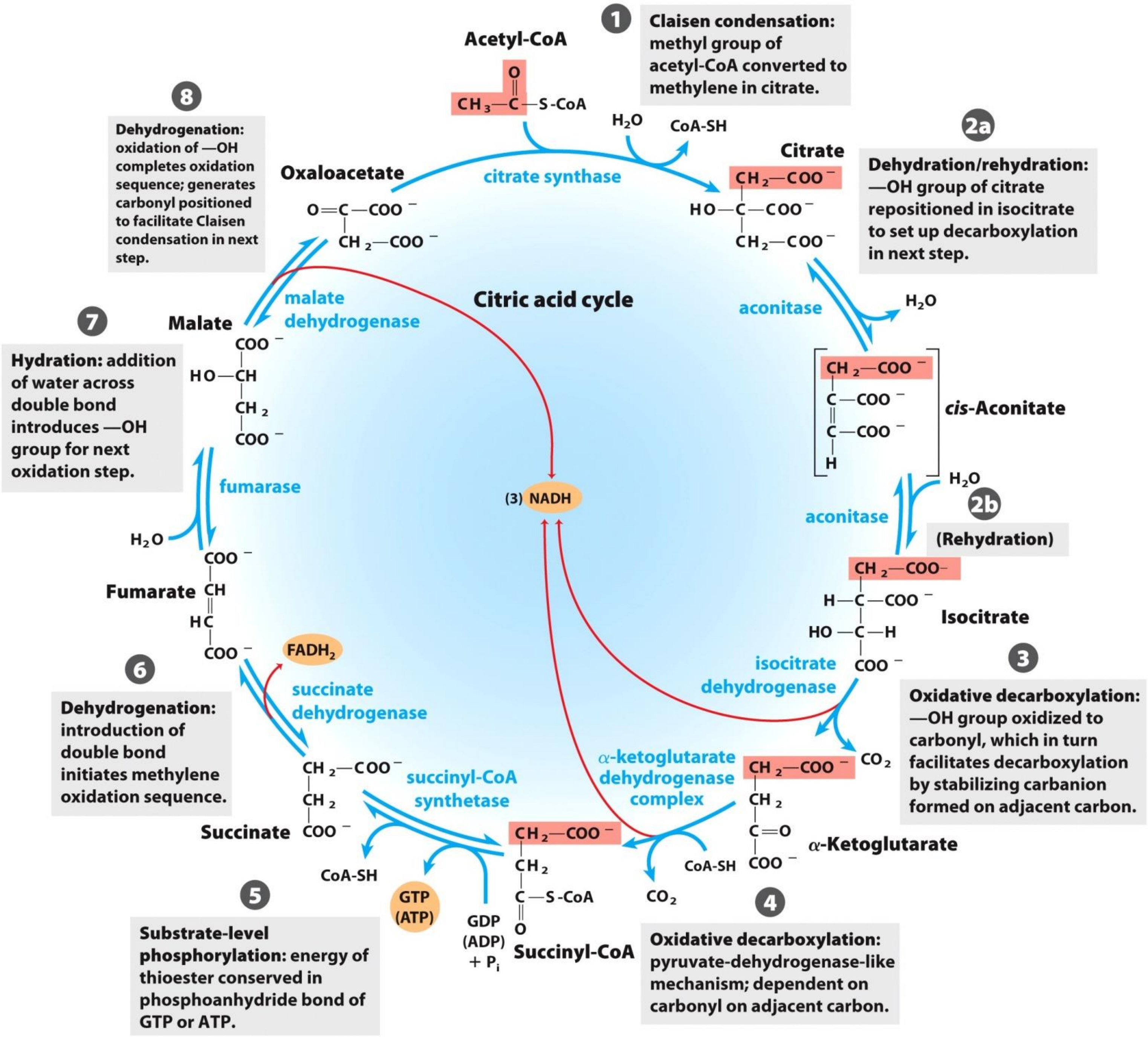
- The long lipoyllysyl arm swings from the active site of E1 to E2 to E3, tethering the intermediates to the enzyme complex to allow substrate channeling.

- The organization of the PDH complex is very similar to that of the enzyme complexes that catalyze the oxidation of α-ketoglutarate and the branched-chain α-keto acids.

16.2 Reactions of the Citric Acid Cycle

• Overview of the citric acid cycle





① **Claisen condensation:** methyl group of acetyl-CoA converted to methylene in citrate.

②a **Dehydration/rehydration:** —OH group of citrate repositioned in isocitrate to set up decarboxylation in next step.

②b (Rehydration)

③ **Oxidative decarboxylation:** —OH group oxidized to carbonyl, which in turn facilitates decarboxylation by stabilizing carbanion formed on adjacent carbon.

④ **Oxidative decarboxylation:** pyruvate-dehydrogenase-like mechanism; dependent on carbonyl on adjacent carbon.

⑤ **Substrate-level phosphorylation:** energy of thioester conserved in phosphoanhydride bond of GTP or ATP.

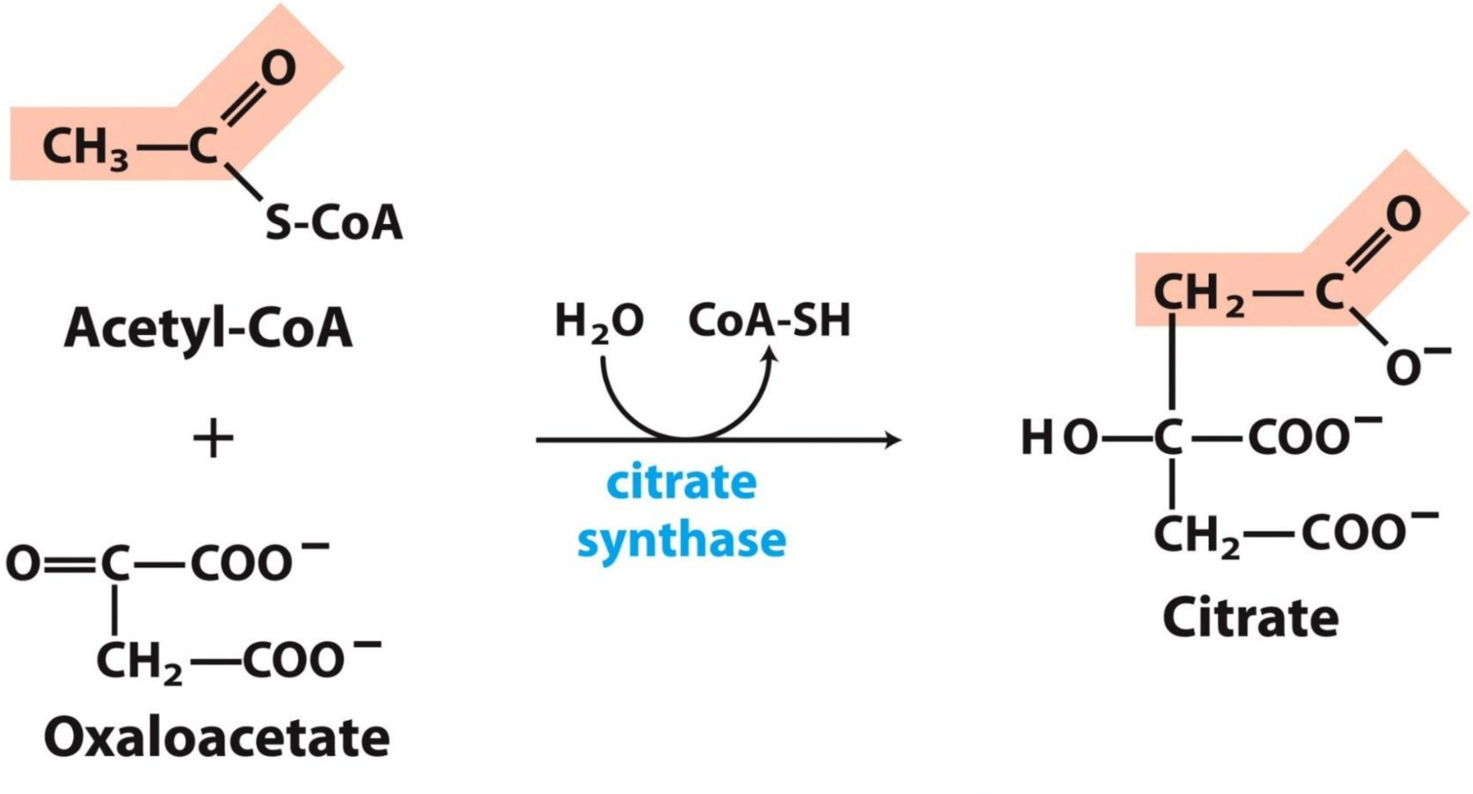
⑥ **Dehydrogenation:** introduction of double bond initiates methylene oxidation sequence.

⑦ **Hydration:** addition of water across double bond introduces —OH group for next oxidation step.

⑧ **Dehydrogenation:** oxidation of —OH completes oxidation sequence; generates carbonyl positioned to facilitate Claisen condensation in next step.

Figure 16-7

① Formation of Citrate



$\Delta G'^{\circ} = -32.2$ kJ/mol

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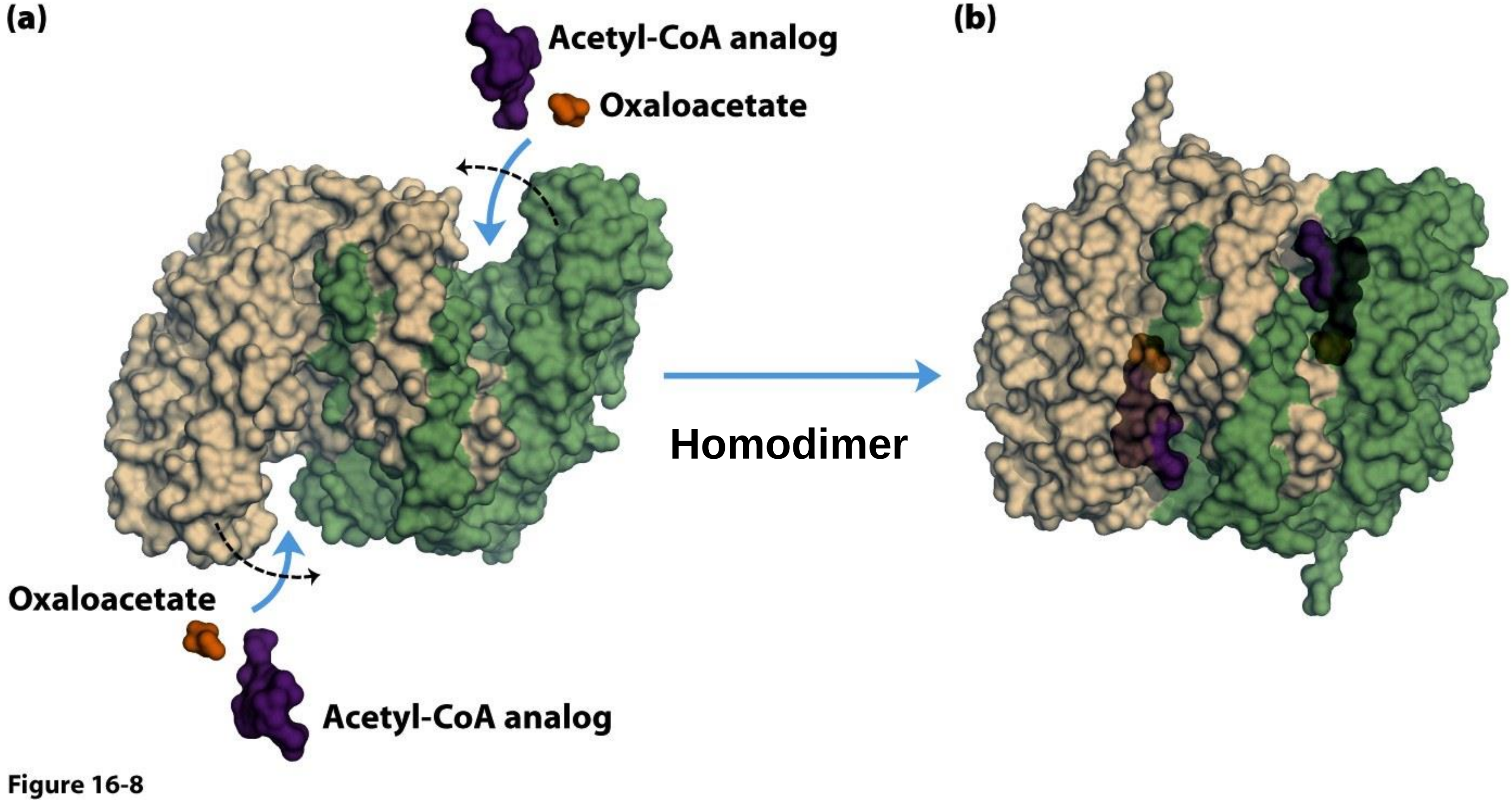
Claisen condensation between a thioester and a ketone

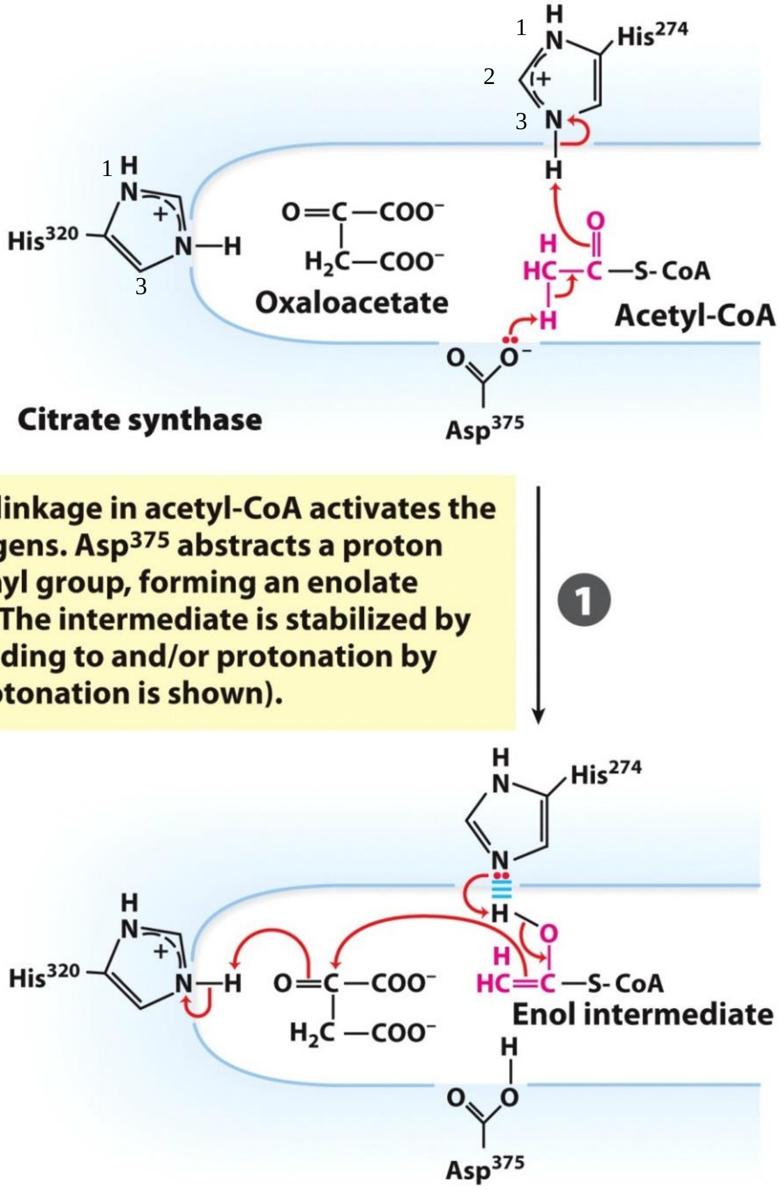
① Formation of Citrate



Structure of citrate synthase

Two successive induced fits of the enzyme to its substrate and intermediate

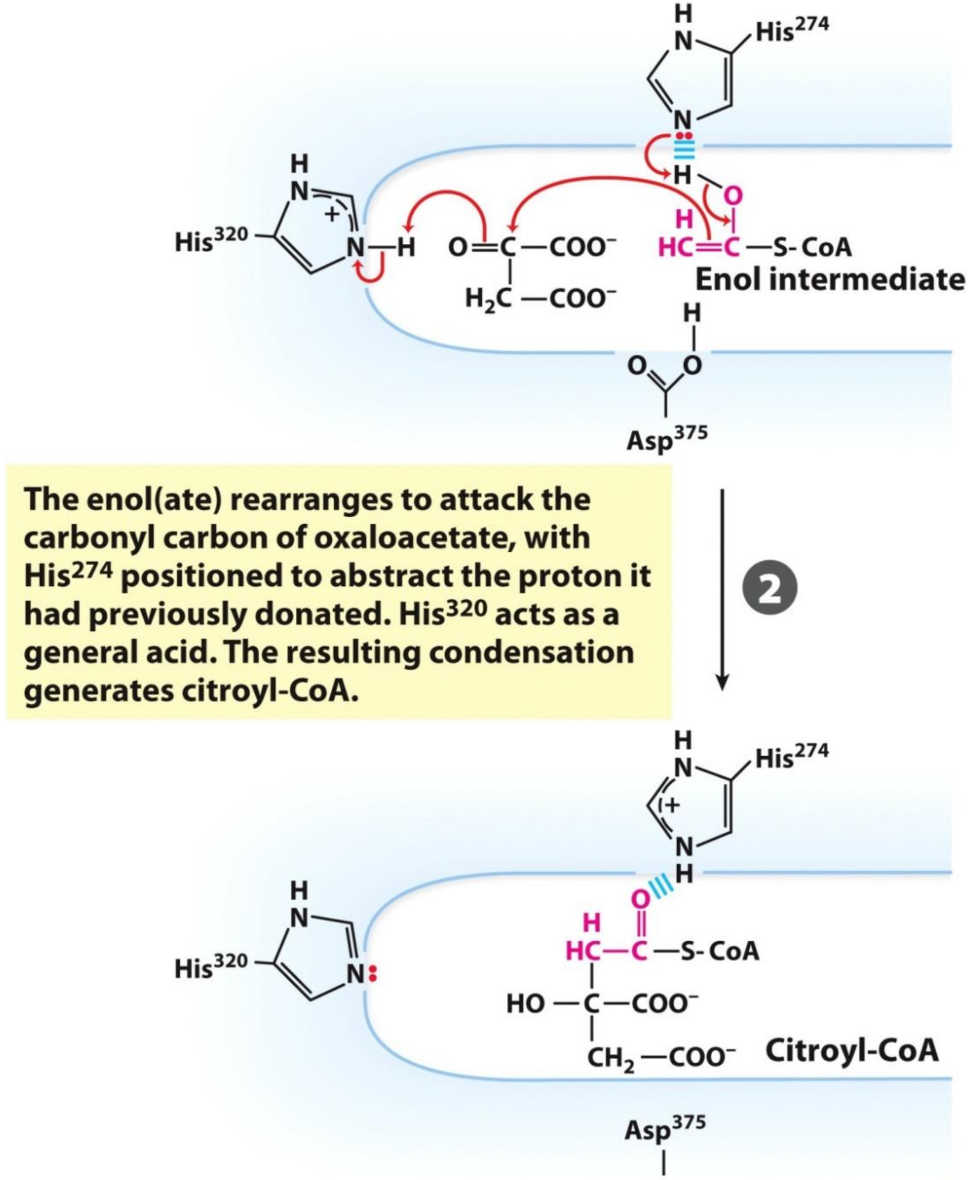
① Formation of Citrate



The thioester linkage in acetyl-CoA activates the methyl hydrogens. Asp^{375} abstracts a proton from the methyl group, forming an enolate intermediate. The intermediate is stabilized by hydrogen bonding to and/or protonation by His^{274} (full protonation is shown).

Figure 16-9 part 1

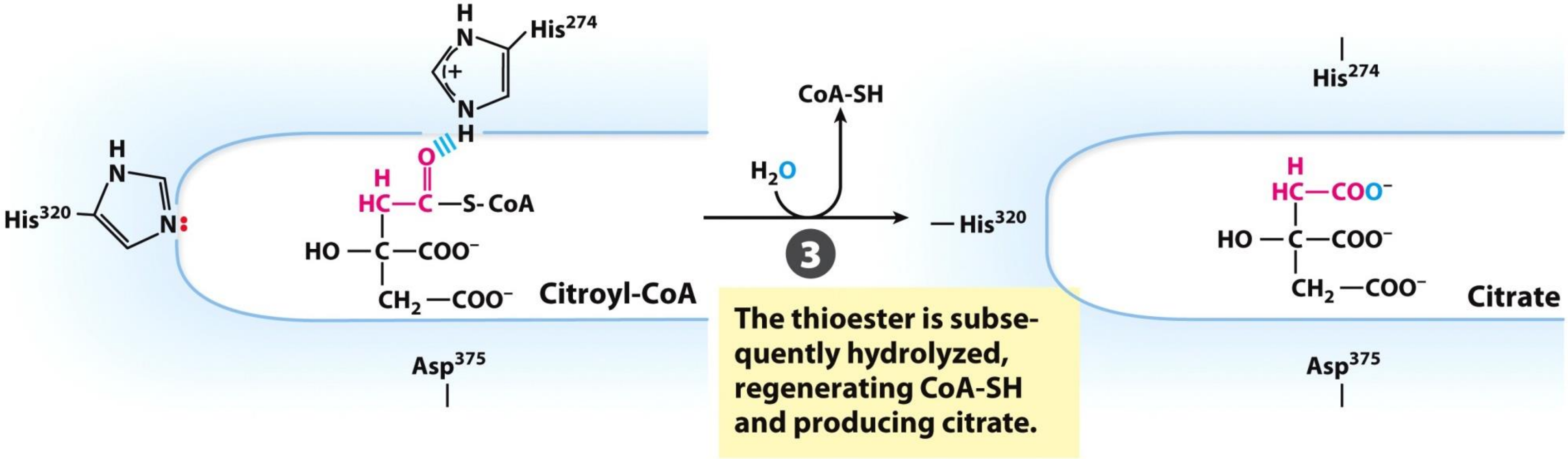
① Formation of Citrate



The enol(ate) rearranges to attack the carbonyl carbon of oxaloacetate, with His^{274} positioned to abstract the proton it had previously donated. His^{320} acts as a general acid. The resulting condensation generates citroyl-CoA.

Figure 16-9 part 2

① Formation of Citrate



The thioester is subsequently hydrolyzed, regenerating CoA-SH and producing citrate.

