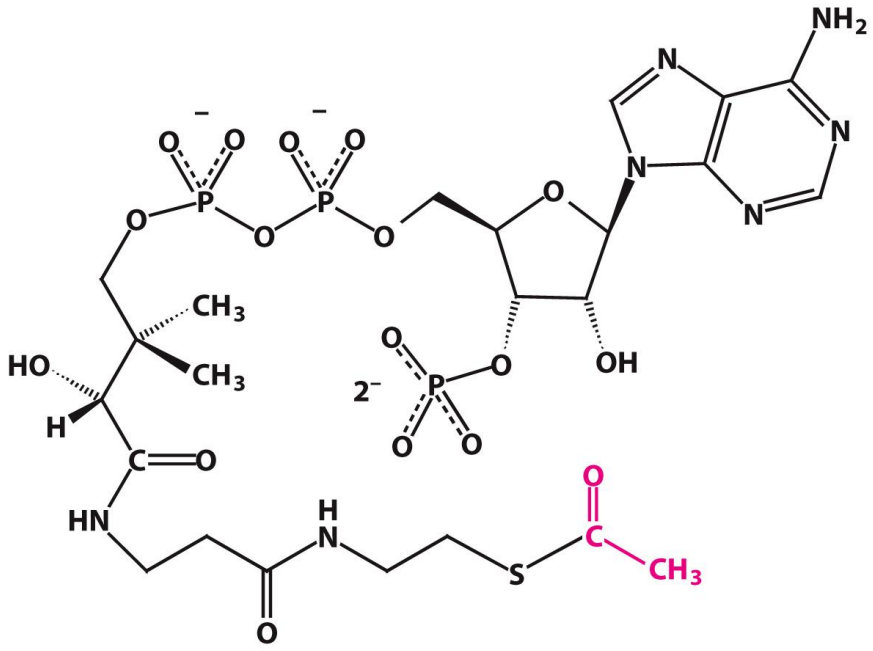
Chapter 17

Pyruvate dehydrogenase
Citric Acid cycle

Under aerobic conditions, pyruvate enters the mitochondria where it is converted into acetyl CoA.

Acetyl CoA is the fuel for the citric acid cycle, which processes the two carbon acetyl unit to two molecules of CO_2 while generating high-energy electrons that can be used to form ATP.



Acetyl coenzyme A (Acetyl CoA)

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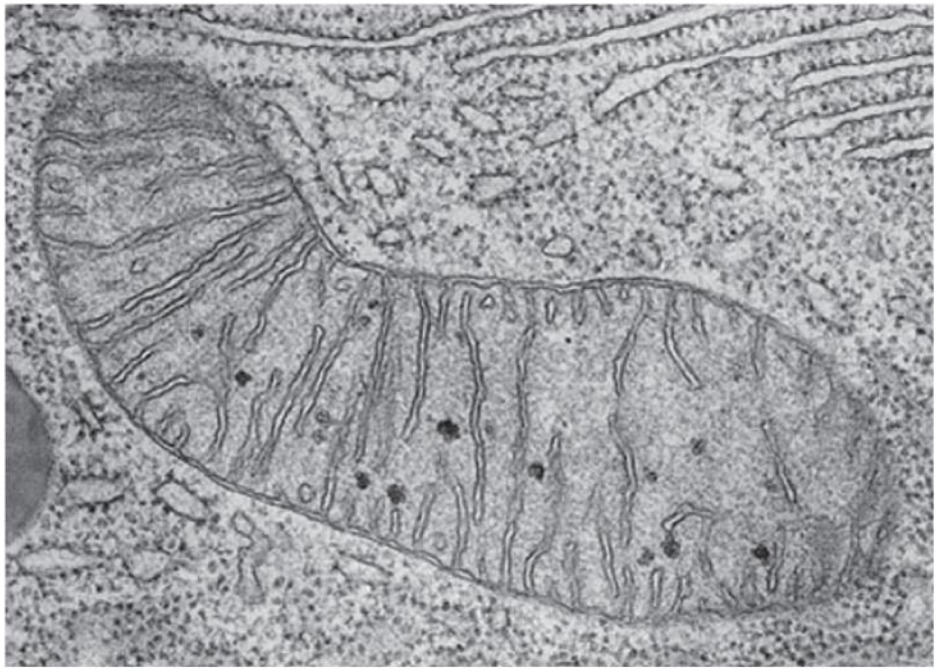
Decarboxylation of pyruvate and Citric acid cycle takes place in mitochondria



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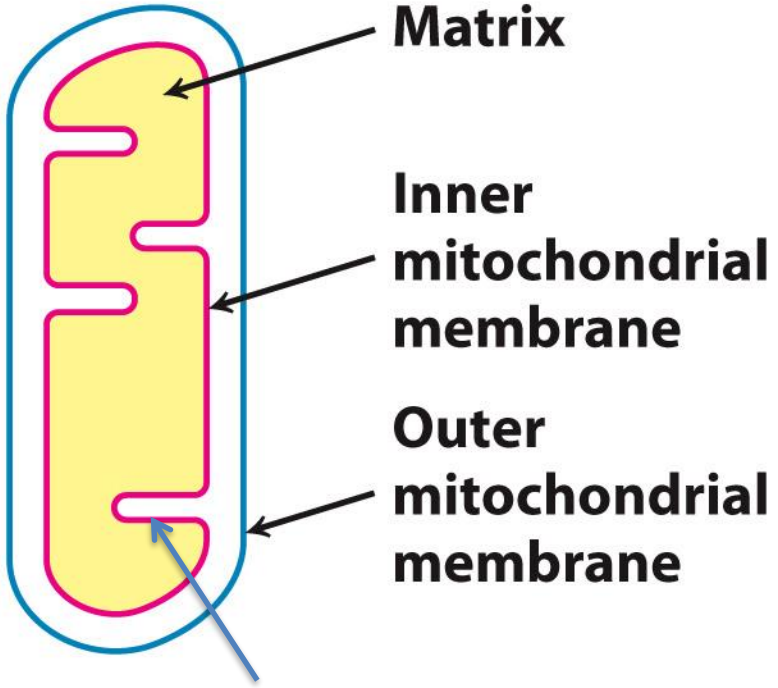
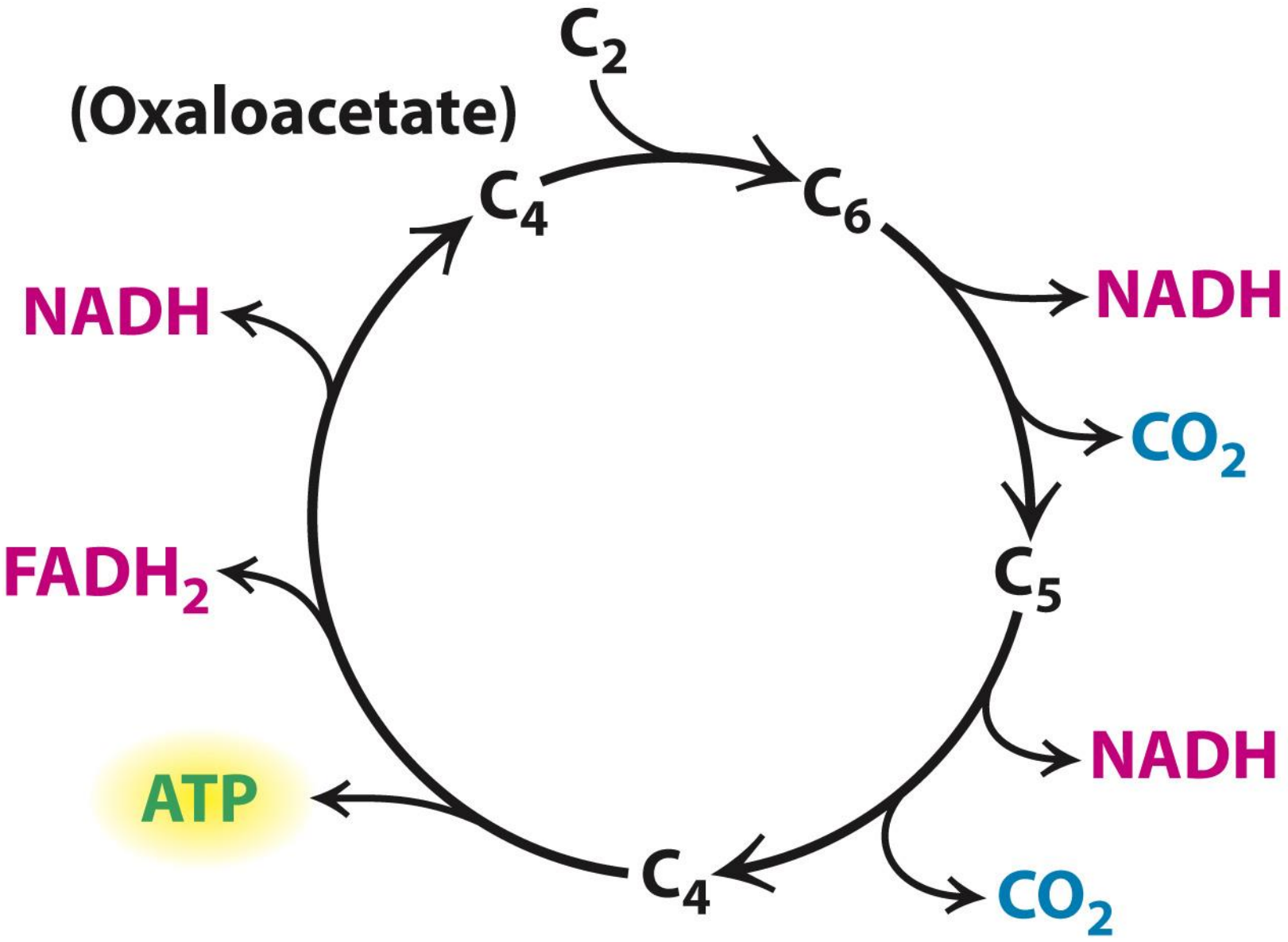


A key function of the citric acid cycle is to harvest high-energy electrons in the form of NADH and $FADH_2$.

The two carbon acetyl unit from acetyl CoA condenses with oxaloacetate to form citrate, which is subsequently oxidized.

The high-energy electrons are used to reduce O_2 to H_2O. This reduction generates a proton gradient that is used to synthesize ATP.



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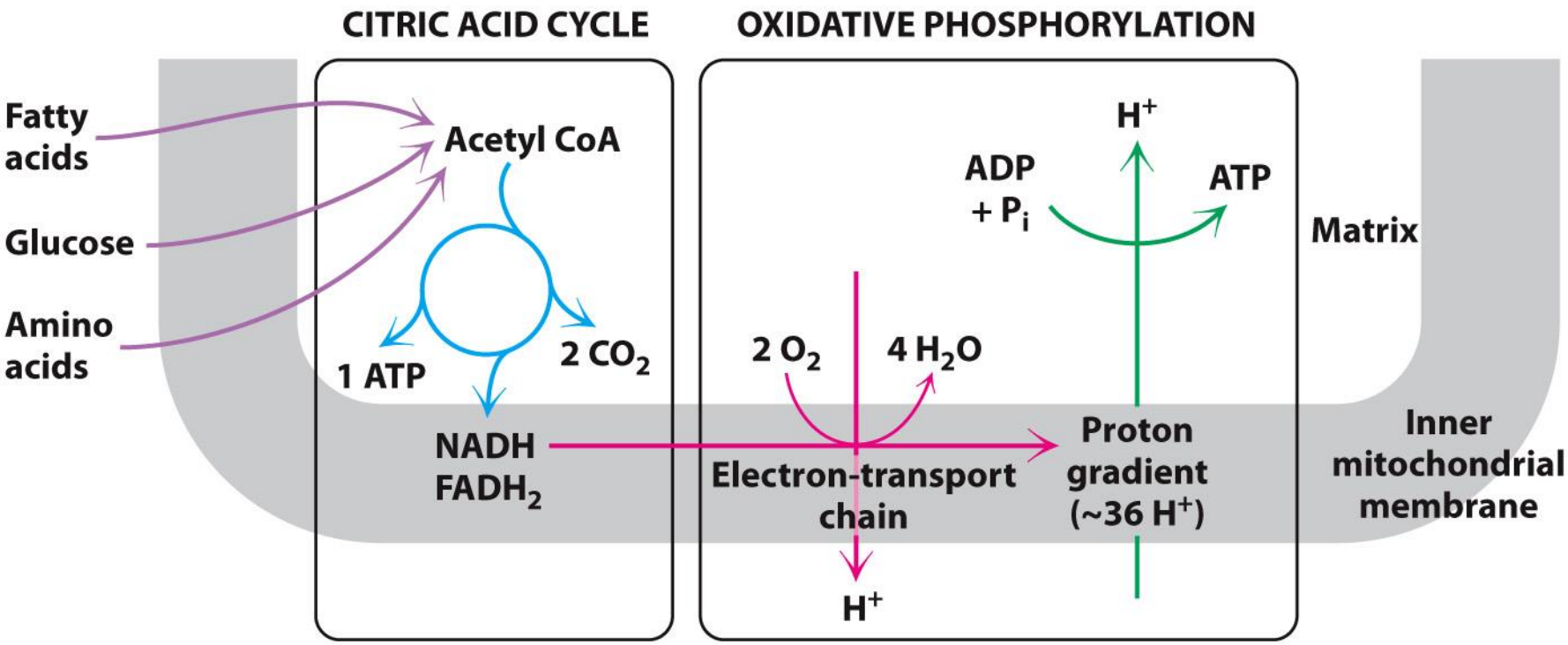