Figure 16-9 part 3
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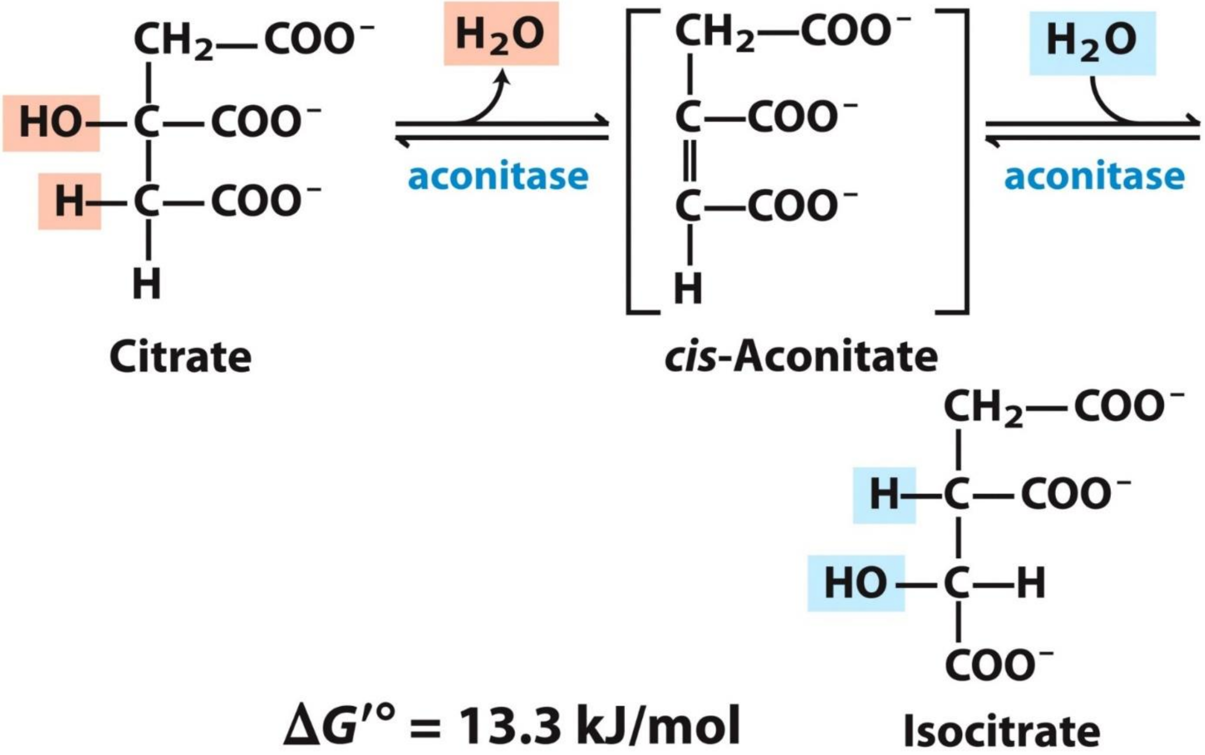
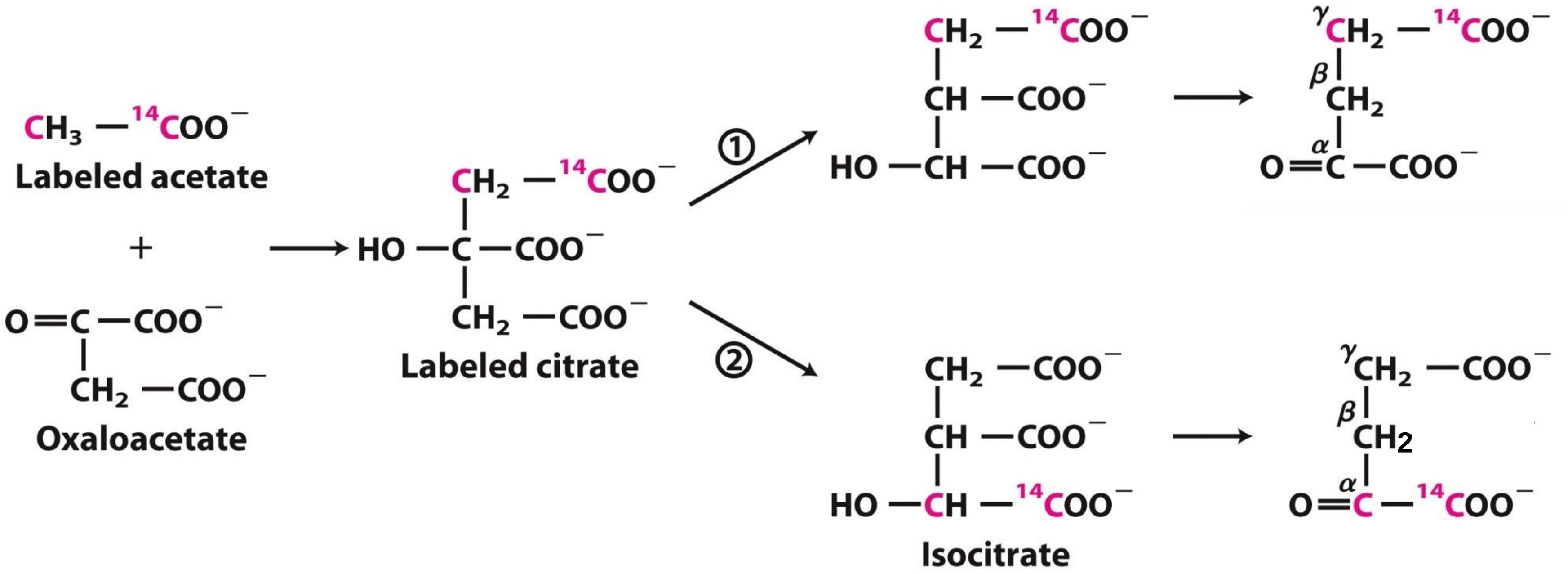
② Formation of Isocitrate via cis-Aconitate



$\Delta G'^\circ = 13.3$ kJ/mol

② Formation of Isocitrate via cis-Aconitate



Box 16-3 figure 1
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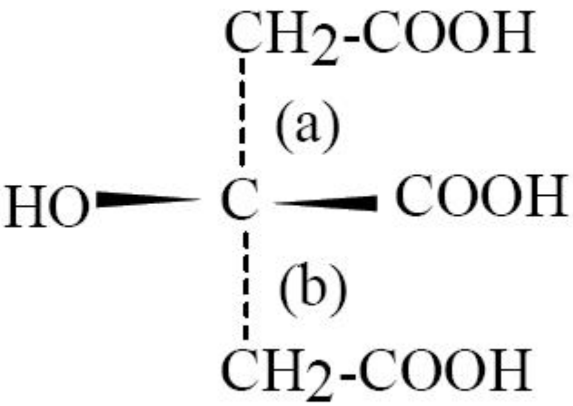
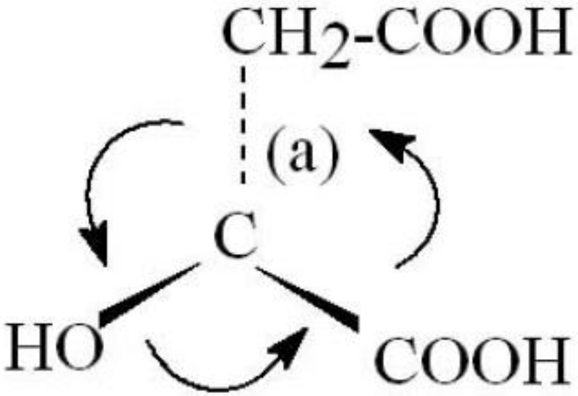
Citrate: A Symmetric Molecule That Reacts Asymmetrically

② Formation of Isocitrate via cis-Aconitate



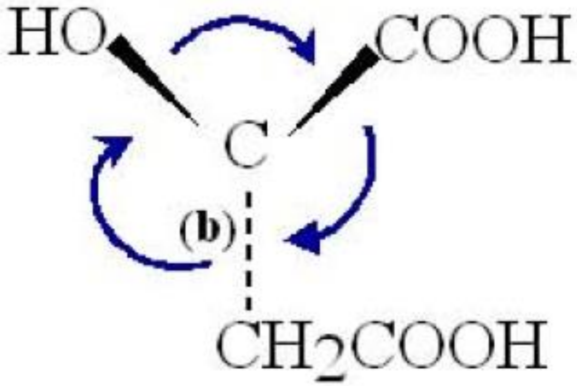
柠檬酸投影式



(b)键垂直并伸向平面里

pro-S

S: *sinister*



(a)键垂直并伸向平面里

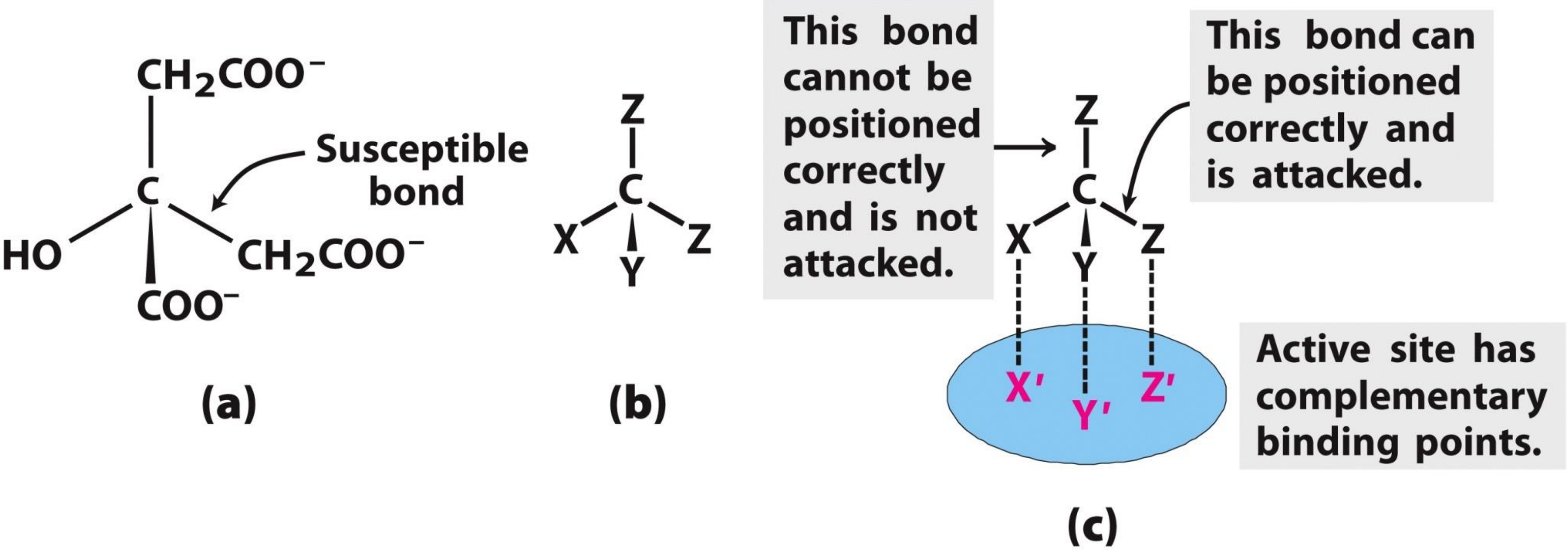
pro-R

R: *rectus*

前手性、潜手性（**pro-chiral)**

Aconitase removes the pro-*R*H of the the pro-*R* arm.

② Formation of Isocitrate via cis-Aconitate



Box 16-3 figure 2

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Aconitase removes the pro-*R*H of the the pro-*R* arm.

② Formation of Isocitrate via cis-Aconitate

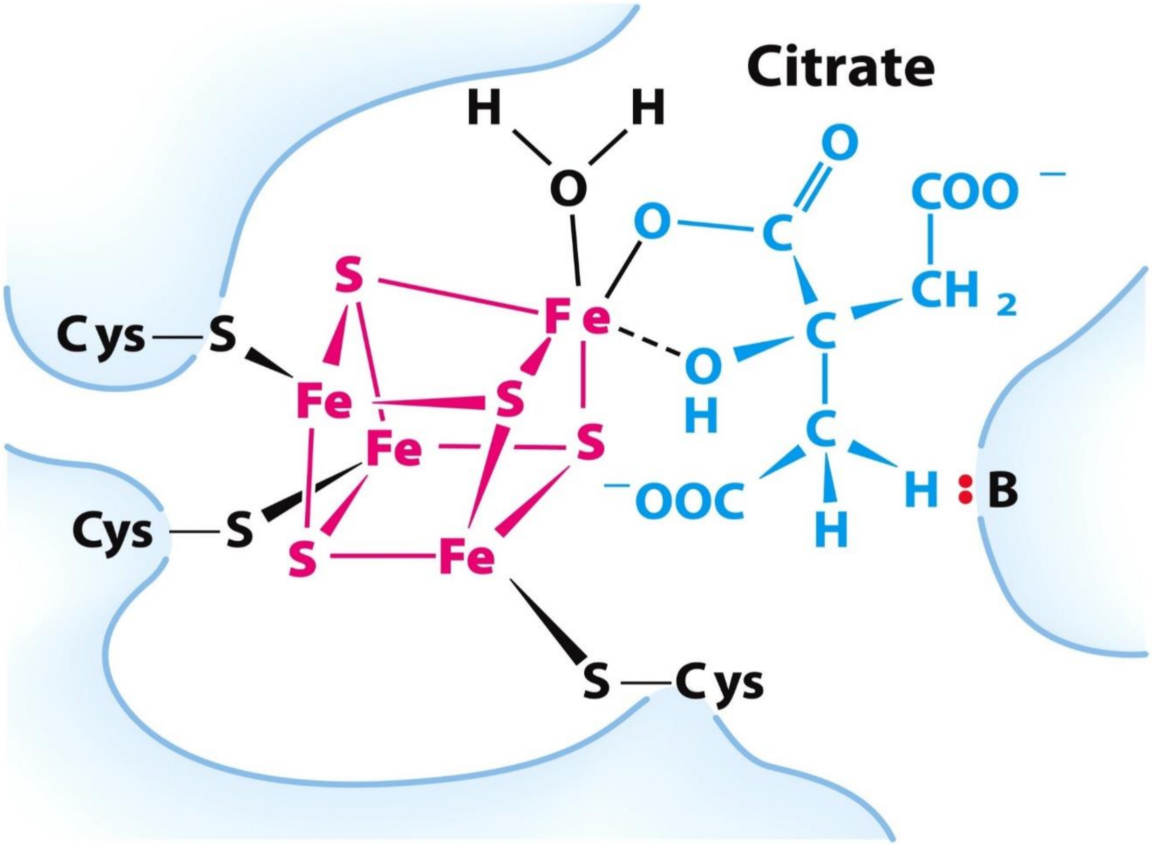
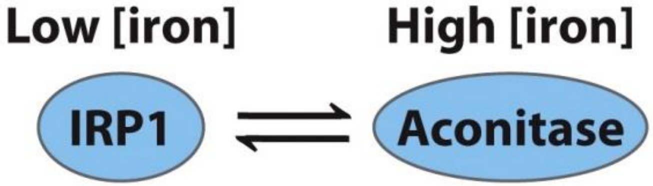


Figure 16-10

Iron-sulfur center in aconitase

Moonlighting Enzymes: Proteins with More Than One Job

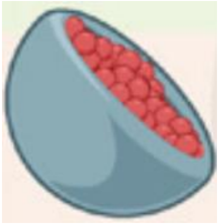


Low [iron] High [iron]

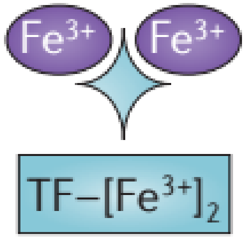
IRP1 ⇌ Aconitase

IRP: iron regulatory protein

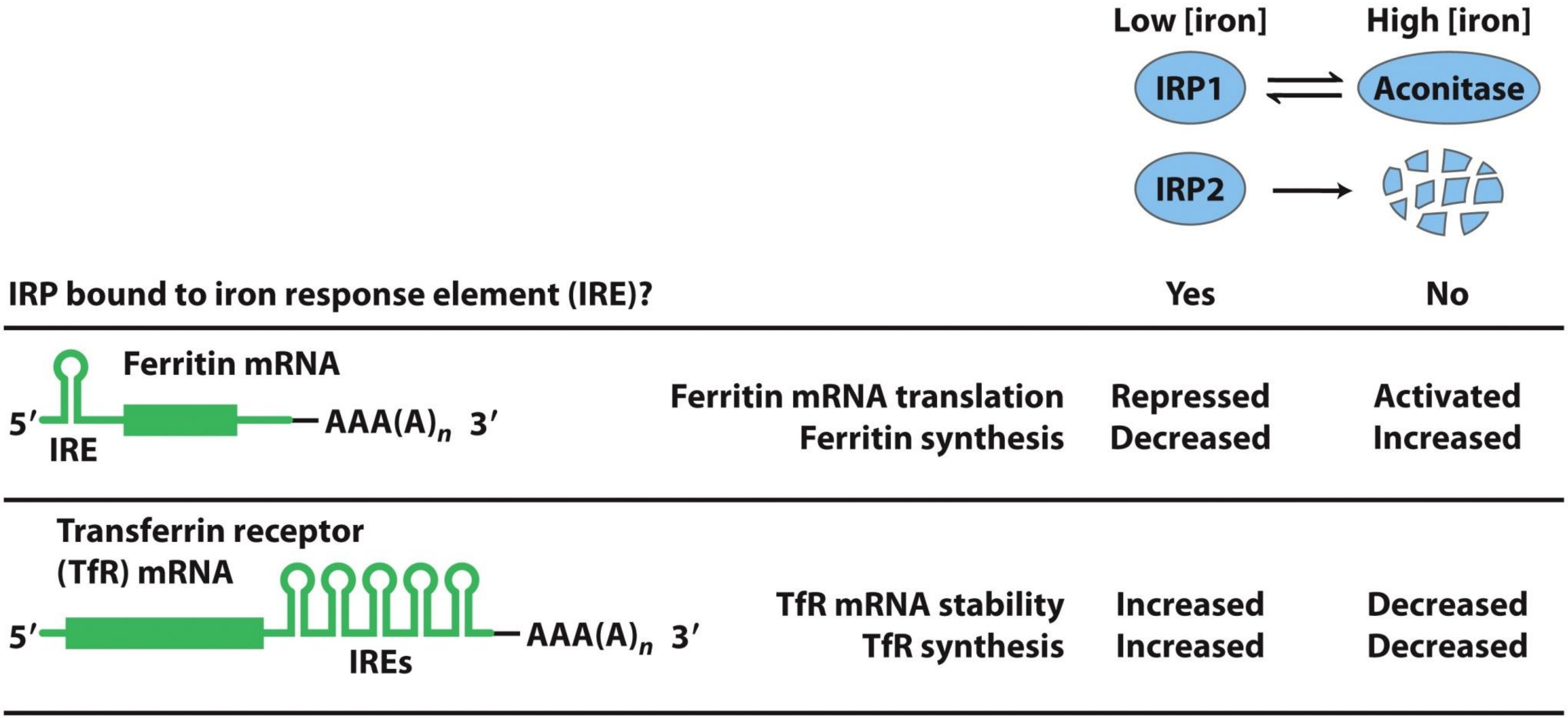
- Ferritin (铁蛋白): store iron in cells. One molecule of ferritin can bind 4500 molecules of ferric.



- Transferrin (转铁蛋白): transport ferric from digestive tract and cellular storage to bone marrow for blood cell production.



Moonlighting Enzymes: Proteins with More Than One Job



	Low [iron]	High [iron]
IRP bound to iron response element (IRE)?	Yes	No
Ferritin mRNA translation	Repressed	Activated
Ferritin synthesis	Decreased	Increased
TfR mRNA stability	Increased	Decreased
TfR synthesis	Increased	Decreased

Box 16-1 figure 1

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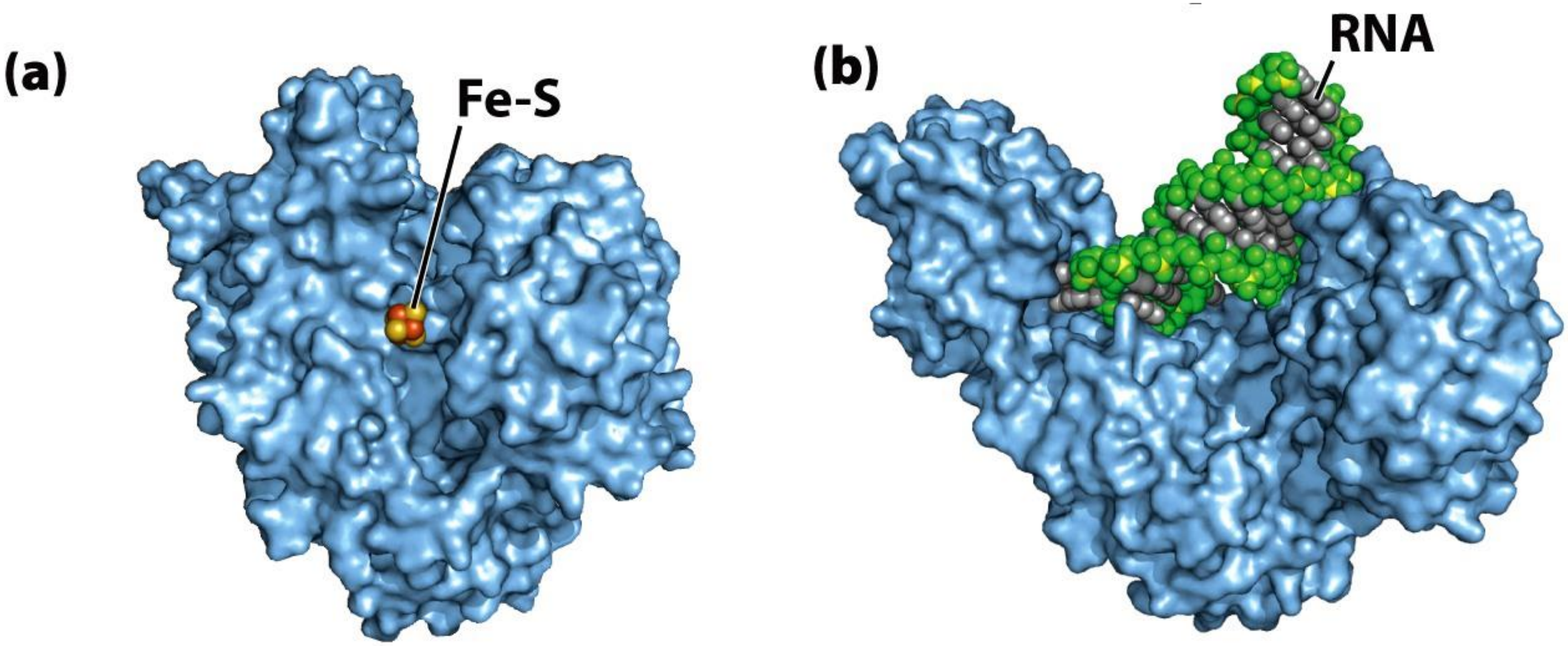
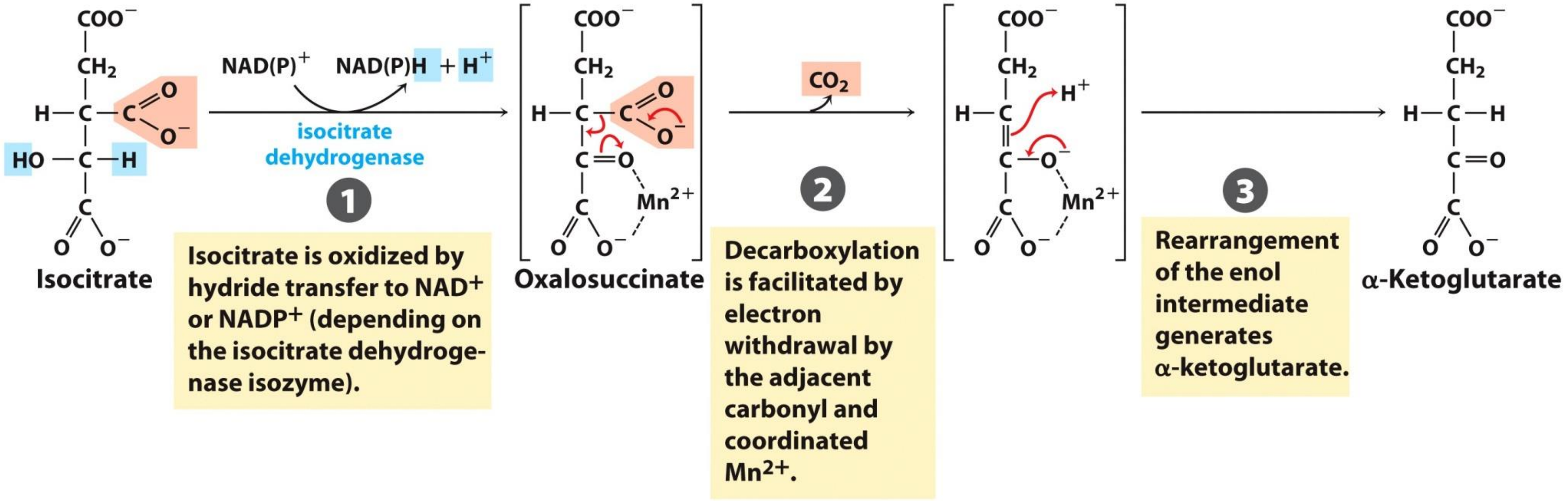
Moonlighting Enzymes: Proteins with More Than One Job