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PYRUVATE DEHYDROGENASE

The pyruvate dehydrogenase complex, a component of the mitochondrial matrix, is composed of three distinct enzymes that oxidatively decarboxylate pyruvate to form acetyl CoA.

This reaction is an irreversible link between glycolysis and the citric acid cycle.

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

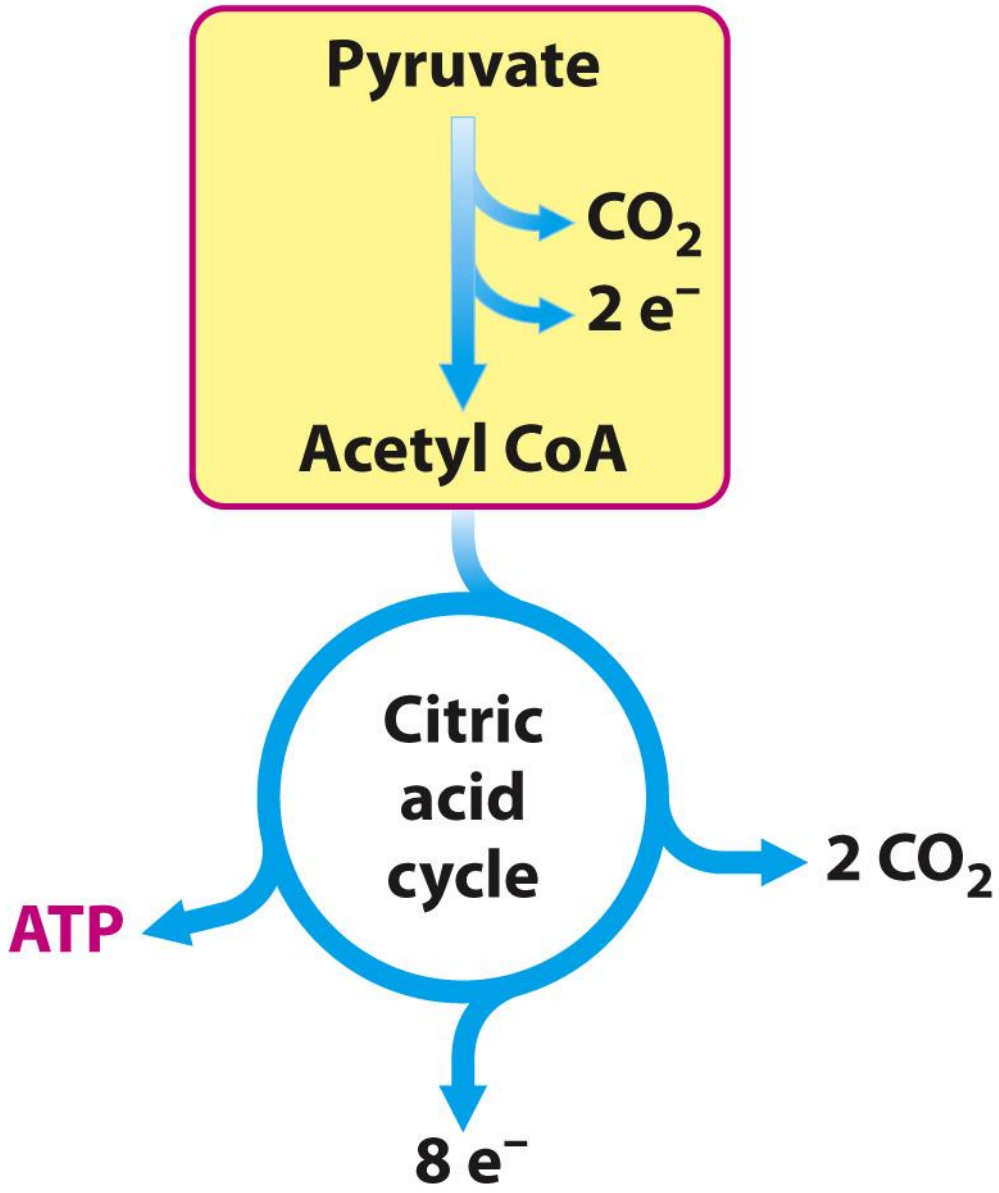

Figure 17.4
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TABLE 17.1 Pyruvate dehydrogenase complex of *E. coli*

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

Table 17.1
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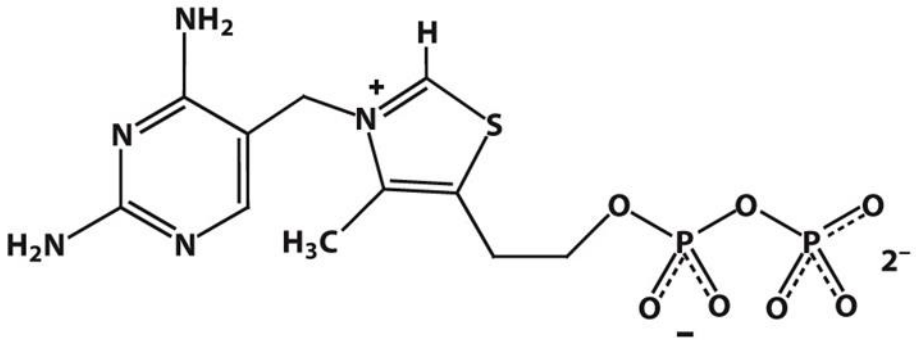
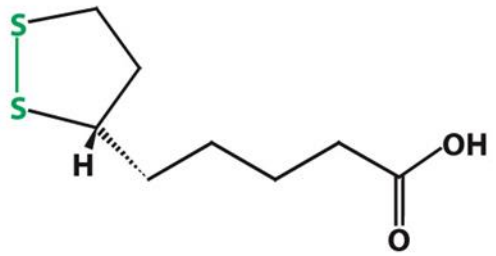


Thiamine pyrophosphate (TPP)



Lipoic acid

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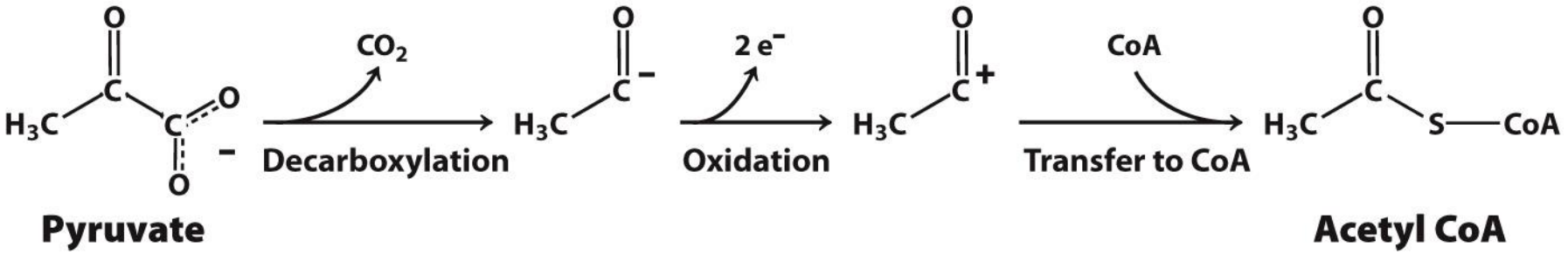
The synthesis of acetyl CoA from pyruvate consists of three steps: a decarboxylation, an oxidation, and the transfer of an acetyl unit to CoA.



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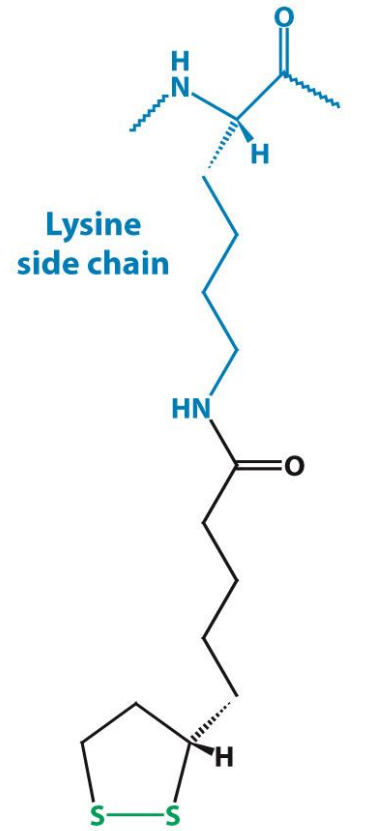
The three enzymes of the pyruvate dehydrogenase complex are structurally integrated, and the lipoamide arm allows rapid movement of substrates and products from one active site of the complex to another.

Dihydrolipoamide is formed by the attachment of the vitamin lipoic acid to a lysine residue in dihydrolipoyl transacetylase (E_2).

The core of the pyruvate dehydrogenase complex is E_2, the transacetylase.