Box 16-1 figure 2
Lehninger Principles of Biochemistry, Sixth Edition

③ Oxidation of isocitrate to α-ketoglutarate and CO_2



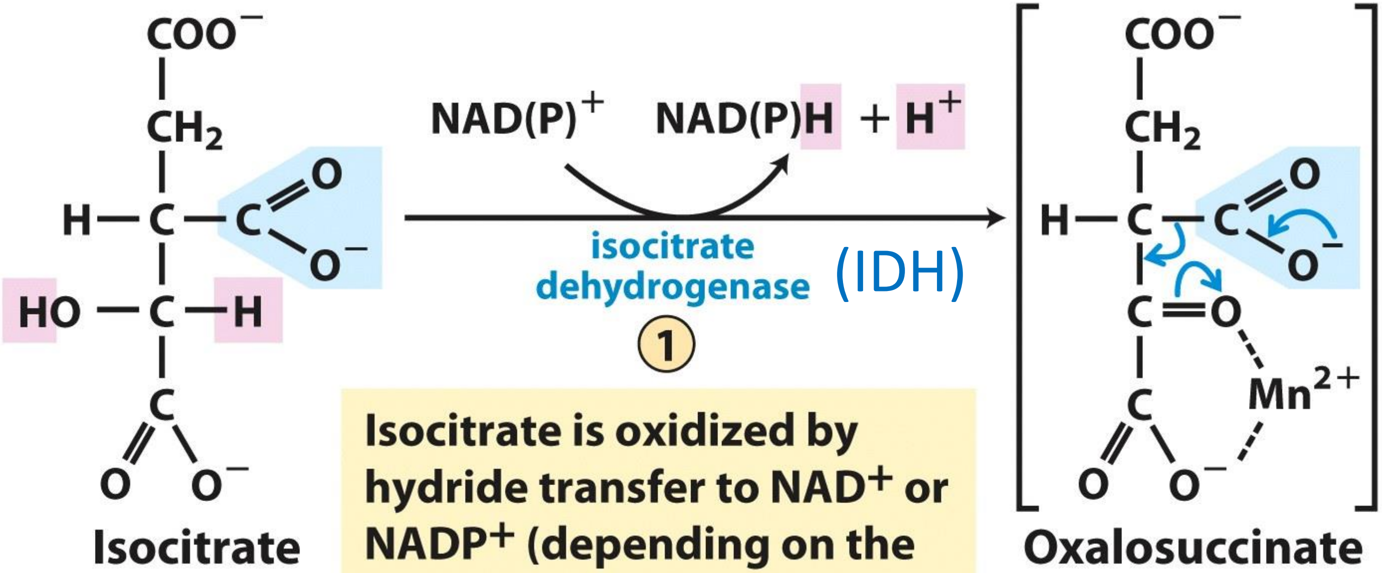
1 Isocitrate is oxidized by hydride transfer to NAD^+ or $NADP^+$ (depending on the isocitrate dehydrogenase isozyme).

2 Decarboxylation is facilitated by electron withdrawal by the adjacent carbonyl and coordinated Mn^{2+}.

3 Rearrangement of the enol intermediate generates α-ketoglutarate.

Figure 16-11

③ Oxidation of isocitrate to α-ketoglutarate and CO_2



Isocitrate is oxidized by hydride transfer to NAD^+ or $NADP^+$ (depending on the isocitrate dehydrogenase isozyme).

Figure 16-11 part 1
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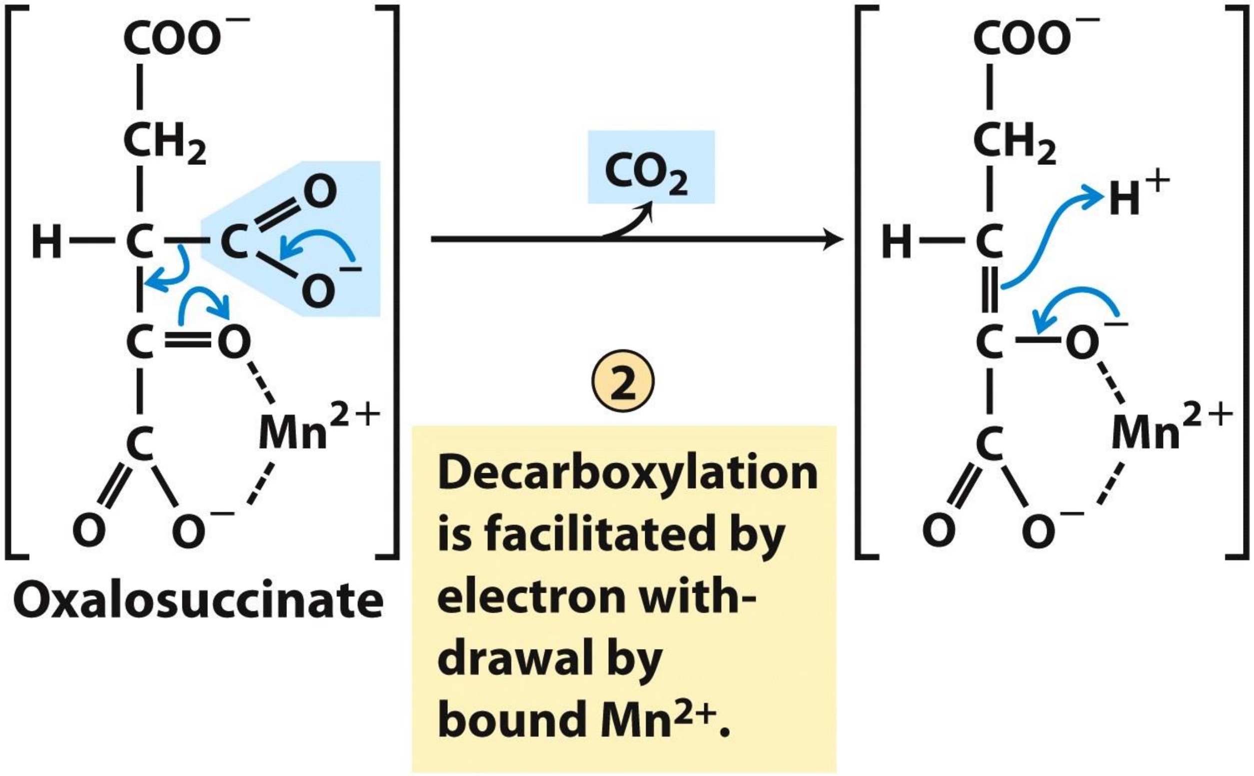
③ Oxidation of isocitrate to α-ketoglutarate and CO_2



Decarboxylation is facilitated by electron withdrawal by bound Mn^{2+}.

Figure 16-11 part 2
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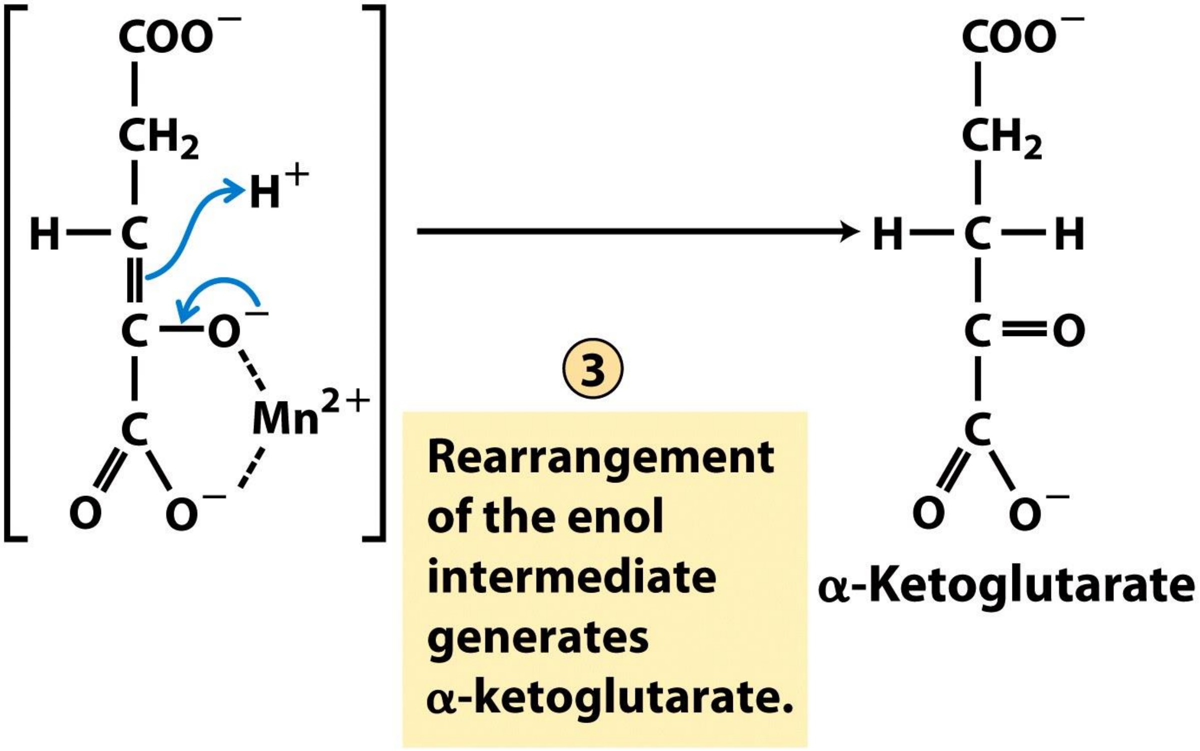
③ Oxidation of isocitrate to α-ketoglutarate and CO_2



Rearrangement of the enol intermediate generates α-ketoglutarate.

α-Ketoglutarate

Figure 16-11 part 3
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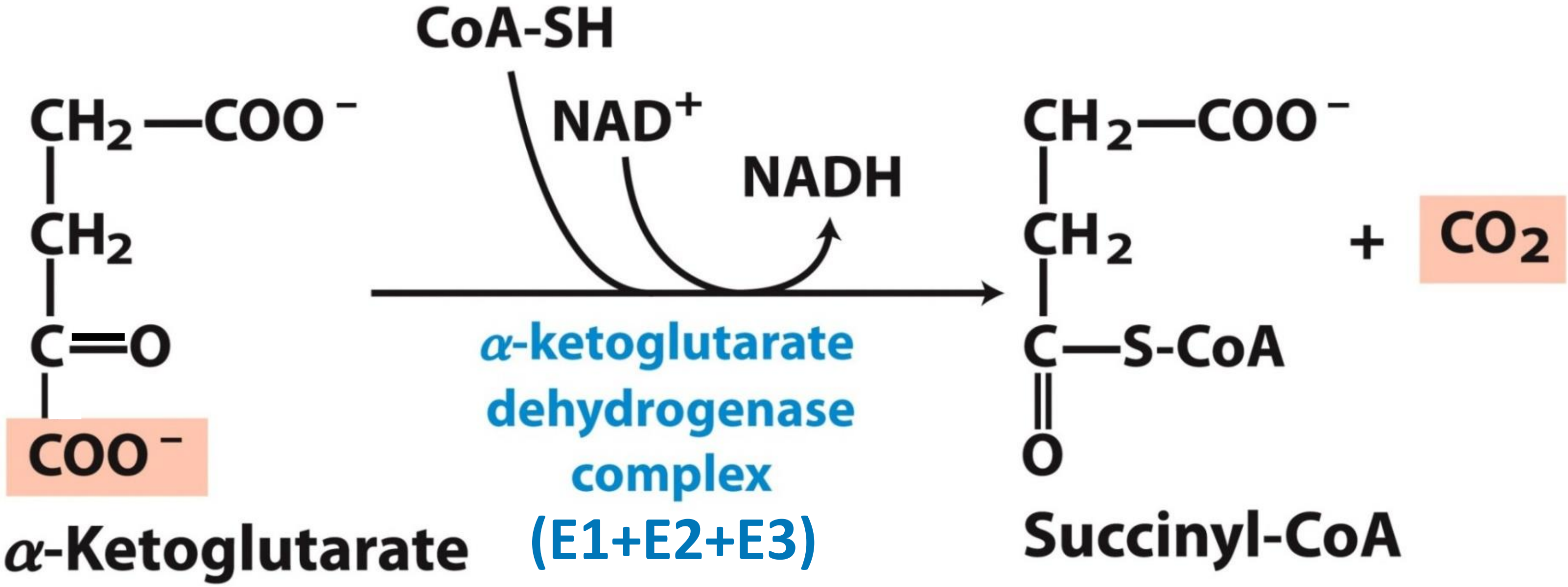
④ Oxidation of α-ketoglutarate to Succinyl-CoA and CO_2



α-ketoglutarate dehydrogenase complex

(E1+E2+E3)

$\Delta G'^\circ = -33.5\ \text{kJ/mol}$

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④ Oxidation of α-ketoglutarate to Succinyl-CoA and CO_2

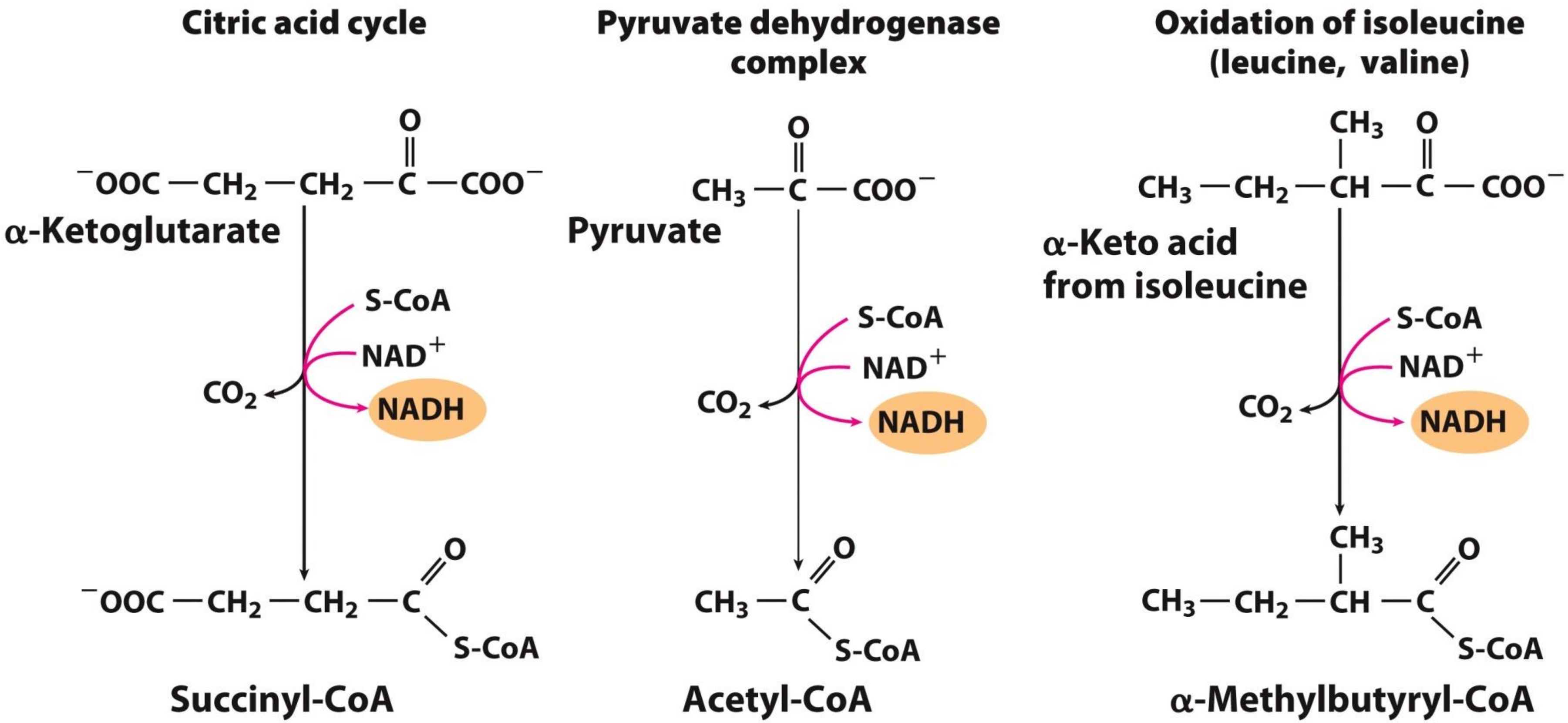

Figure 16-12
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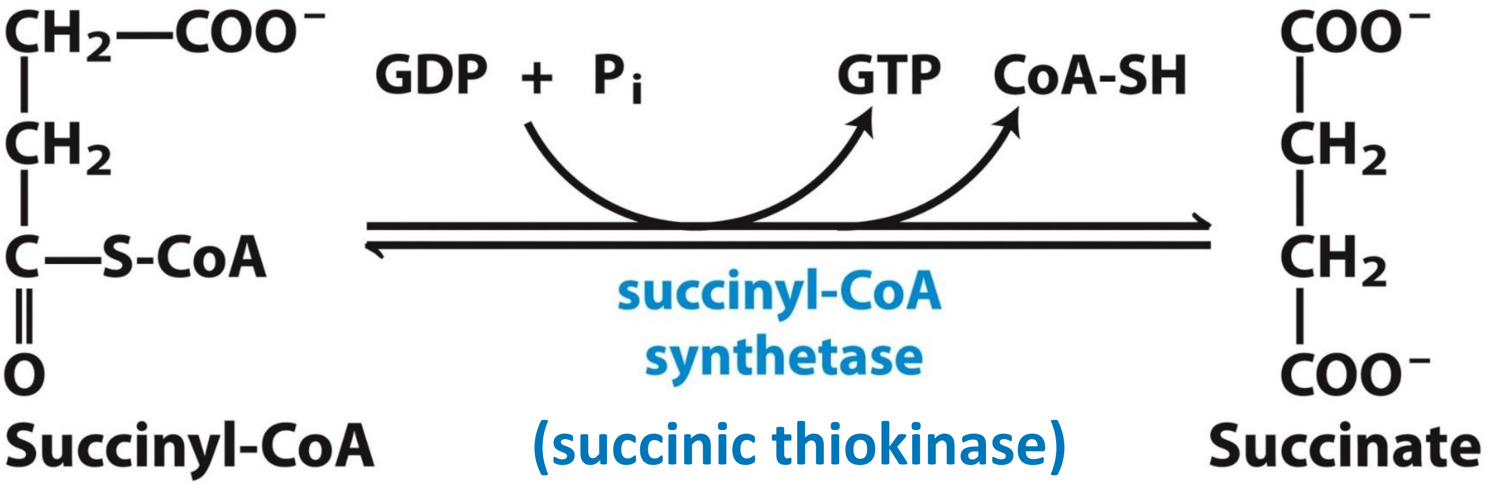
Conserved mechanism for oxidative decarboxylation

Divergent evolution

⑤ Conversion of Succinyl-CoA to Succinate



$\Delta G'^\circ = -2.9\ \text{kJ/mol}$

Unnumbered 16 p645
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$$\text{GTP + ADP} \xrightleftharpoons{\text{nucleoside diphosphokinase}} \text{GDP + ATP}$$