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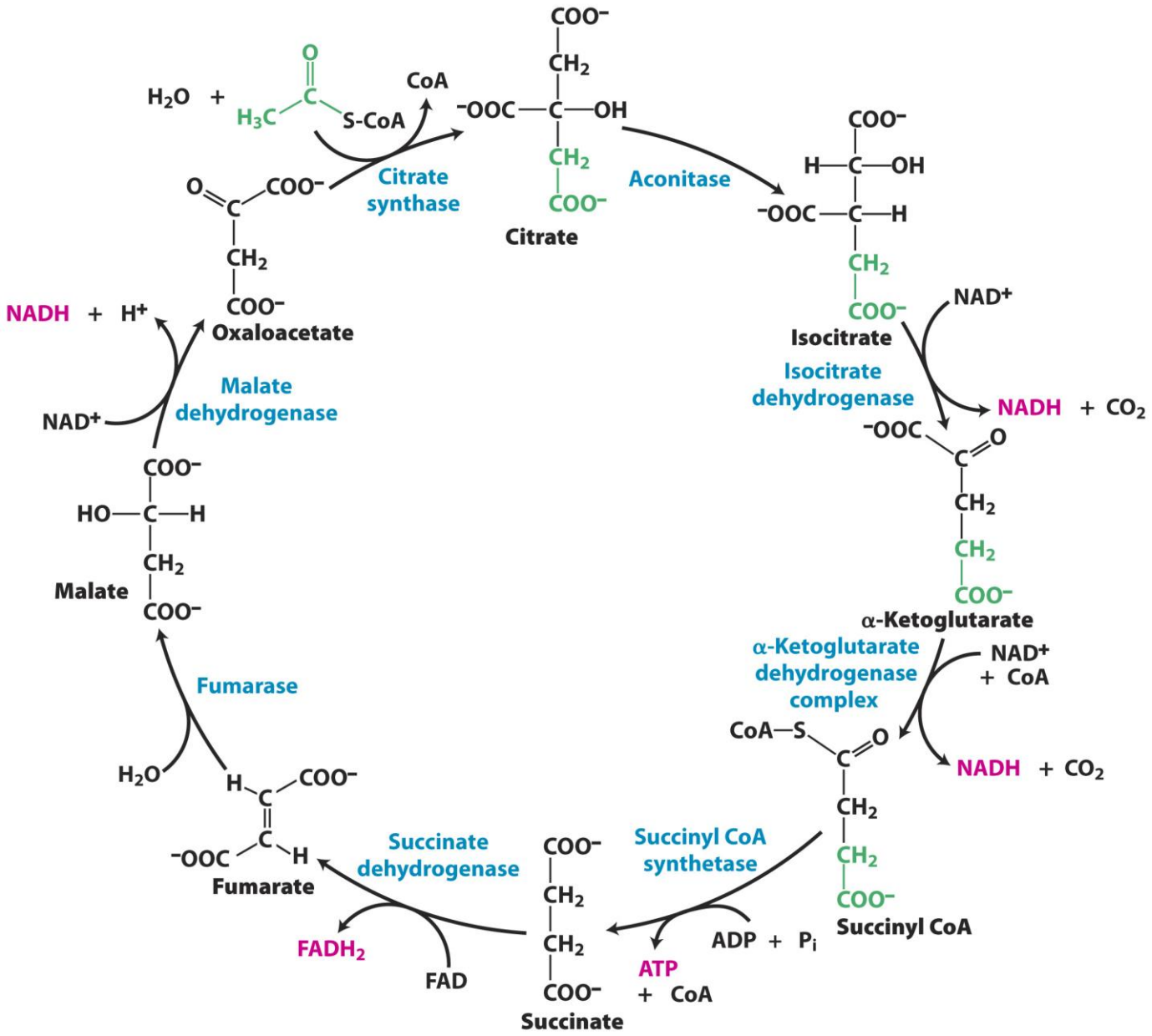

Figure 17.15
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The net reaction of the citric acid cycle is:

$$\text{Acetyl CoA} + 3\,NAD^+ + FAD + ADP + P_i + 2\,H_2O \longrightarrow 2\,CO_2 + 3\,NADH + FADH_2 + ATP + 2\,H^+ + CoA$$

The electrons from $FADH_2$ will power the synthesis of 1.5 ATP with the reduction of oxygen in the electron-transport chain.

TABLE 17.2 Citric acid cycle

Step	Reaction	Enzyme	Prosthetic group	Type*	$\Delta G^{\circ\prime}$ kJ mol^{-1}	$\Delta G^{\circ\prime}$ kcal mol^{-1}
1	Acetyl CoA + oxaloacetate + $H_2O \rightarrow$ citrate + CoA + H^+	Citrate synthase		a	–31.4	–7.5
2a	Citrate $\rightleftharpoons$ *cis*-aconitate + H_2O	Aconitase	Fe-S	b	+8.4	+2.0
2b	*cis*-Aconitate + $H_2O \rightleftharpoons$ isocitrate	Aconitase	Fe-S	c	−2.1	−0.5
3	Isocitrate + $NAD^+ \rightleftharpoons$ α-ketoglutarate + CO_2 + NADH	Isocitrate dehydrogenase		d + e	−8.4	−2.0
4	α-Ketoglutarate + NAD^+ + CoA $\rightleftharpoons$ succinyl CoA + CO_2 + NADH	α-Ketoglutarate dehydrogenase complex	Lipoic acid, FAD, TPP	d + e	−30.1	−7.2
5	Succinyl CoA + P_i + ADP $\rightleftharpoons$ succinate + ATP + CoA	Succinyl CoA synthetase		f	−3.3	−0.8
6	Succinate + FAD (enzyme-bound) $\rightleftharpoons$ fumarate + $FADH_2$(enzyme-bound)	Succinate dehydrogenase	FAD, Fe-S	e	0	0
7	Fumarate + $H_2O \rightleftharpoons$ L-malate	Fumarase		c	−3.8	−0.9
8	L-Malate + $NAD^+ \rightleftharpoons$ oxaloacetate + NADH + H^+	Malate dehydrogenase		e	+29.7	+7.1

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

Table 17.2
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Controls of citric acid cycle

Pyruvate dehydrogenase complex is regulated allosterically and by reversible phosphorylation

The formation of acetyl CoA from pyruvate is irreversible in animal cells.

Acetyl CoA has two principle fates: metabolism by the citric acid cycle or incorporation into fatty acids.

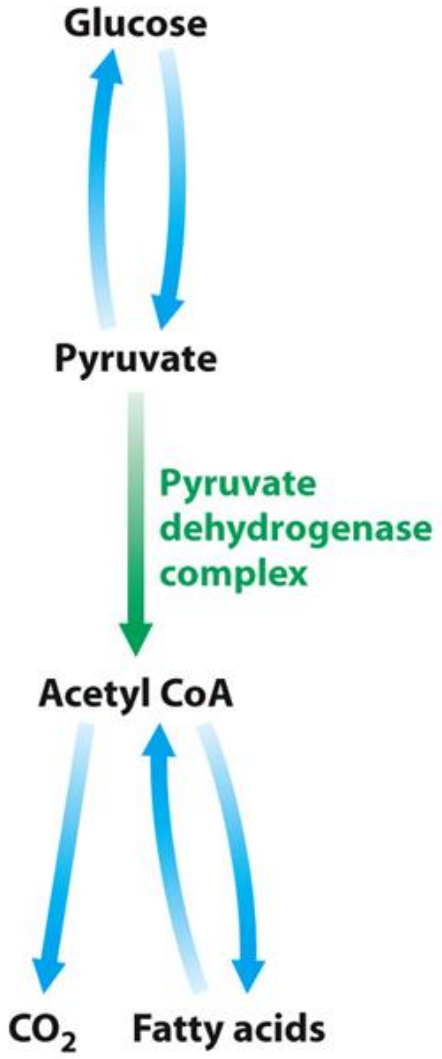

Figure 17.16
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Pyruvate dehydrogenase control

Enzyme E_1 is a key site of regulation. A kinase associated with the complex phosphorylates and inactivates E_1.

A phosphatase, also associated with the complex, removes the phosphate and thereby activates the enzyme.

The pyruvate dehydrogenase complex is also regulated by energy charge.

ATP, acetyl CoA, and NADH inhibit the complex.

ADP and pyruvate stimulate the complex.

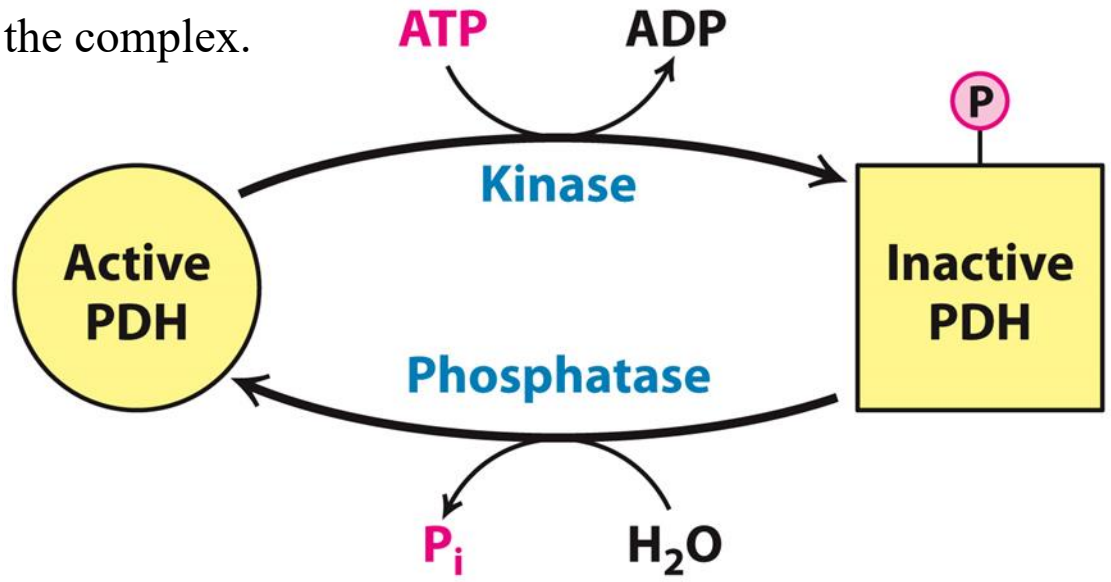

Figure 17.17
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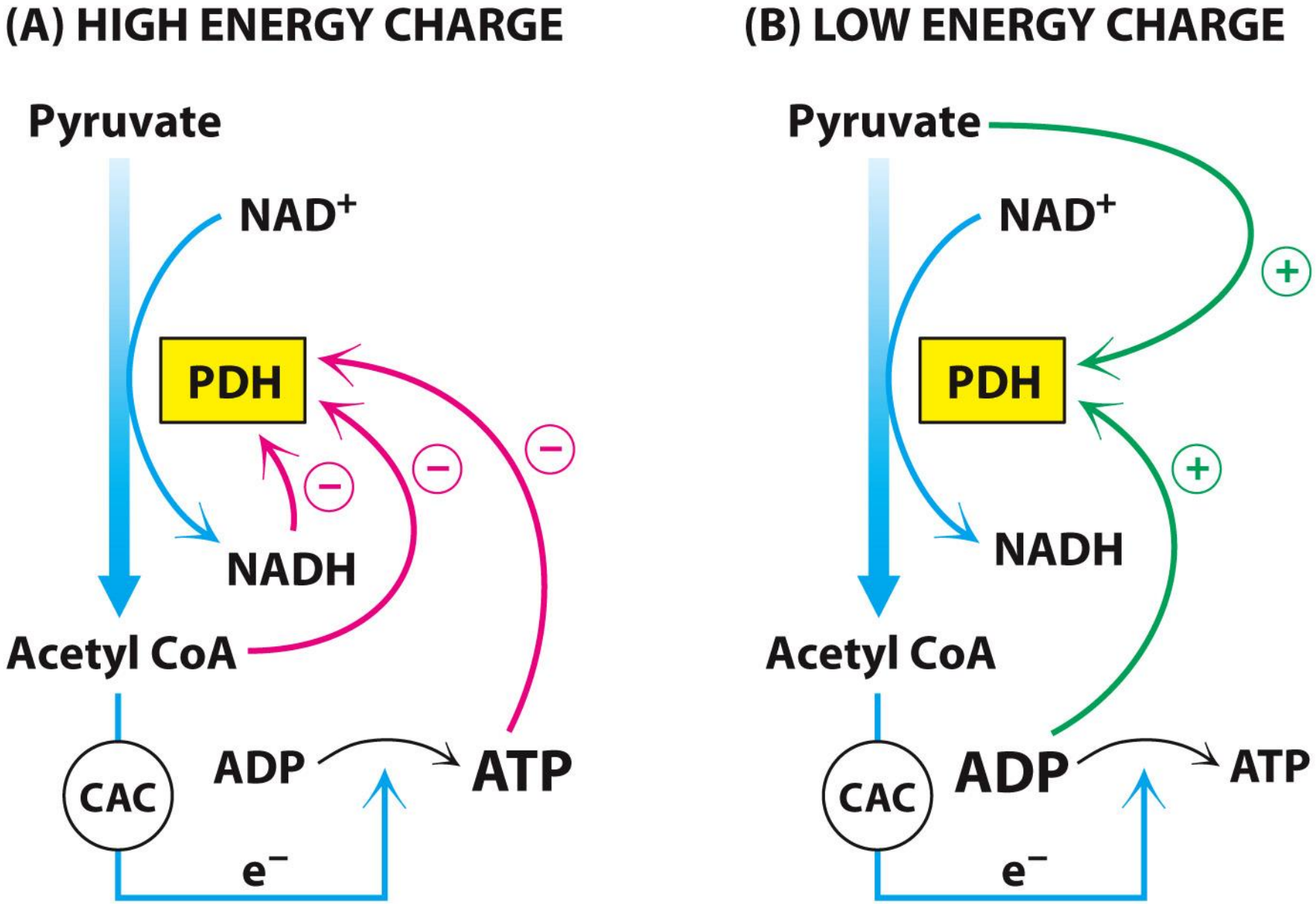

Figure 17.18
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Many of the components of the citric acid cycle are precursors for biosynthesis of key biomolecules.