⑤ Conversion of Succinyl-CoA to Succinate

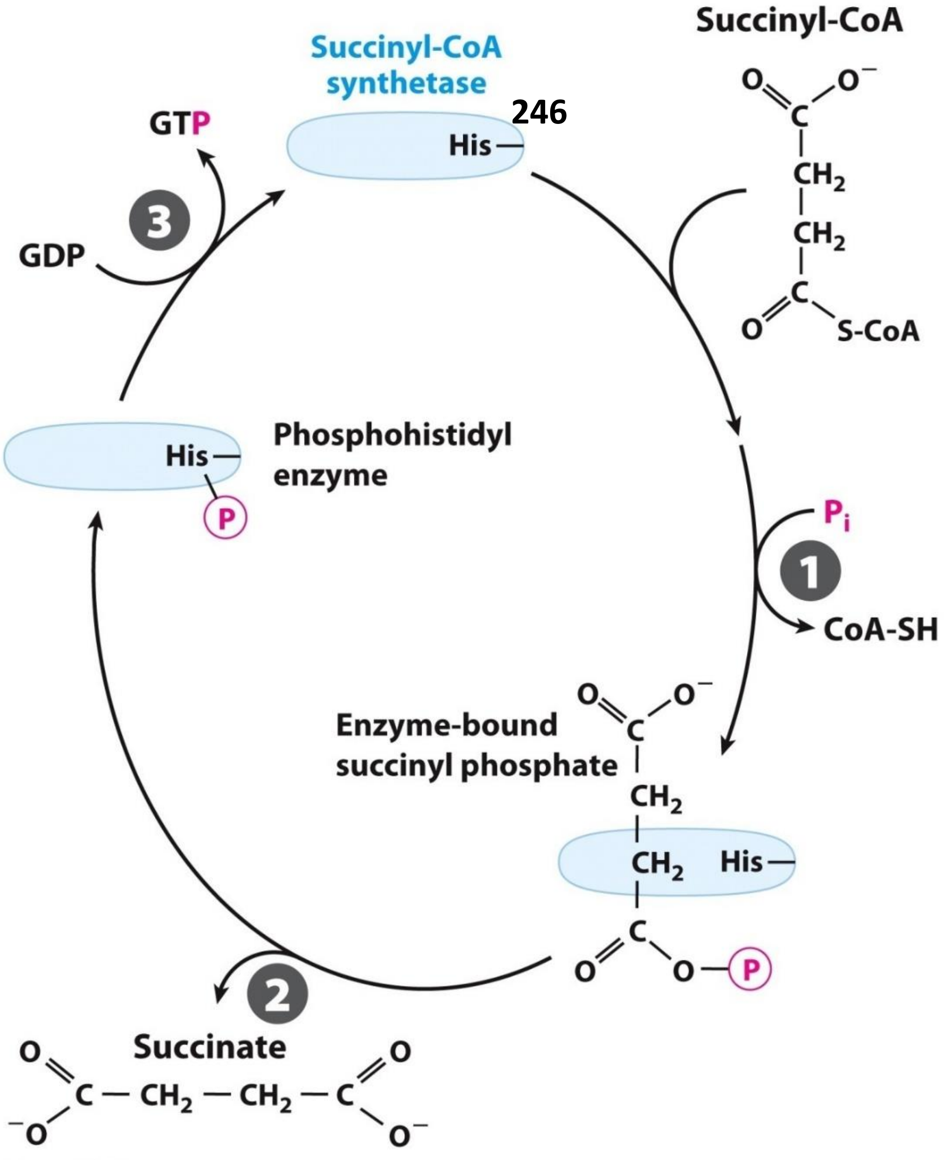

Figure 16-13a

The succinyl-CoA synthetase reaction

⑤ Conversion of Succinyl-CoA to Succinate

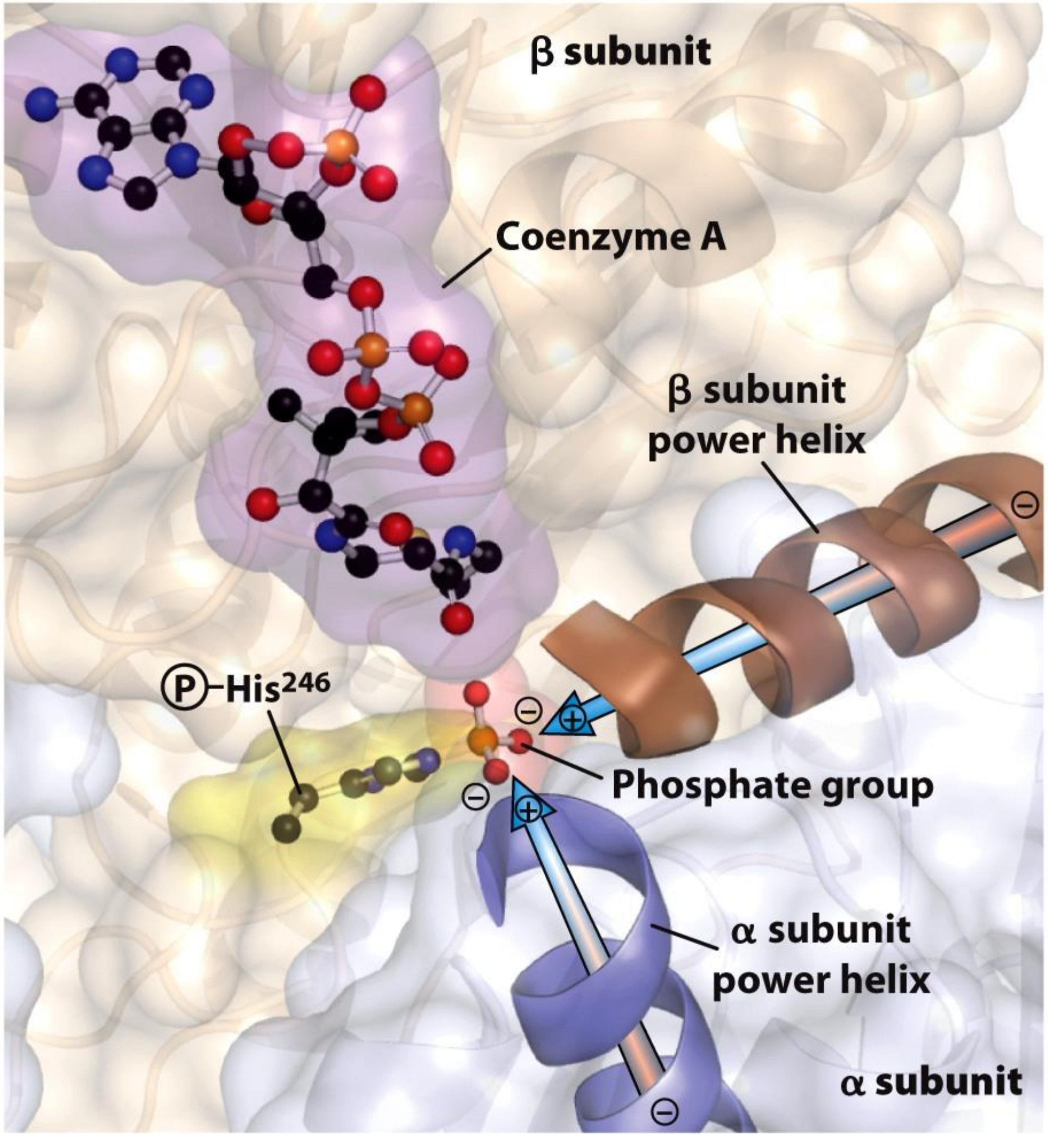

Figure 16-13b
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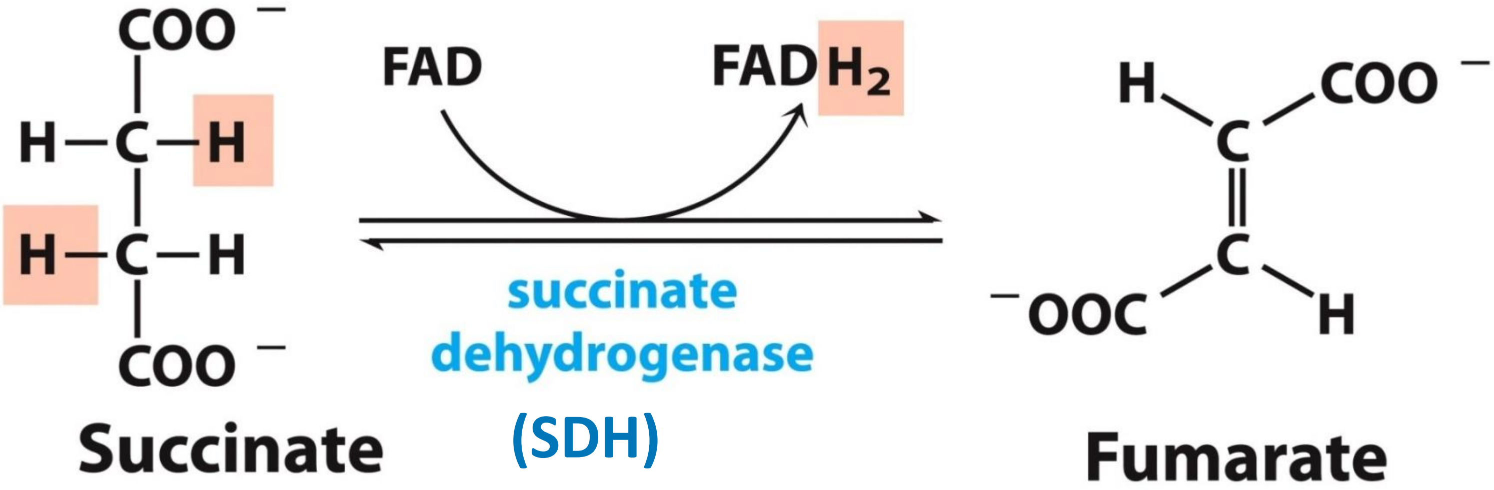
Names of enzymes

- **Synthase：**
- catalyze condensation reactions in which no nucleoside triphosphate (ATP,GTP, and so forth) is required as an energy source.
- **Synthetase：**
- catalyze condensation reactions that do use ATP or another nucleoside triphosphate as a source of energy for the synthetic reaction.
- **Ligase：**
- catalyze condensation reactions in which two atoms are joined, using ATP or another energy source.
- **Lyase:**
- catalyze cleavages (or, in the reverse direction, additions) in which electronic rearrangements occur.
- **Kinase** *v.s.* **phosphatase** *v.s.* **phosphorylase**

⑥ Conversion of Succinate to Fumarate



$\Delta G'^{\circ} = 0\ \text{kJ/mol}$

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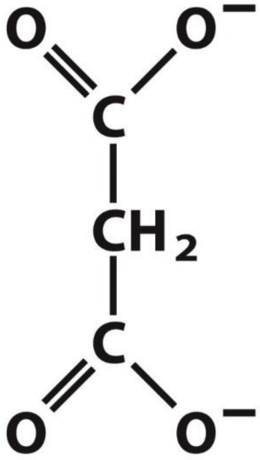
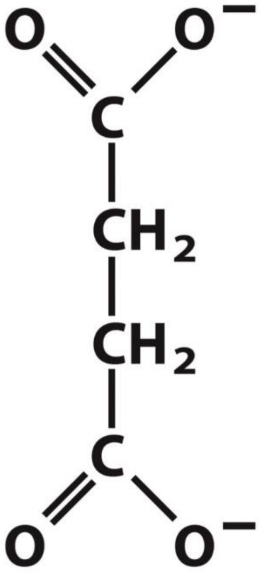
This enzyme is tightly bound to the mitochondrial inner membrane

⑥ Conversion of Succinate to Fumarate



Malonate



Succinate

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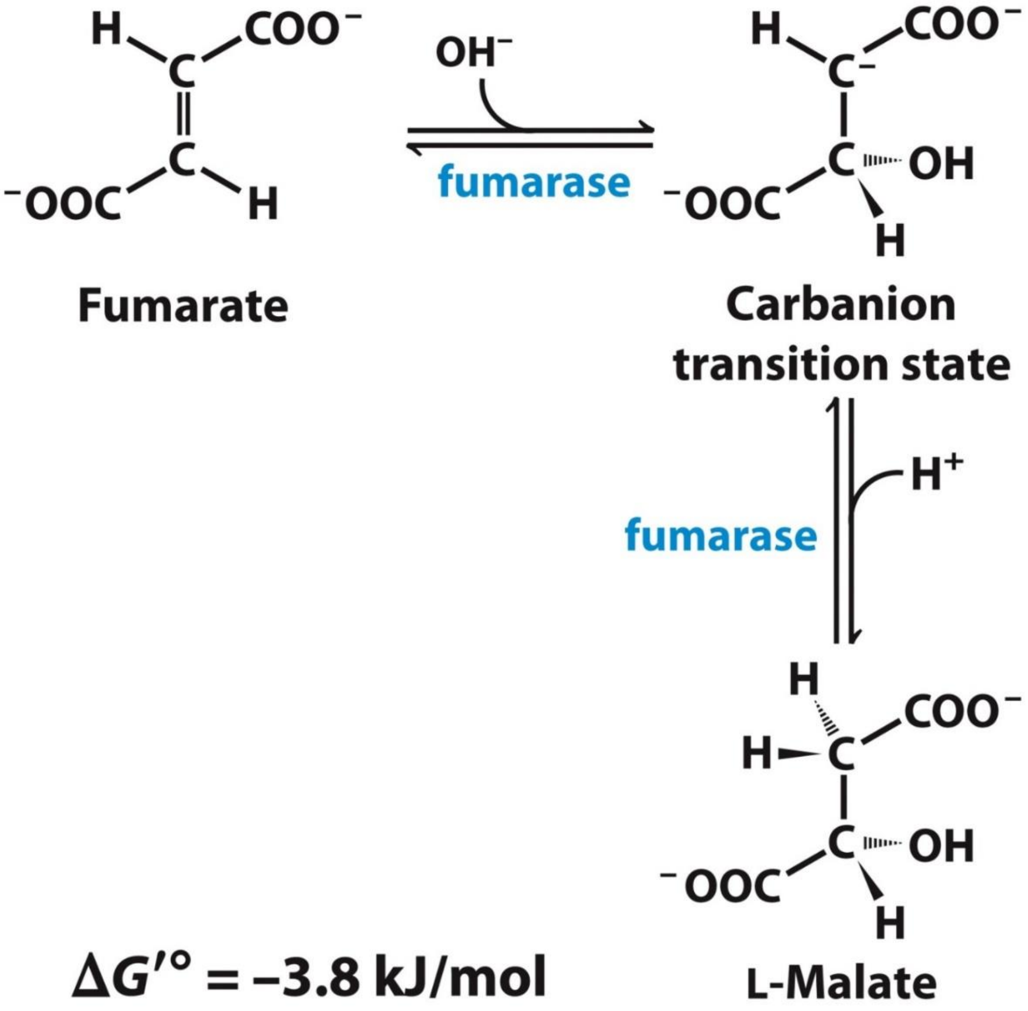
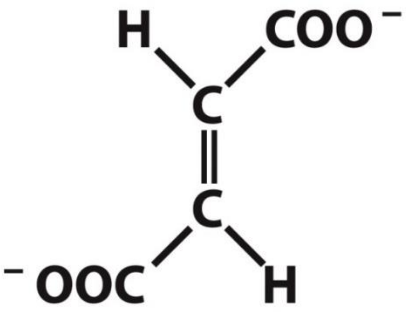
Malonate is a competitive inhibitor of succinate dehydrogenase

⑦ Hydration of Fumarate to Malate

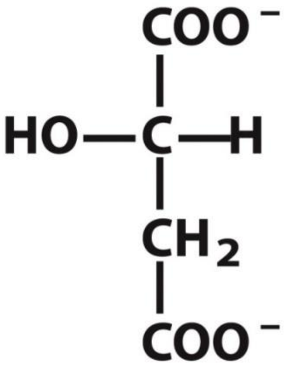


$\Delta G'^{\circ} = -3.8\ \text{kJ/mol}$

⑦ Hydration of Fumarate to Malate

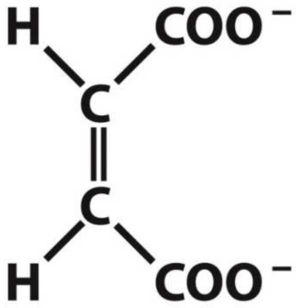


Fumarate

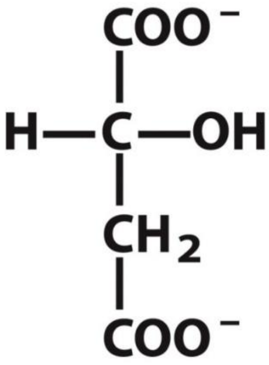


L-Malate

Yes



Maleate

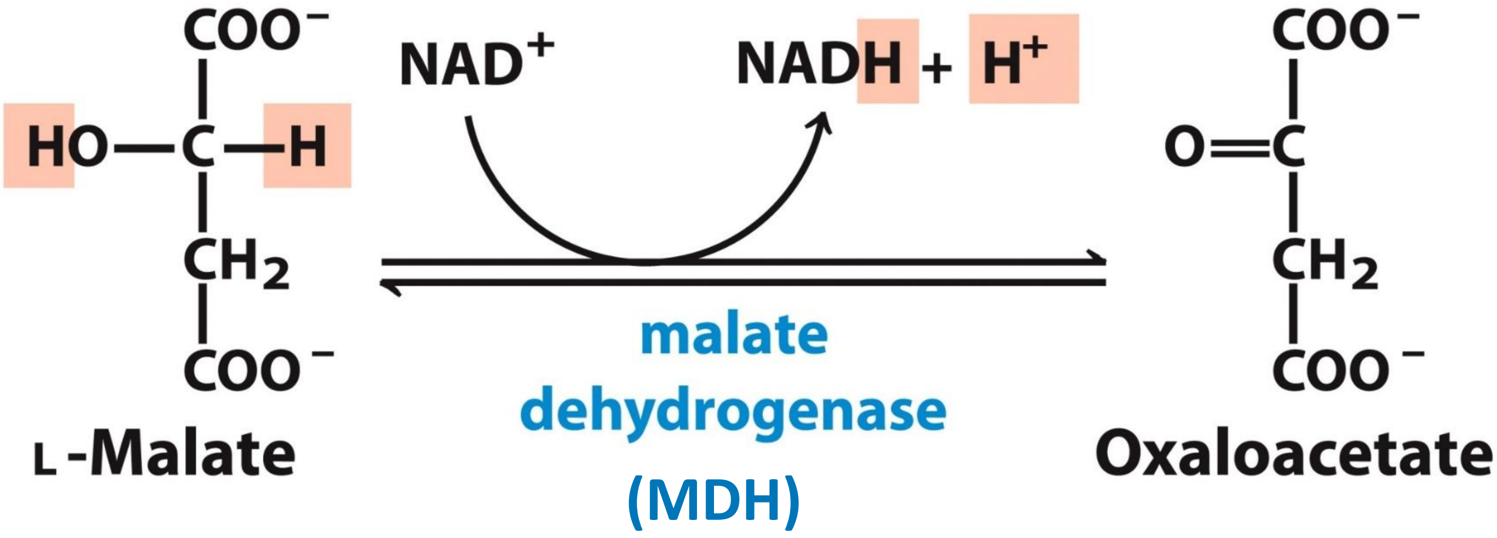


D-Malate

No

Fumarase is stereospecific

⑧ Oxidation of Malate to Oxaloacetate



$\Delta G'^\circ = 29.7\ \text{kJ/mol}$

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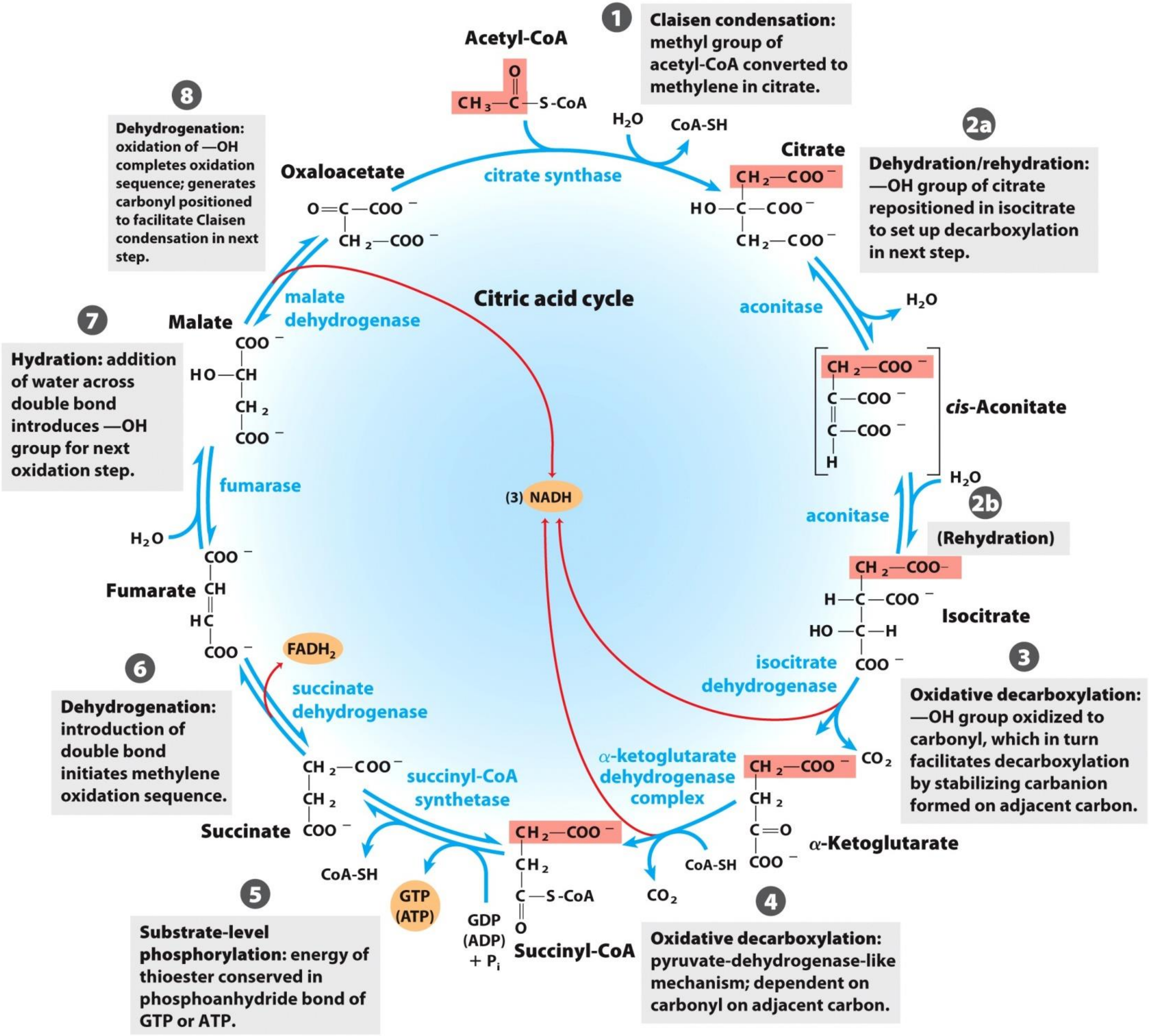


1 **Claisen condensation:** methyl group of acetyl-CoA converted to methylene in citrate.

2a **Dehydration/rehydration:** —OH group of citrate repositioned in isocitrate to set up decarboxylation in next step.

2b (Rehydration)

3 **Oxidative decarboxylation:** —OH group oxidized to carbonyl, which in turn facilitates decarboxylation by stabilizing carbanion formed on adjacent carbon.

4 **Oxidative decarboxylation:** pyruvate-dehydrogenase-like mechanism; dependent on carbonyl on adjacent carbon.

5 **Substrate-level phosphorylation:** energy of thioester conserved in phosphoanhydride bond of GTP or ATP.

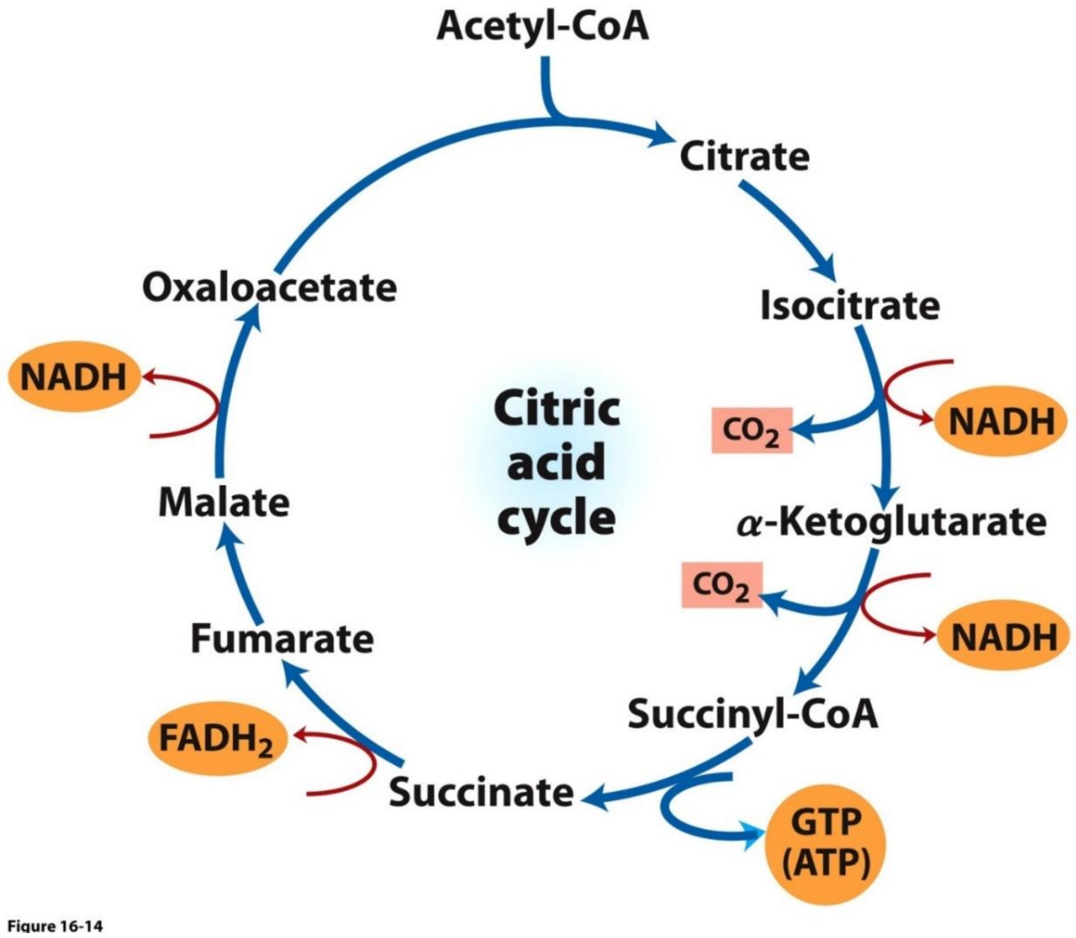
6 **Dehydrogenation:** introduction of double bond initiates methylene oxidation sequence.

7 **Hydration:** addition of water across double bond introduces —OH group for next oxidation step.

8 **Dehydrogenation:** oxidation of —OH completes oxidation sequence; generates carbonyl positioned to facilitate Claisen condensation in next step.

Figure 16-7

The energy of oxidations in the cycle is conserved



NADH→2.5ATP

$FADH_2$→1.5ATP

$$\text{Acetyl CoA} + 3\,\text{NAD}^+ + \text{FAD} + \text{ADP} + \text{P}_i + 2\,\text{H}_2\text{O} \longrightarrow 2\,\text{CO}_2 + 3\,\text{NADH} + \text{FADH}_2 + \text{ATP} + 2\,\text{H}^+ + \text{CoA}$$

• Fully oxidation of glucose generates 32 ATP

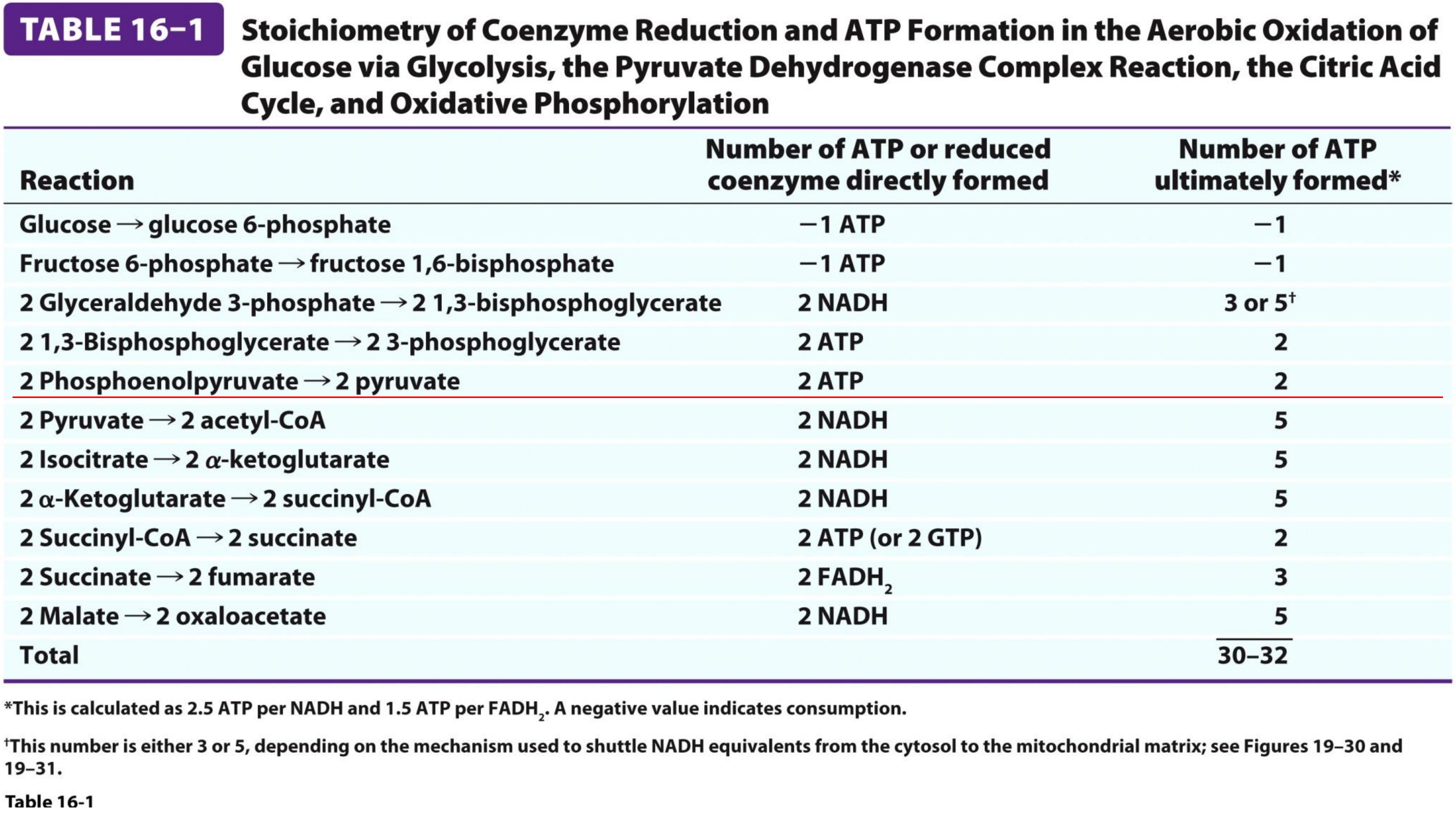


TABLE 16–1 **Stoichiometry of Coenzyme Reduction and ATP Formation in the Aerobic Oxidation of Glucose via Glycolysis, the Pyruvate Dehydrogenase Complex Reaction, the Citric Acid Cycle, and Oxidative Phosphorylation**

Reaction	Number of ATP or reduced coenzyme directly formed	Number of ATP ultimately formed*
Glucose → glucose 6-phosphate	−1 ATP	−1
Fructose 6-phosphate → fructose 1,6-bisphosphate	−1 ATP	−1
2 Glyceraldehyde 3-phosphate → 2 1,3-bisphosphoglycerate	2 NADH	3 or 5†
2 1,3-Bisphosphoglycerate → 2 3-phosphoglycerate	2 ATP	2
2 Phosphoenolpyruvate → 2 pyruvate	2 ATP	2
2 Pyruvate → 2 acetyl-CoA	2 NADH	5
2 Isocitrate → 2 α-ketoglutarate	2 NADH	5
2 α-Ketoglutarate → 2 succinyl-CoA	2 NADH	5
2 Succinyl-CoA → 2 succinate	2 ATP (or 2 GTP)	2
2 Succinate → 2 fumarate	2 $FADH_2$	3
2 Malate → 2 oxaloacetate	2 NADH	5
Total		30–32

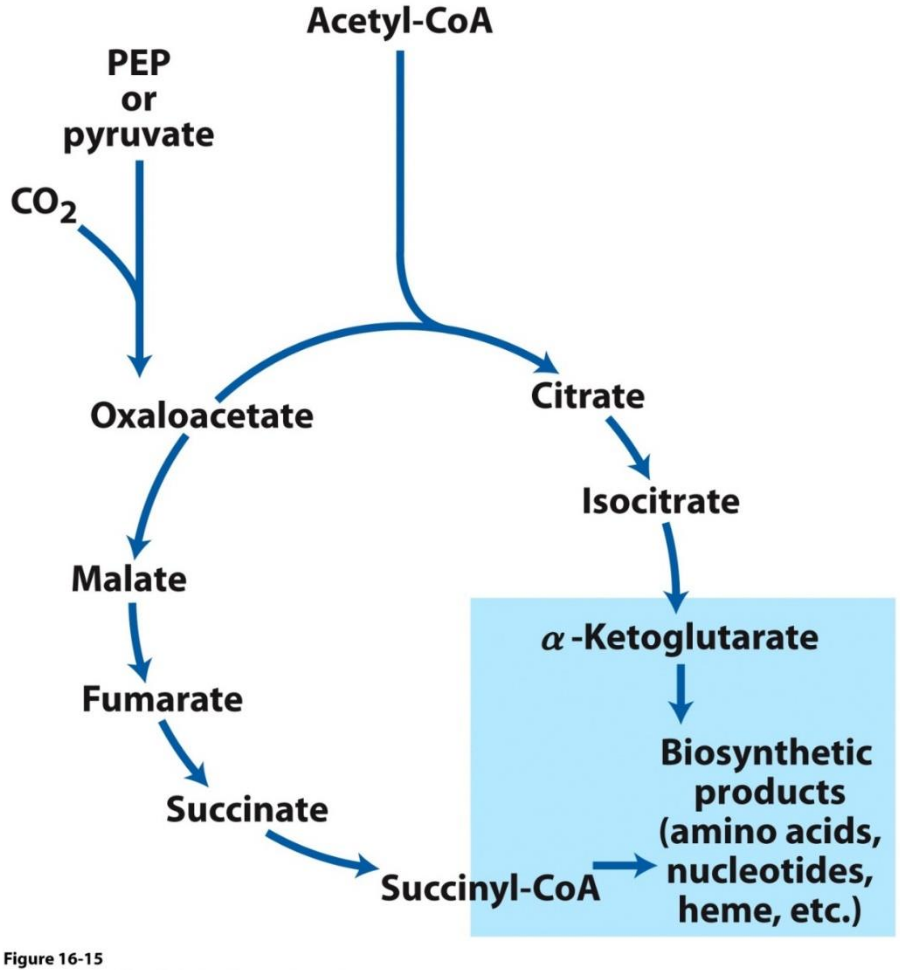
*This is calculated as 2.5 ATP per NADH and 1.5 ATP per $FADH_2$. A negative value indicates consumption.

†This number is either 3 or 5, depending on the mechanism used to shuttle NADH equivalents from the cytosol to the mitochondrial matrix; see Figures 19–30 and 19–31.

Table 16-1

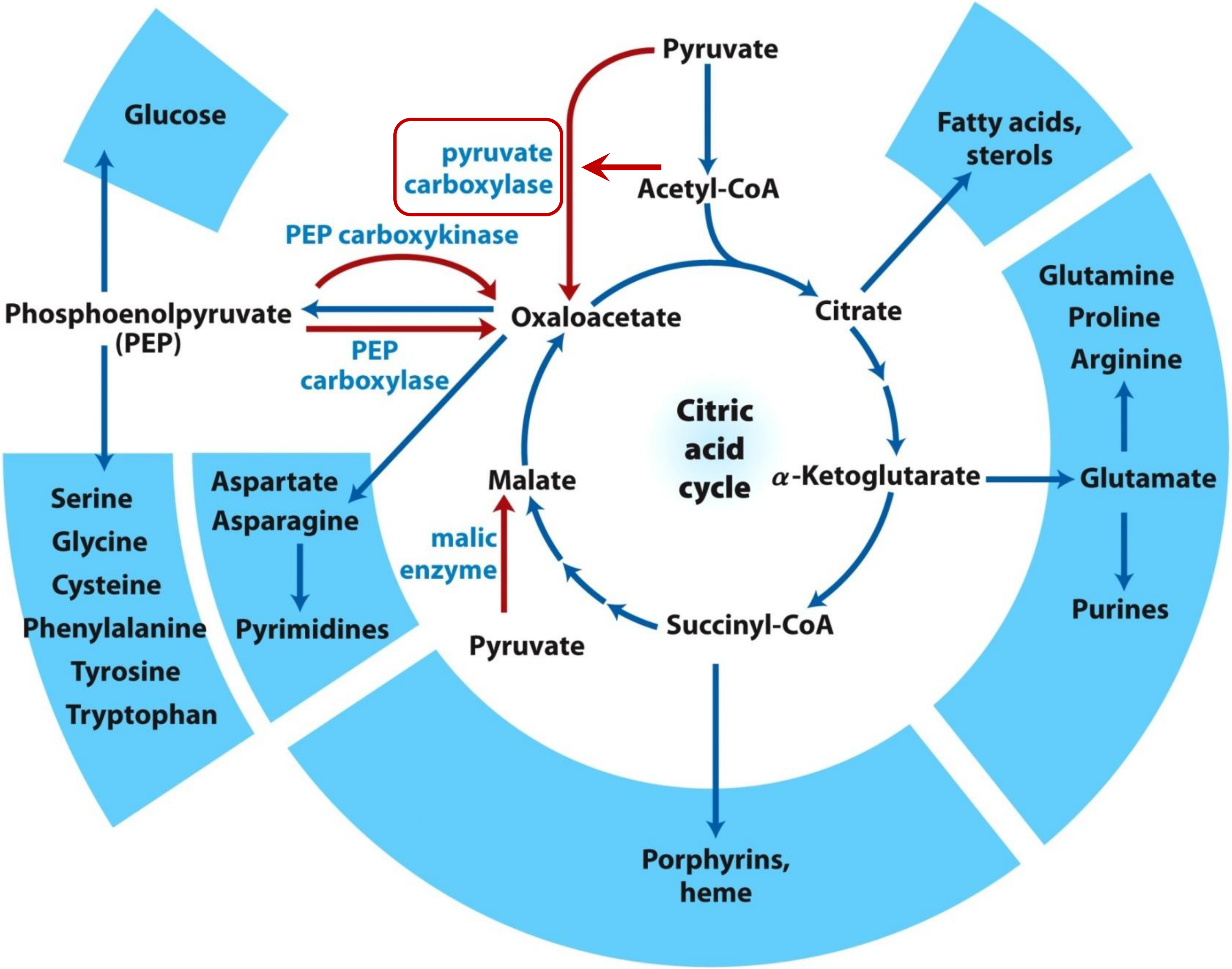
The efficiency of energy conservation for glucose degraded through glycolysis, TCA cycle and oxidative phosphorylation is close to 65%.

• The citric acid cycle is an amphibolic pathway



Biosynthetic precursors produced by an incomplete citric acid cycle in anaerobic bacteria

- **Anaplerotic reations**



• Anaplerotic reations

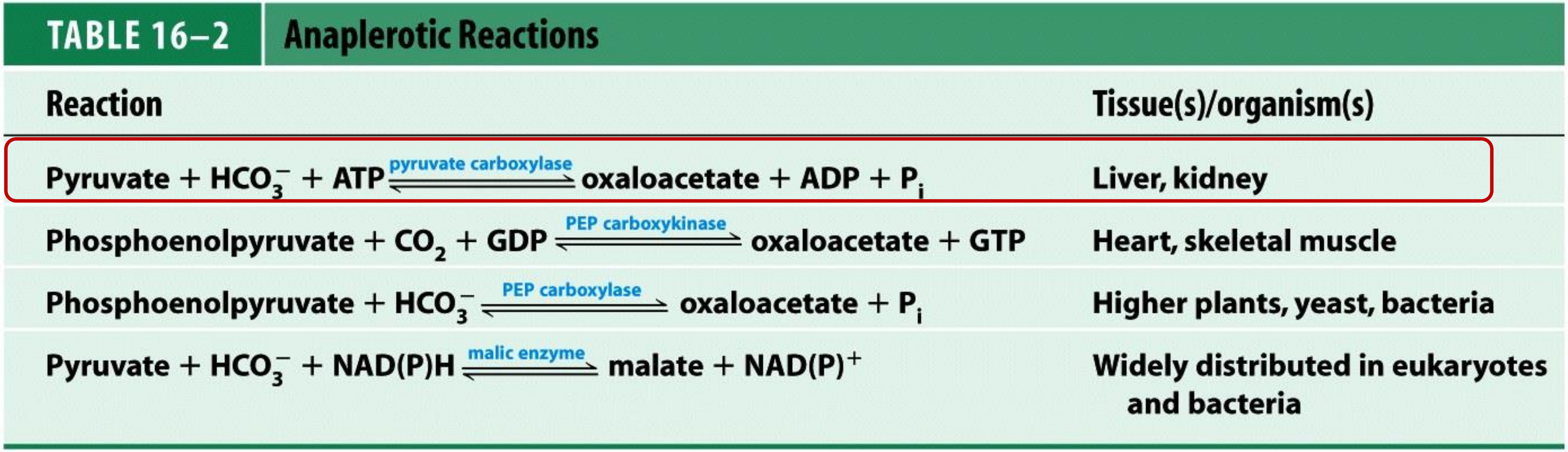


TABLE 16–2 **Anaplerotic Reactions**

Reaction	Tissue(s)/organism(s)
Pyruvate + HCO_3^- + ATP $\xrightleftharpoons{\text{pyruvate carboxylase}}$ oxaloacetate + ADP + P_i	Liver, kidney
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 bacteria

Table 16-2

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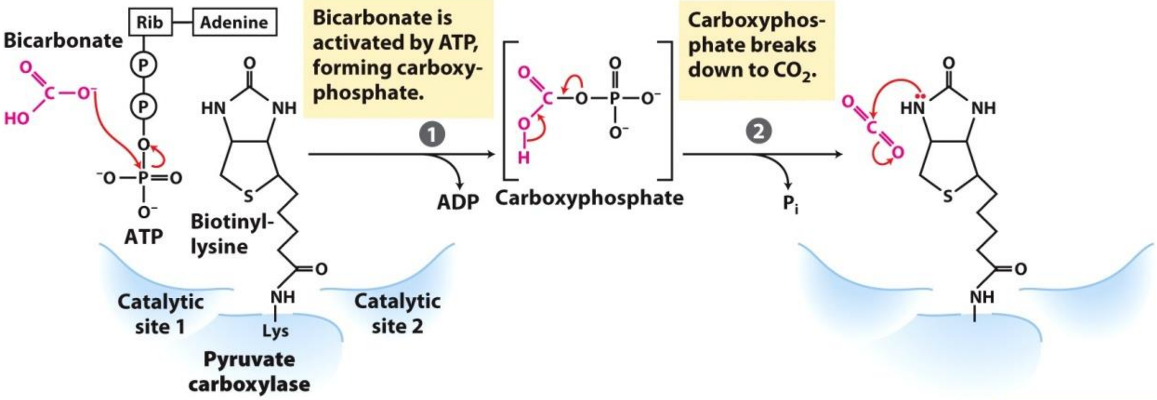
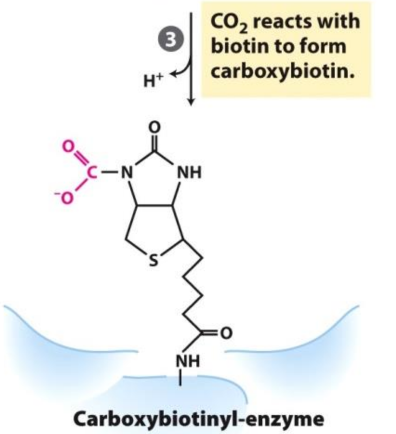
- **Pyruvate carboxylase (PC)**

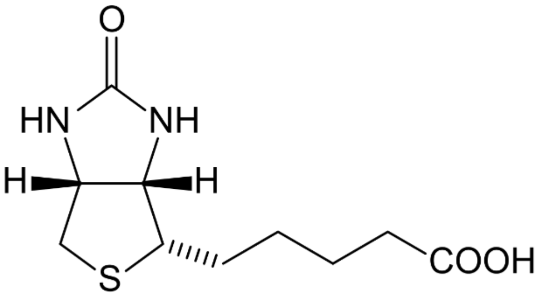


Bicarbonate is activated by ATP, forming carboxyphosphate.

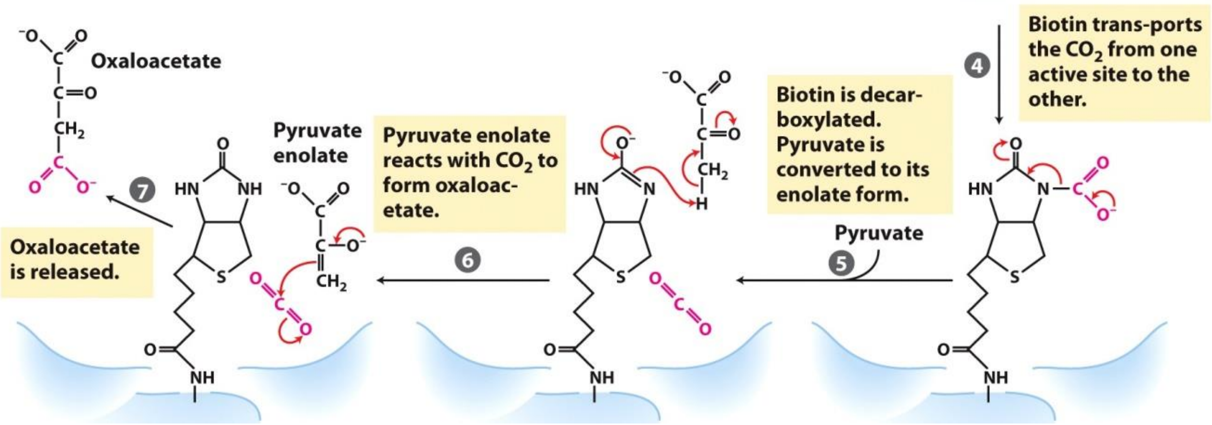
Carboxyphosphate breaks down to CO_2.



CO_2 reacts with biotin to form carboxybiotin.



biotin



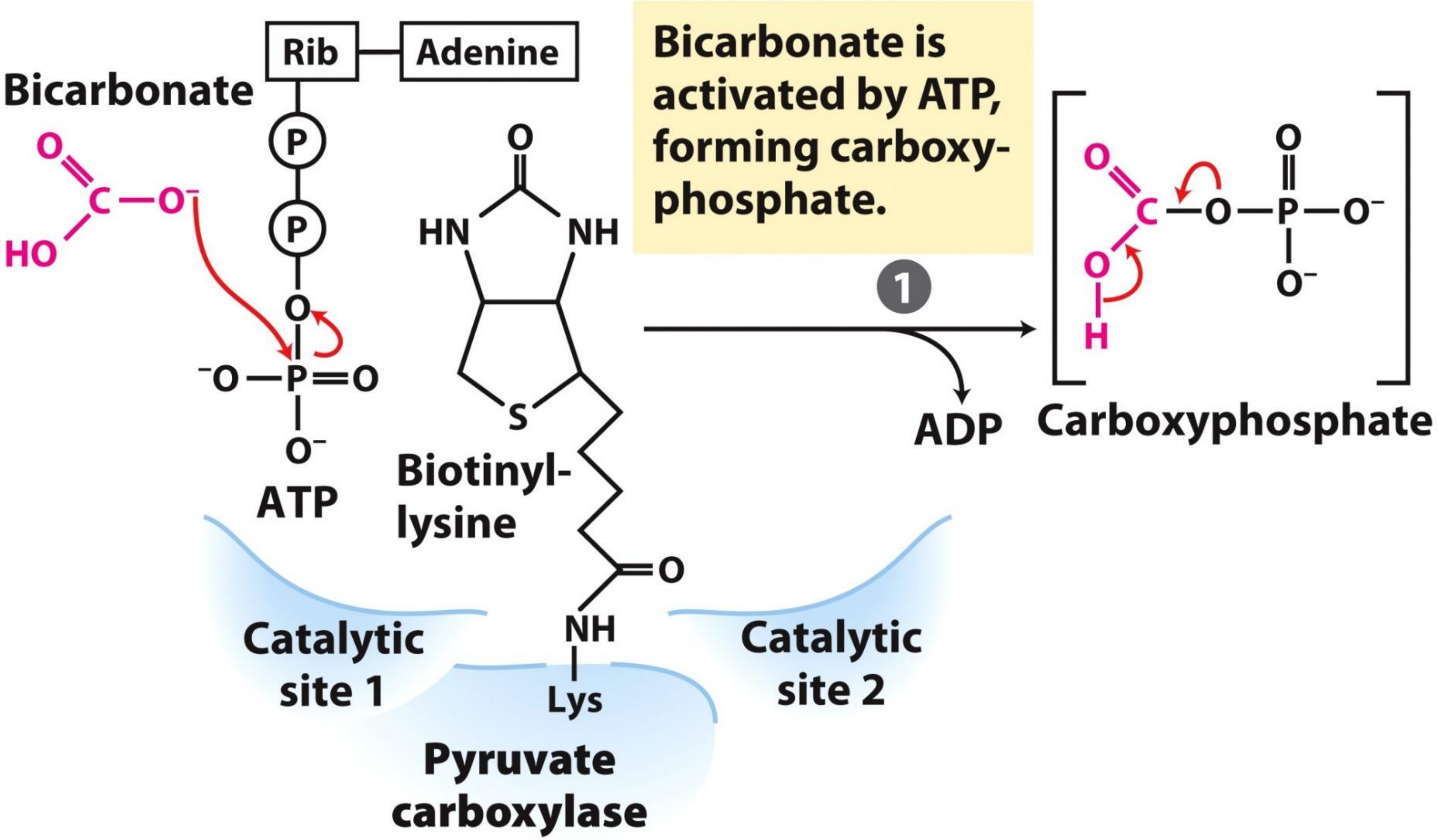
Biotin trans-ports the CO_2 from one active site to the other.

Biotin is decarboxylated. Pyruvate is converted to its enolate form.

Pyruvate enolate reacts with CO_2 to form oxaloacetate.

Oxaloacetate is released.

• Pyruvate carboxylase (PC)



Bicarbonate is activated by ATP, forming carboxyphosphate.

Figure 16-17 part 1
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Pyruvate carboxylase (PC)

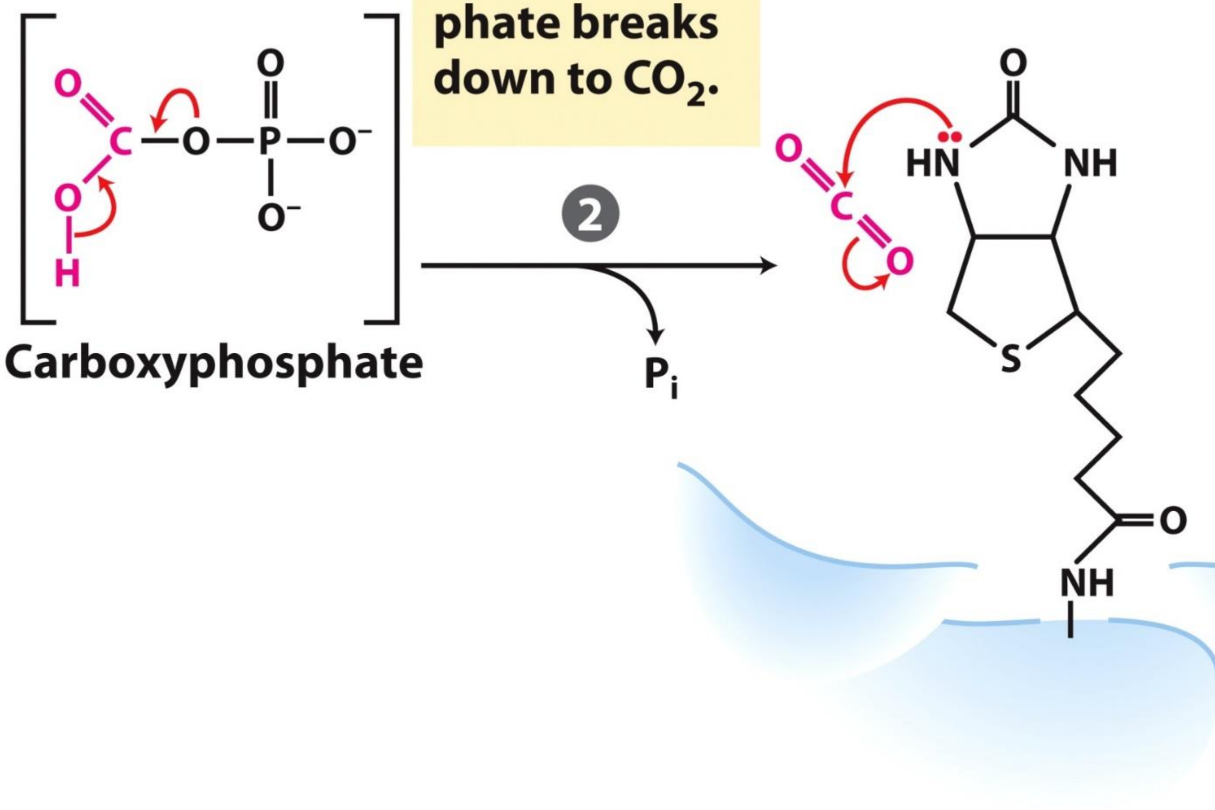

Figure 16-17 part 2
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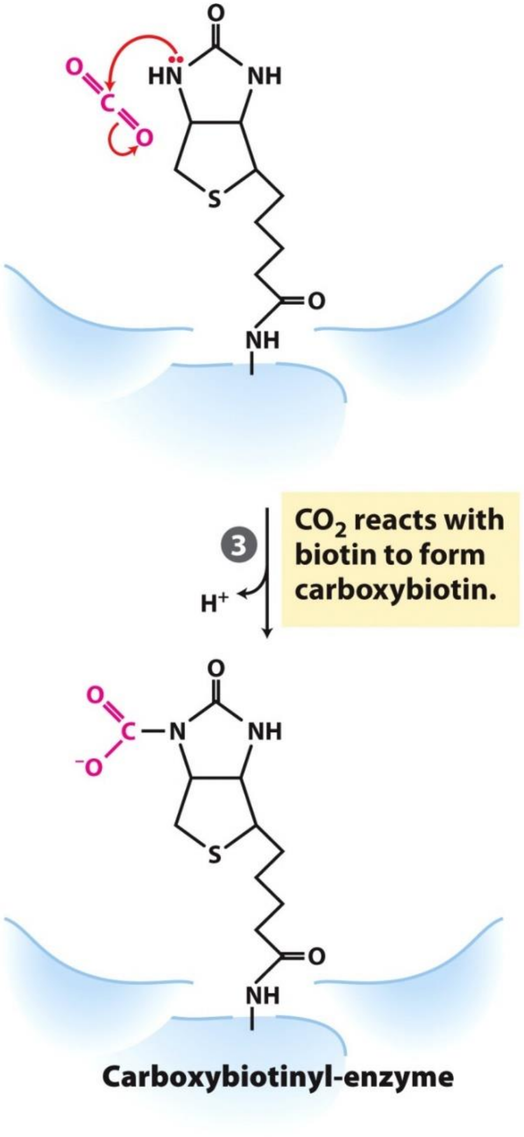
• Pyruvate carboxylase (PC)



CO_2 reacts with biotin to form carboxybiotin.

Figure 16-17 part 3
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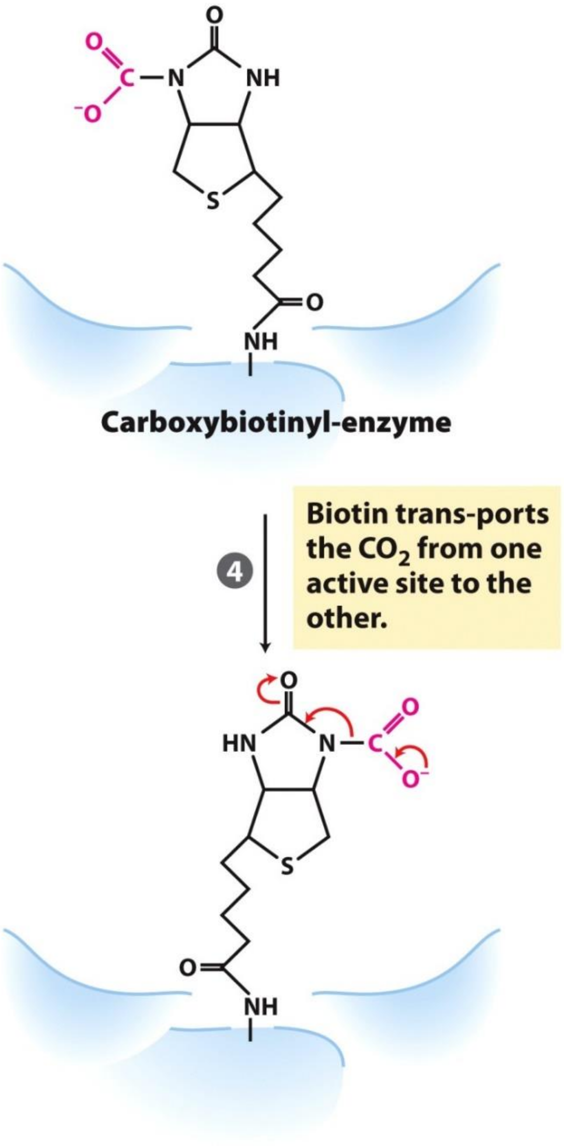
• Pyruvate carboxylase (PC)



Biotin trans-ports the CO_2 from one active site to the other.

Figure 16-17 part 4
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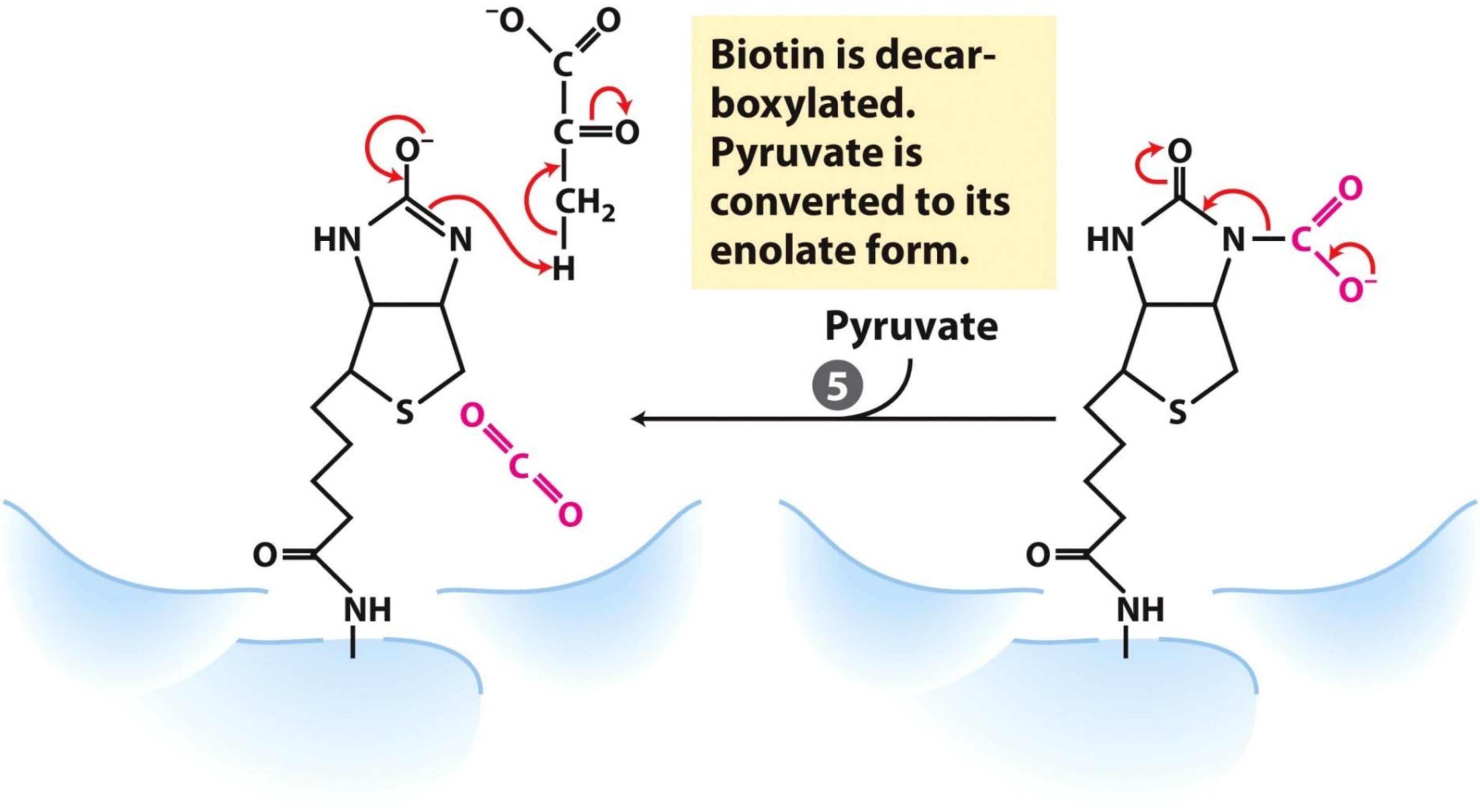
• Pyruvate carboxylase (PC)



Biotin is decarboxylated. Pyruvate is converted to its enolate form.

Figure 16-17 part 5
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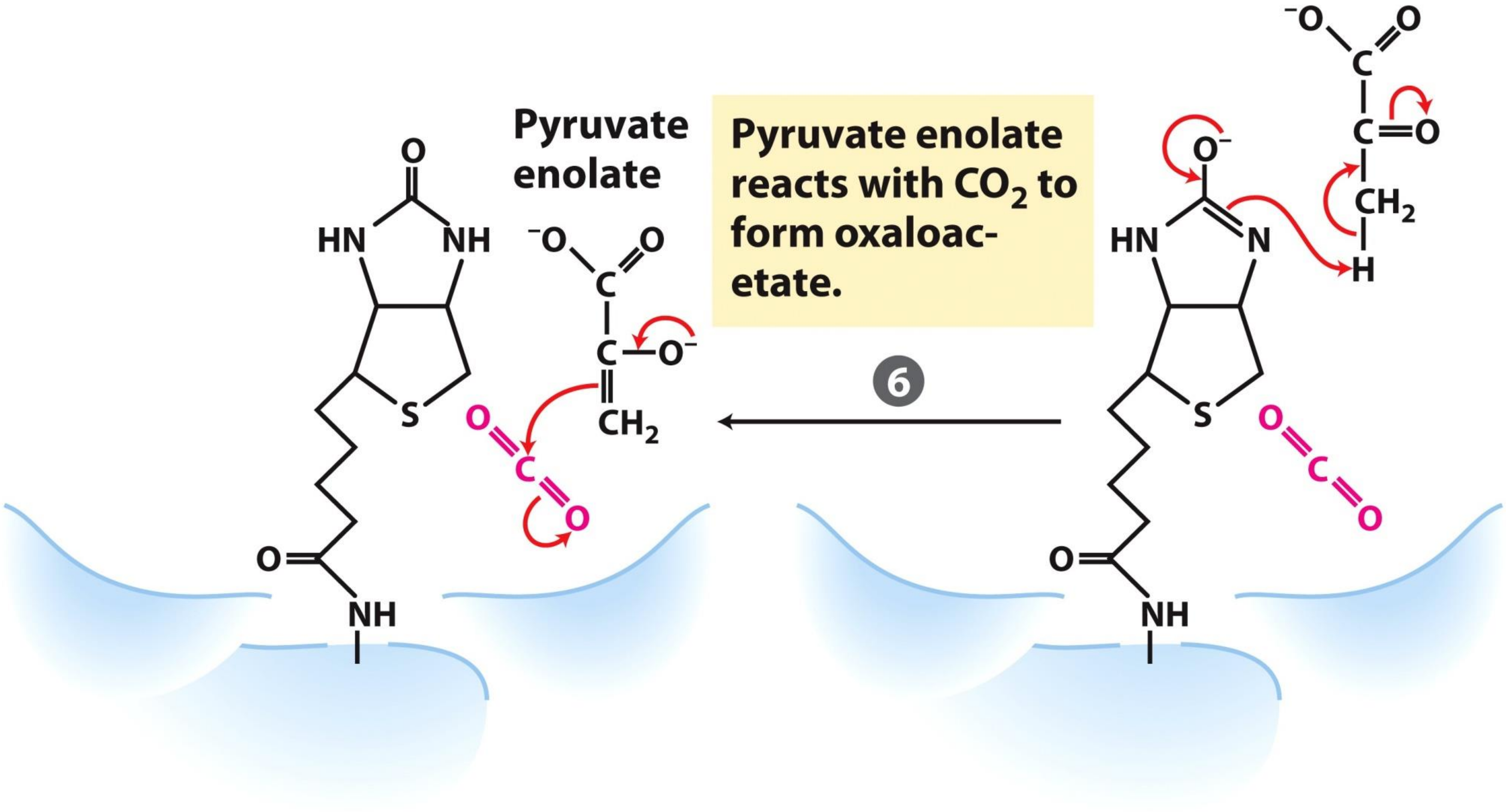
• Pyruvate carboxylase (PC)



Pyruvate enolate reacts with CO_2 to form oxaloacetate.

Figure 16-17 part 6
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• Pyruvate carboxylase (PC)

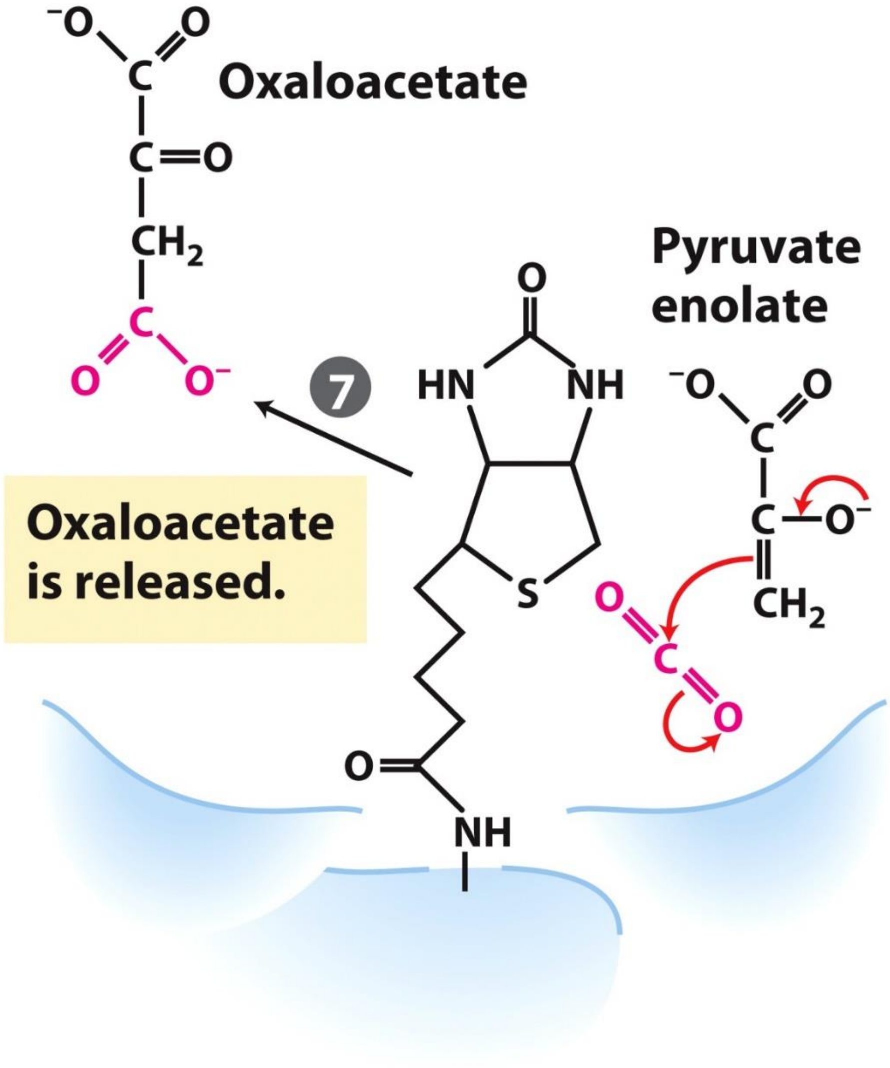

Figure 16-17 part 7
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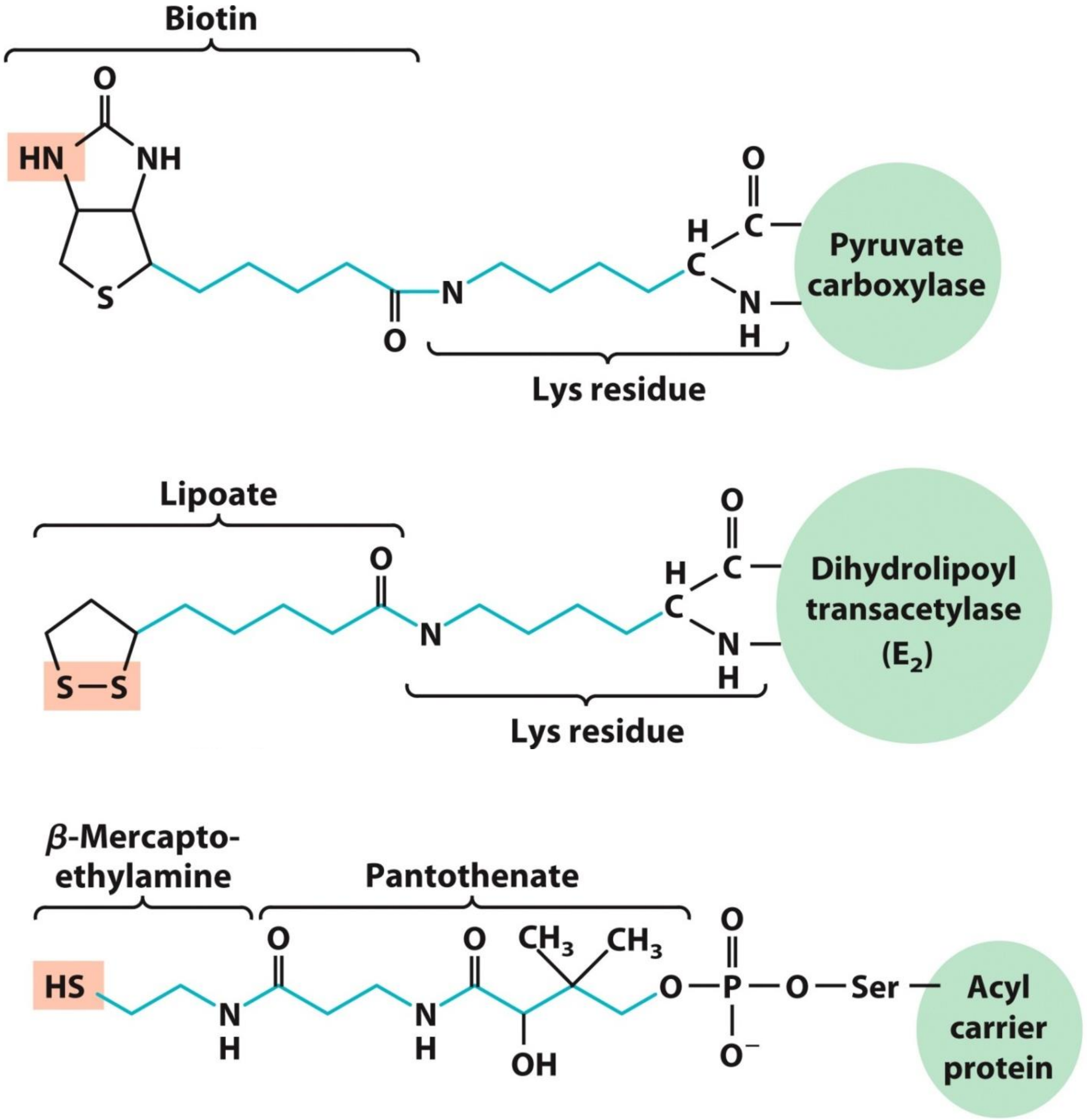
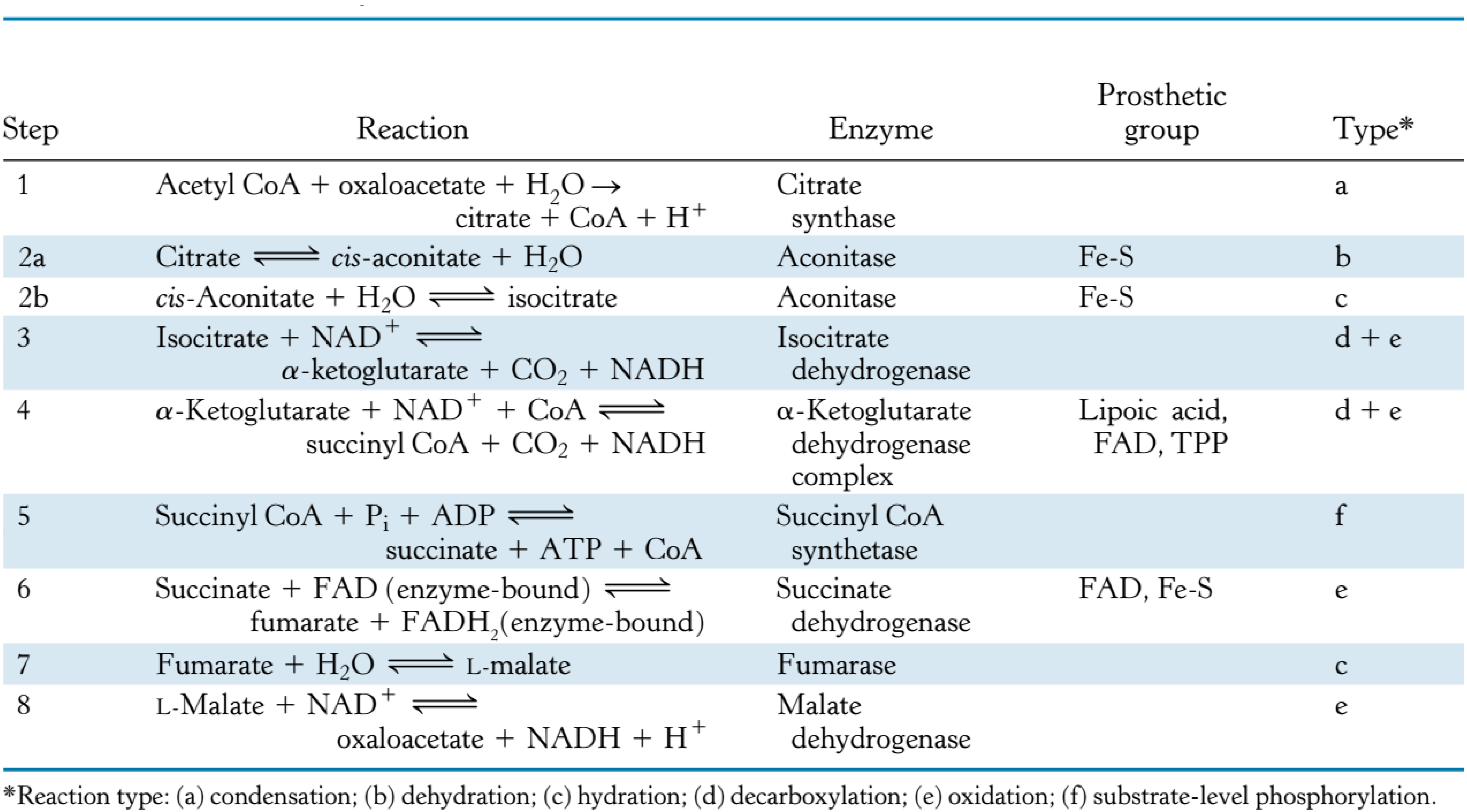
- **Biological tethers**



• Summary 16.2



Step	Reaction	Enzyme	Prosthetic group	Type*
1	Acetyl CoA + oxaloacetate + $H_2O \rightarrow$ citrate + CoA + H^+	Citrate synthase		a
2a	Citrate $\rightleftharpoons$ *cis*-aconitate + H_2O	Aconitase	Fe-S	b
2b	*cis*-Aconitate + $H_2O \rightleftharpoons$ isocitrate	Aconitase	Fe-S	c
3	Isocitrate + $NAD^+ \rightleftharpoons$ α-ketoglutarate + CO_2 + NADH	Isocitrate dehydrogenase		d + e
4	α-Ketoglutarate + NAD^+ + CoA $\rightleftharpoons$ succinyl CoA + CO_2 + NADH	α-Ketoglutarate dehydrogenase complex	Lipoic acid, FAD, TPP	d + e
5	Succinyl CoA + P_i + ADP $\rightleftharpoons$ succinate + ATP + CoA	Succinyl CoA synthetase		f
6	Succinate + FAD (enzyme-bound) $\rightleftharpoons$ fumarate + $FADH_2$(enzyme-bound)	Succinate dehydrogenase	FAD, Fe-S	e
7	Fumarate + $H_2O \rightleftharpoons$ L-malate	Fumarase		c
8	L-Malate + $NAD^+ \rightleftharpoons$ oxaloacetate + NADH + H^+	Malate dehydrogenase		e

*Reaction type: (a) condensation; (b) dehydration; (c) hydration; (d) decarboxylation; (e) oxidation; (f) substrate-level phosphorylation.

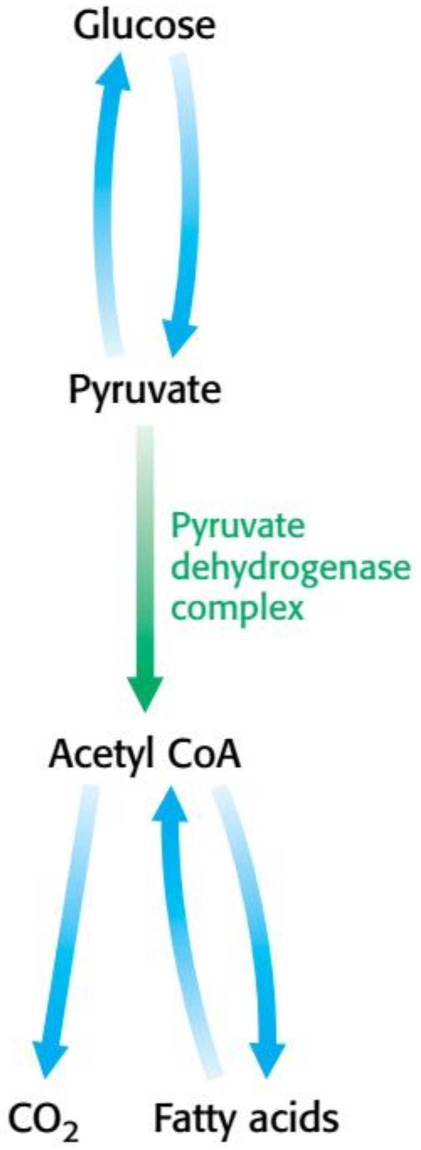
• Summary 16.2

- The citric acid cycle is amphibolic, serving in both catabolism and anabolism; cycle intermediates can be drawn off and used as the starting material for a variety of biosynthetic products.

- When intermediates are shunted from the citric acid cycle to other pathways, they are replenished by several anaplerotic reactions, which produce four-carbon intermediates by carboxylation of three-carbon compounds; these reactions are catalyzed by pyruvate carboxylase, PEP carboxykinase, PEP carboxylase, and malic enzyme. Enzymes that catalyze carboxylations commonly employ biotin to activate CO_2 and to carry it to acceptors such as pyruvate or phosphoenolpyruvate.

16.3 Regulation of the Citric Acid Cycle

• PDH is regulated by allosteric and covalent mechanisms



Glucose

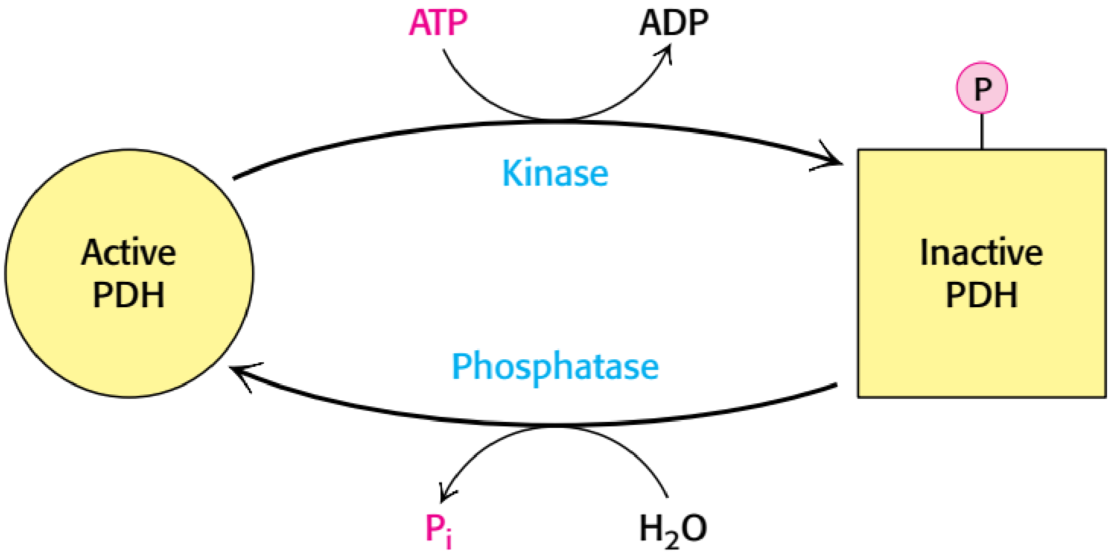
Pyruvate

Pyruvate dehydrogenase complex

Acetyl CoA

CO_2

Fatty acids



ATP

ADP

Kinase

P

Active PDH

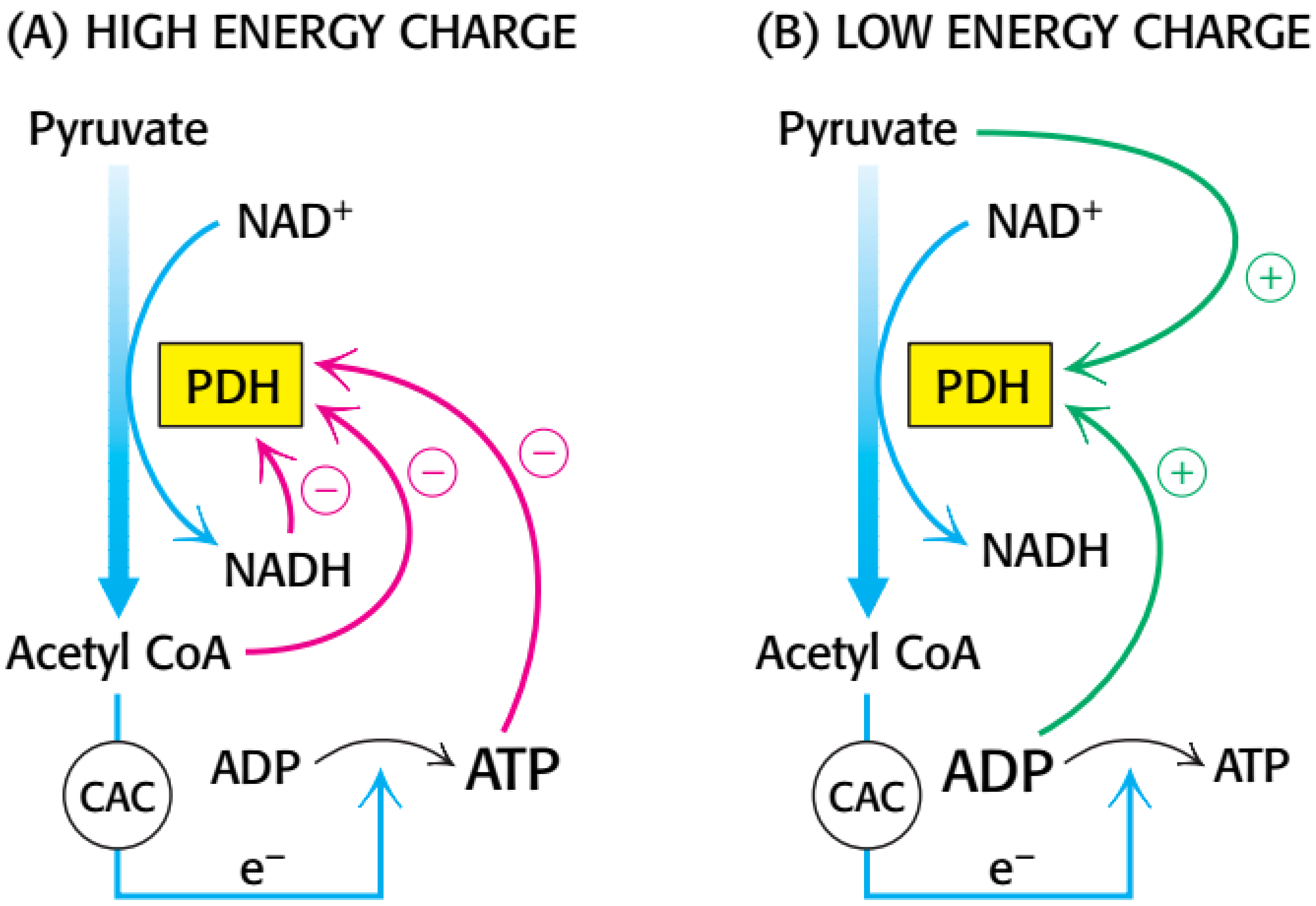
Inactive PDH

Phosphatase

P_i

H_2O

• PDH is regulated by allosteric and covalent mechanisms



• The citric acid cycle is controlled at several points

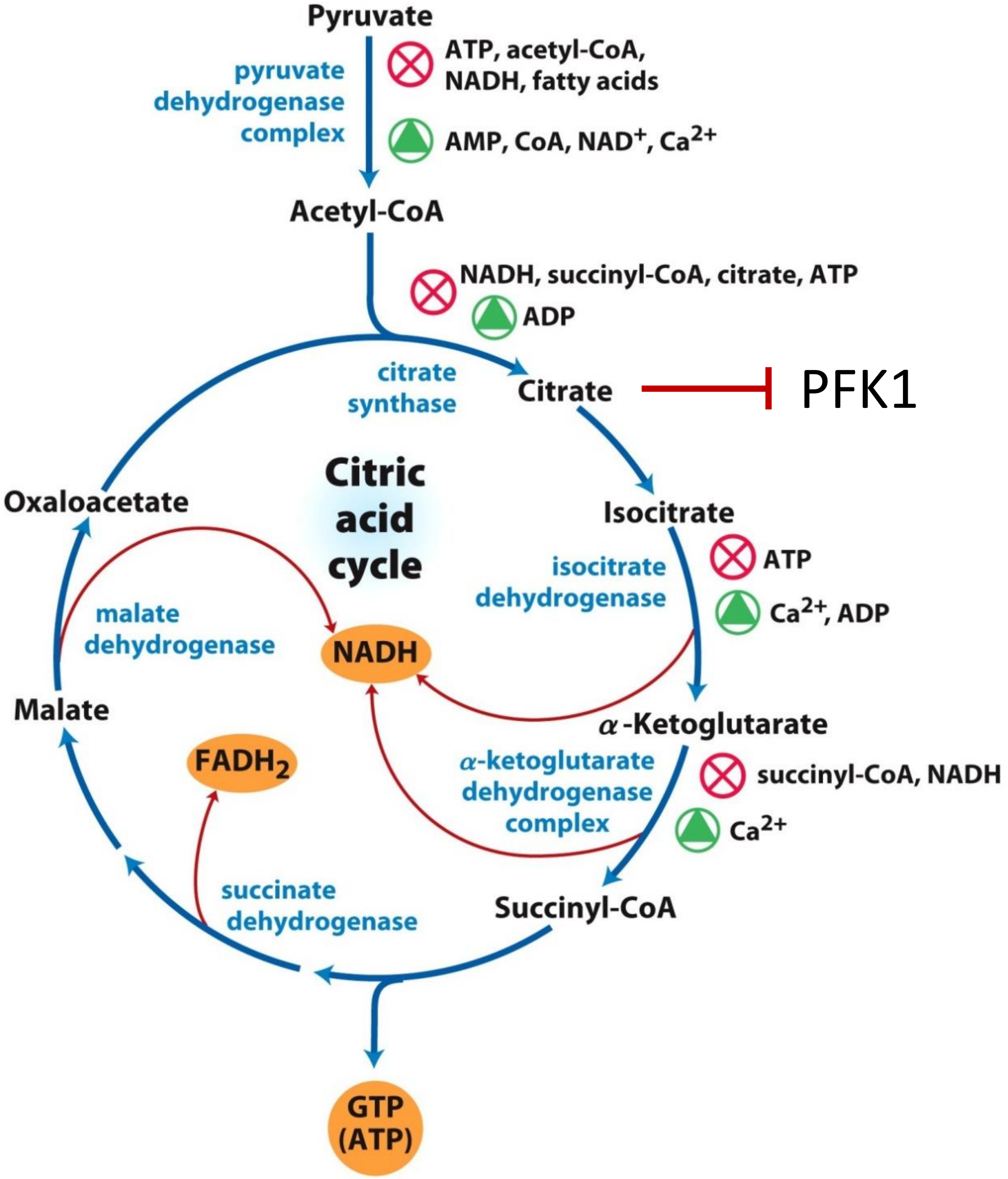
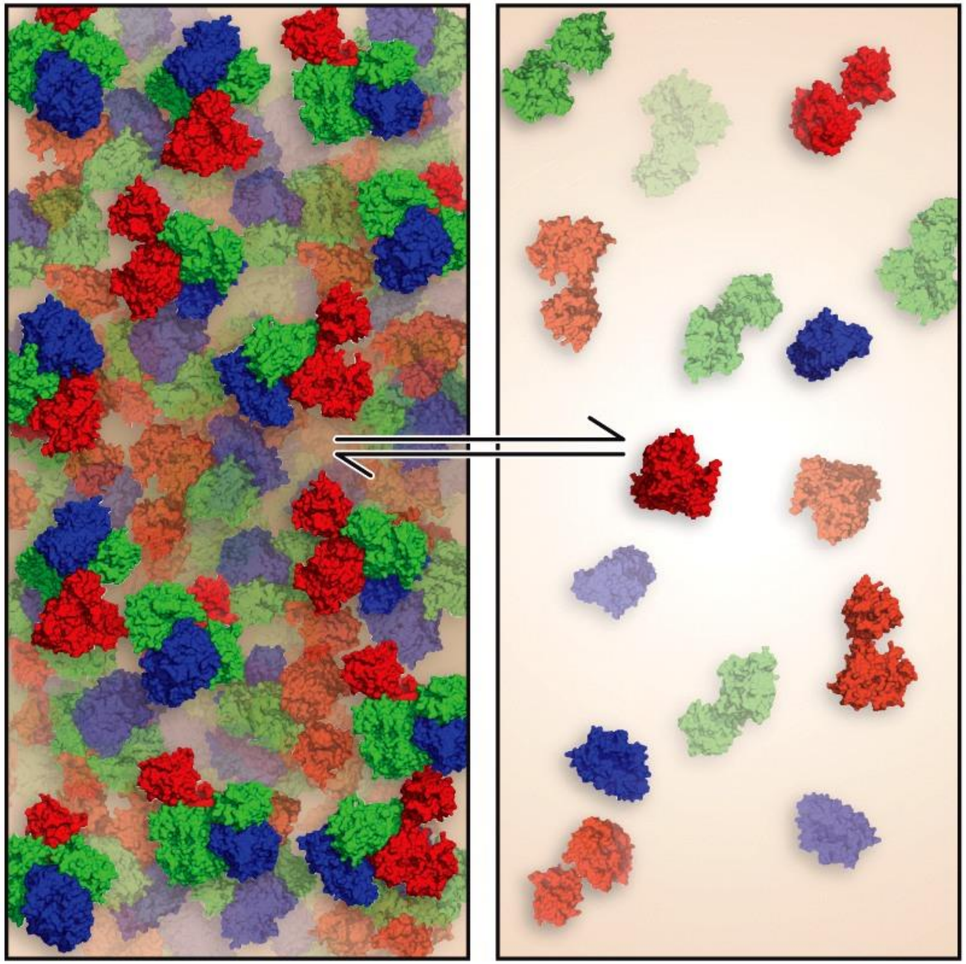


Figure 16-19

• Substrate channeling in citric acid cycle



In the cytosol, high concentrations of enzymes 1, 2, and 3 favor their association.

In extract of broken cells, dilution by buffer reduces the concentrations of enzymes 1, 2, and 3, favoring their dissociation.

Figure 16-20

Substrate channeling through multienzyme complexes may occur in the citric acid cycle

metabolon

Some mutations in enzymes of the CAC lead to cancer

- Loss-of-function
  - Fumarase
  - Succinate dehydrogenase

- Gain-of-function
  - Isocitrate dehydrogenase 1/2

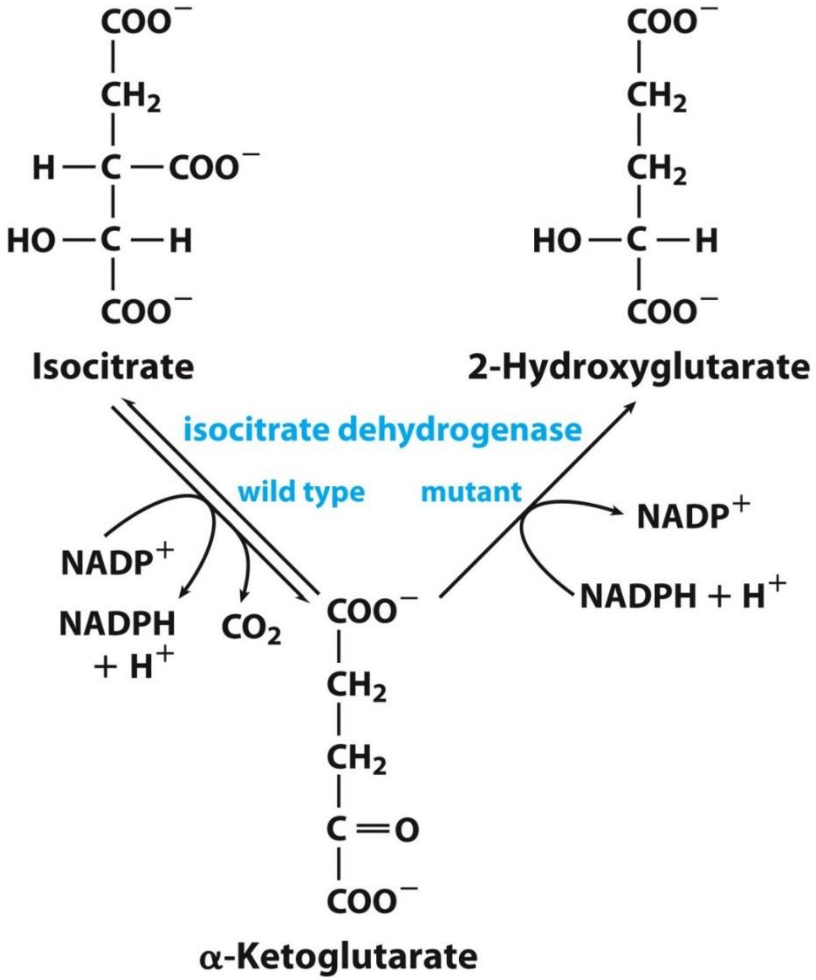
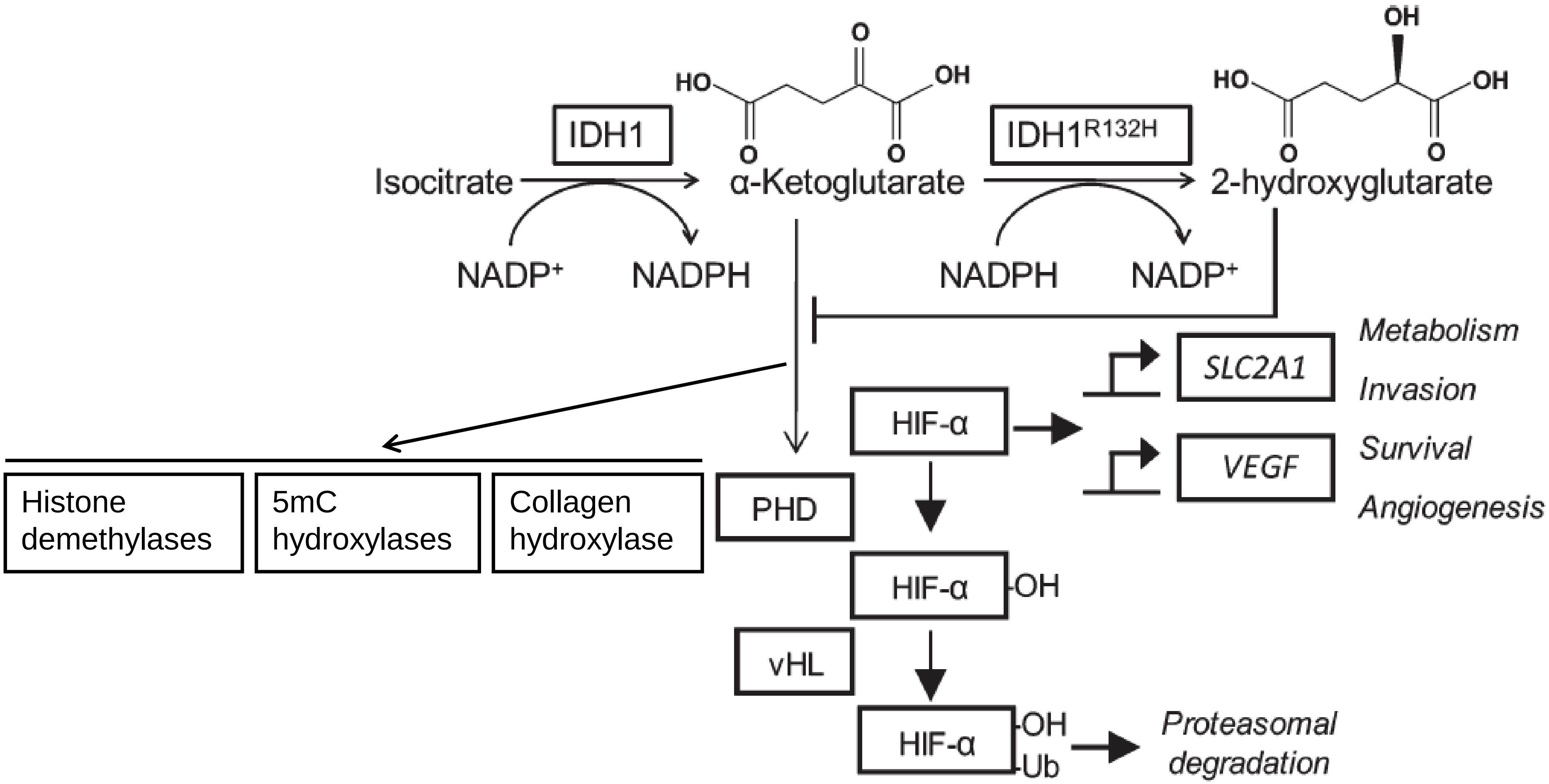


Figure 16-21

• IDH1 is mutated in many diffuse gliomas



PHD: HIF prolyl hydroxylase; vHL: von Hippel Lindau protein (E3); VEGF: vascular endothelial growth factor; SLC2A: solute carrier family 2 member 1

Summary 16.3

- The overall rate of the citric acid cycle is controlled by the rate of conversion of pyruvate to acetyl-CoA and by the flux through citrate synthase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase. These fluxes are largely determined by the concentrations of substrates and products: the end products ATP and NADH are inhibitory, and the substrates NAD^+ and ADP are stimulatory.
- The production of acetyl-CoA for the citric acid cycle by the PDH complex is inhibited allosterically by metabolites that signal a sufficiency of metabolic energy (ATP, acetyl-CoA, NADH, and fatty acids) and stimulated by metabolites that indicate a reduced energy supply (AMP, NAD^+ , CoA).
- Complexes of consecutive enzymes in a pathway allow substrate channeling between them.

16.4 The Glyoxylate Cycle

- **Vertebrates cannot convert acetyl-CoA into glucose**

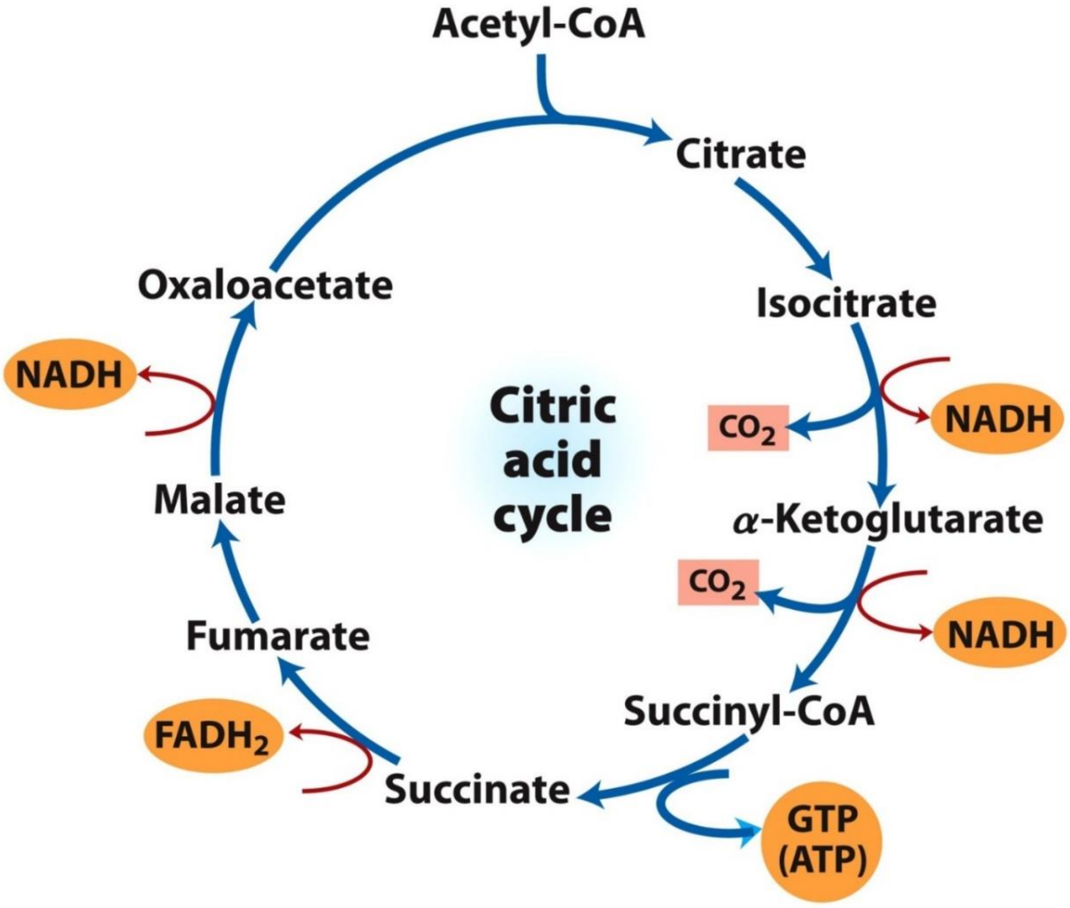
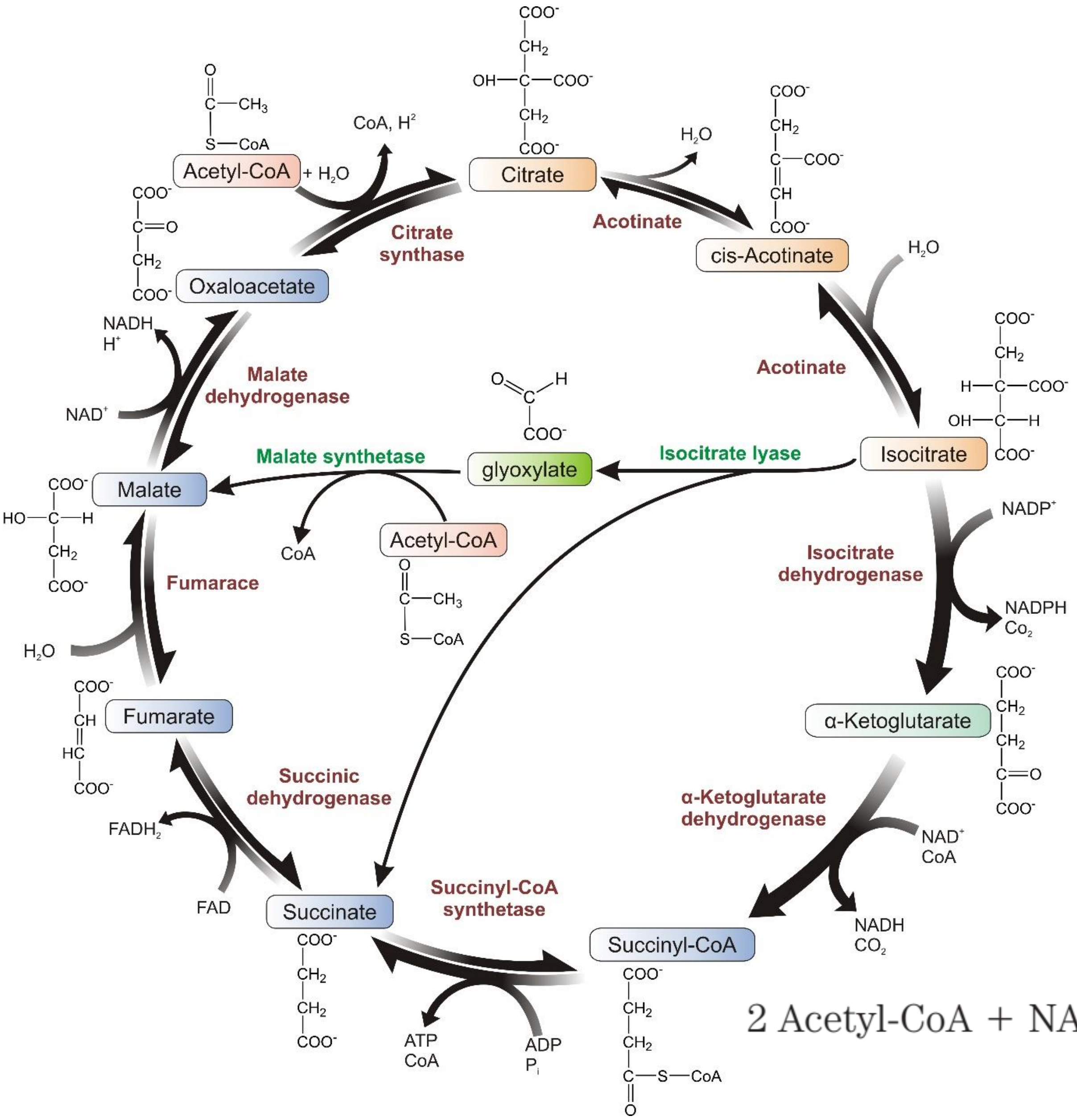


Figure 16-14

• The glyoxylate cycle



Vertebrates lack **isocitrate lyase** and **malate synthase**

$$2\ \text{Acetyl-CoA} + \text{NAD}^+ + 2\text{H}_2\text{O} \longrightarrow \text{succinate} + 2\text{CoA} + \text{NADH} + \text{H}^+$$

• Glyoxysome

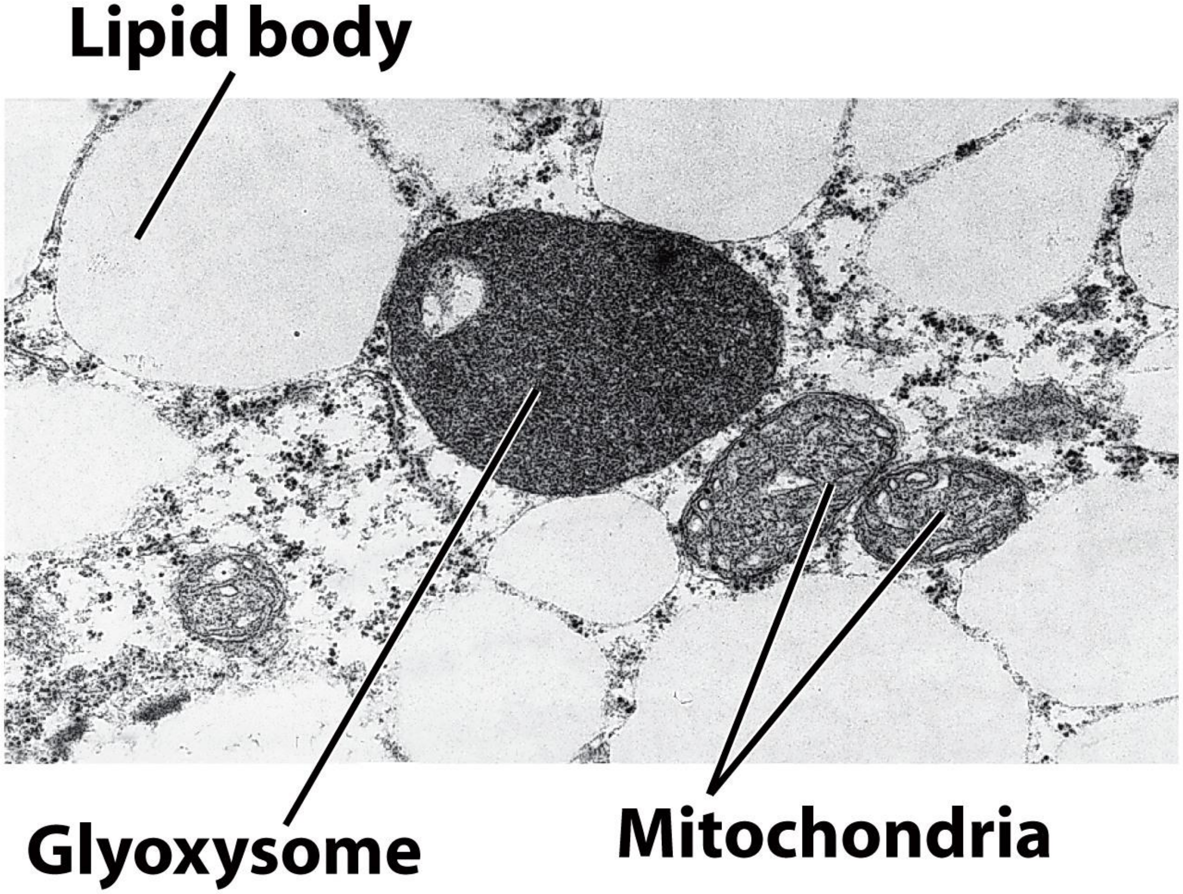
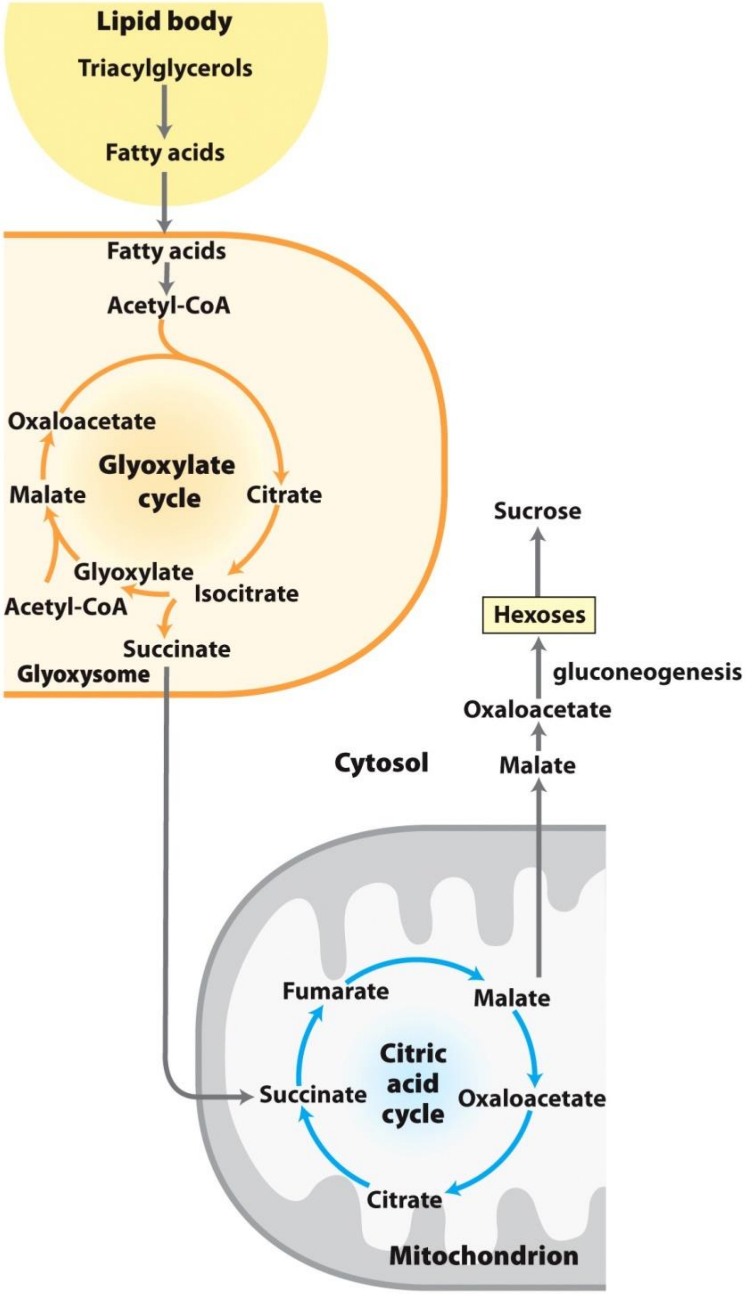


Figure 16-23

Electron micrograph of a germinating cucumber seed, showing a glyoxysome, mitochondria, and surrounding lipid bodies

• Relationship between the glyoxylate and citric acid cycles



• Citric acid and glyoxylate cycle are coordinately regulated

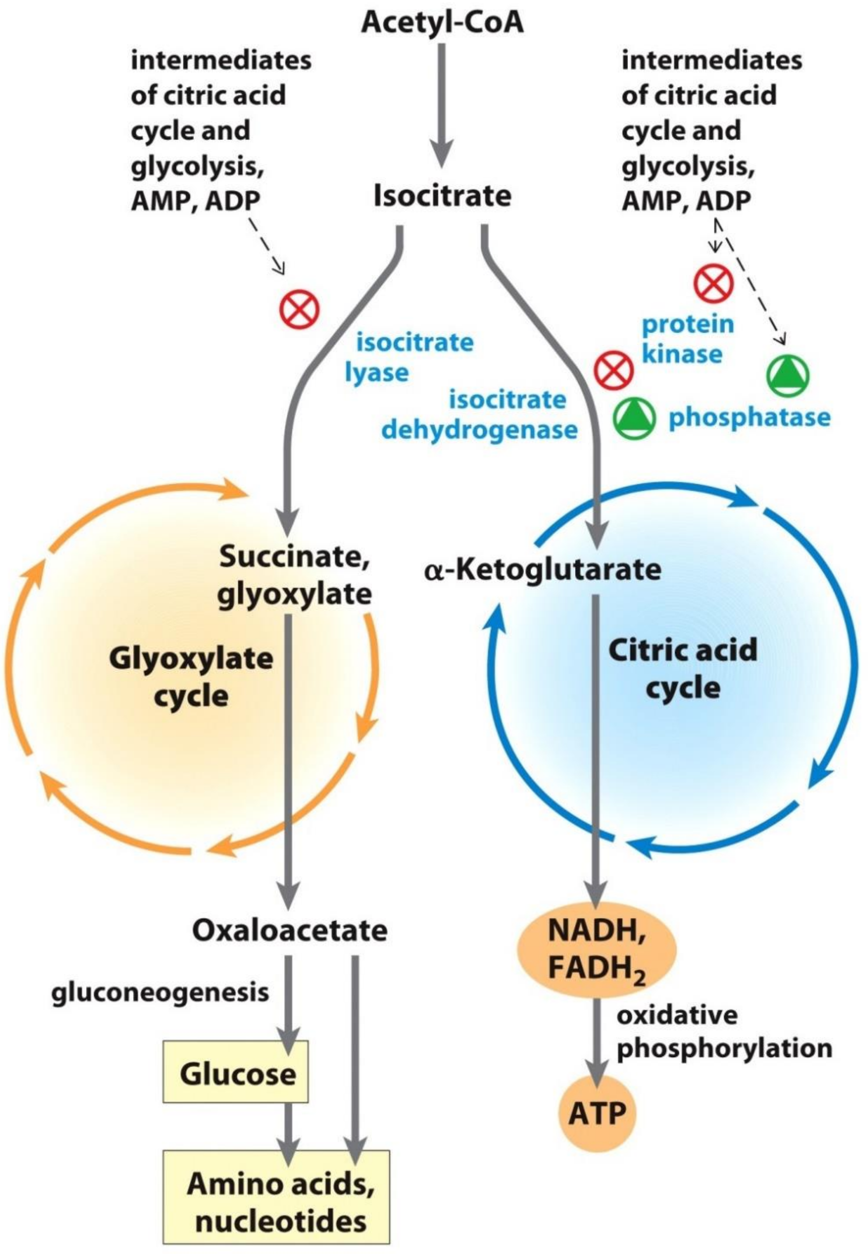


Figure 16-25

• Summary 16.4

- The glyoxylate cycle is active in the germinating seeds of some plants and in certain microorganisms that can live on acetate as the sole carbon source. In plants, the pathway takes place in glyoxysomes in seedlings. It involves several citric acid cycle enzymes and two additional enzymes: isocitrate lyase and malate synthase.
- In the glyoxylate cycle, the bypassing of the two decarboxylation steps of the citric acid cycle makes possible the *net* formation of succinate, oxaloacetate, and other cycle intermediates from acetyl-CoA. Oxaloacetate thus formed can be used to synthesize glucose via gluconeogenesis.

• Summary 16.4

- Vertebrates lack the glyoxylate cycle and **cannot** synthesize glucose from acetate or the fatty acids that give rise to acetyl-CoA.

- The partitioning of isocitrate between the citric acid cycle and the glyoxylate cycle is controlled at the level of isocitrate dehydrogenase, which is regulated by reversible phosphorylation.