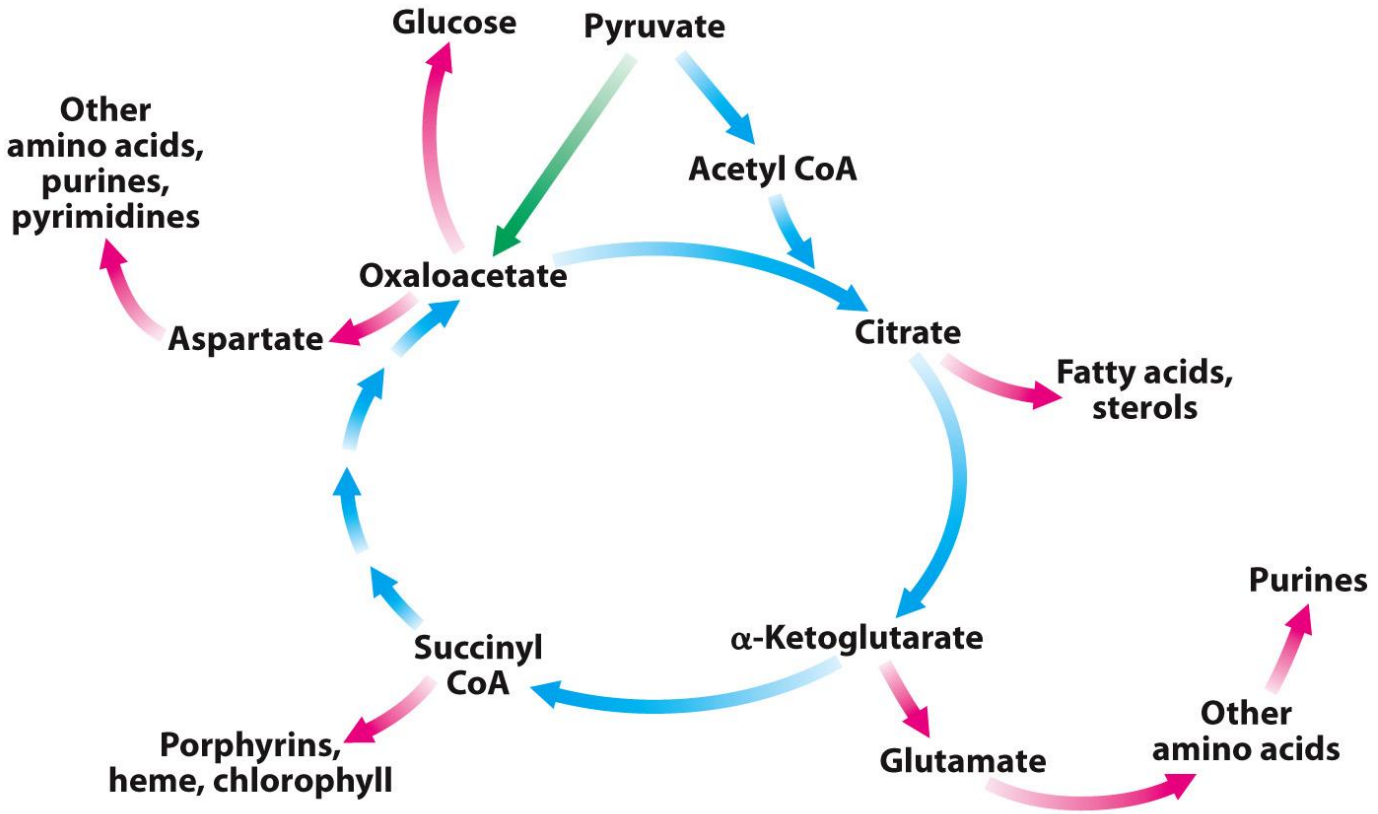

Figure 17.20
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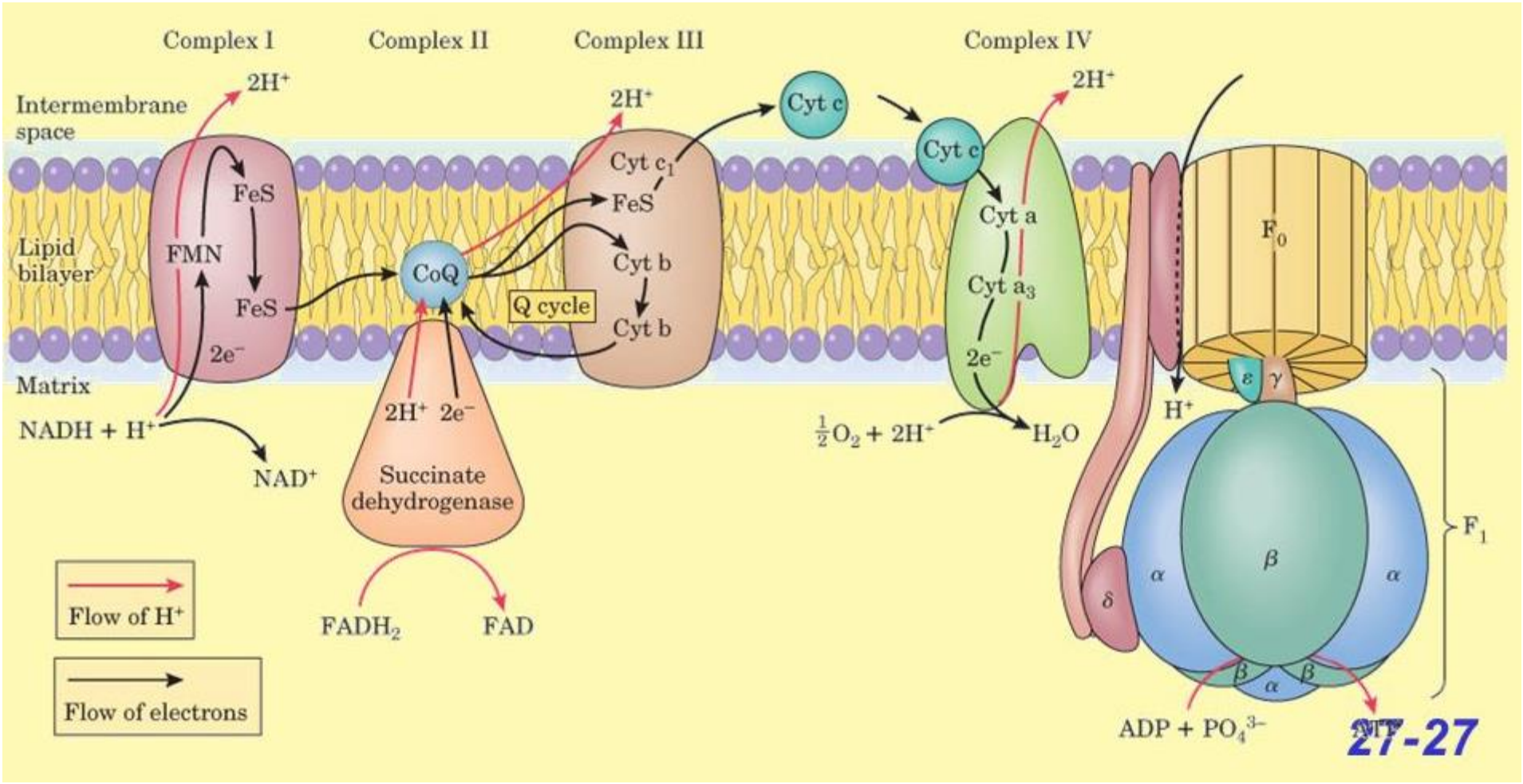
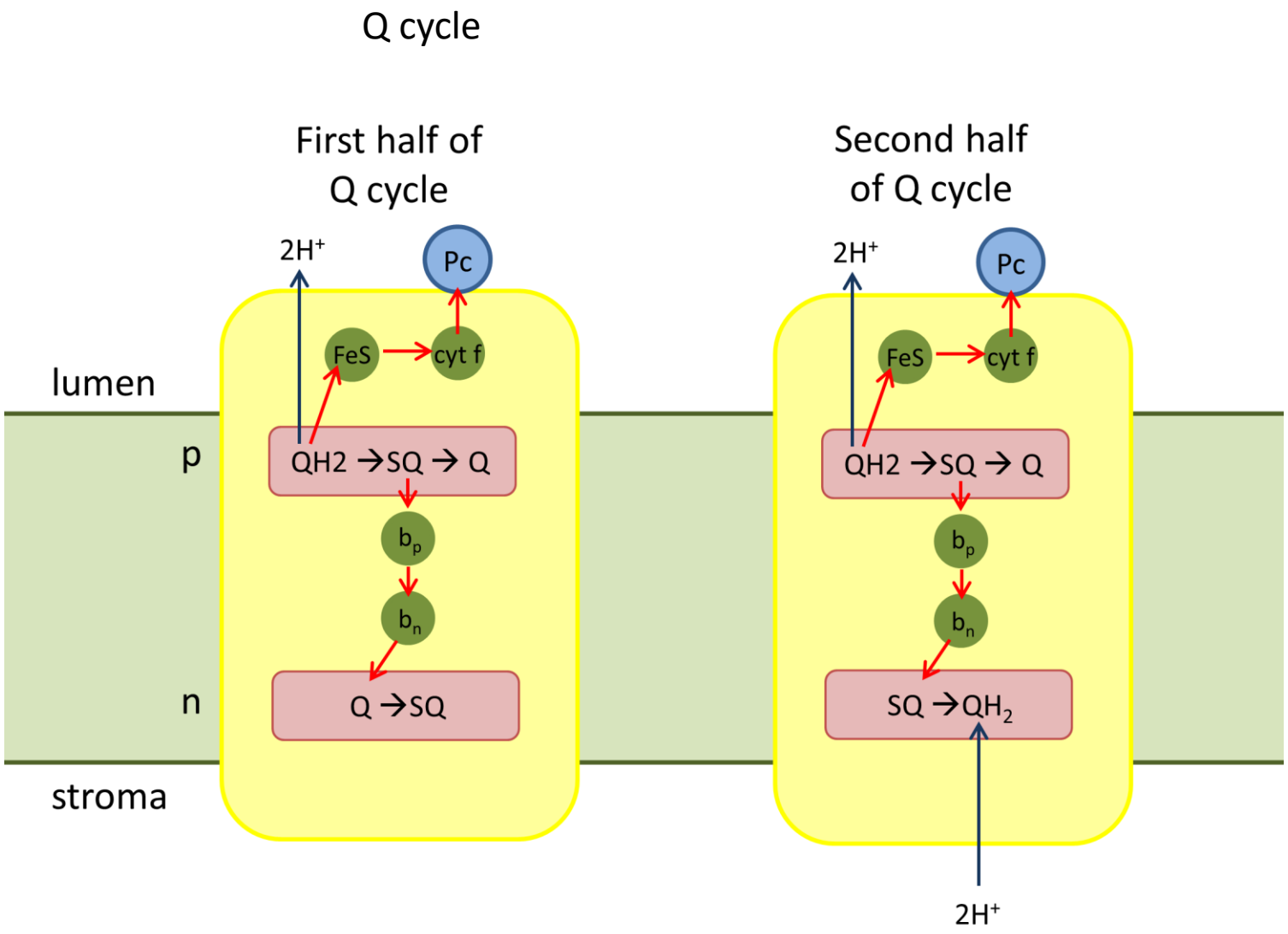
Oxidative phosphorylation




Q cycle
First half of Q cycle
Second half of Q cycle
2H+
Pc
FeS
cyt f
lumen
p
QH2 →SQ → Q
bp
bn
n
Q →SQ
SQ →QH2
stroma
2H+

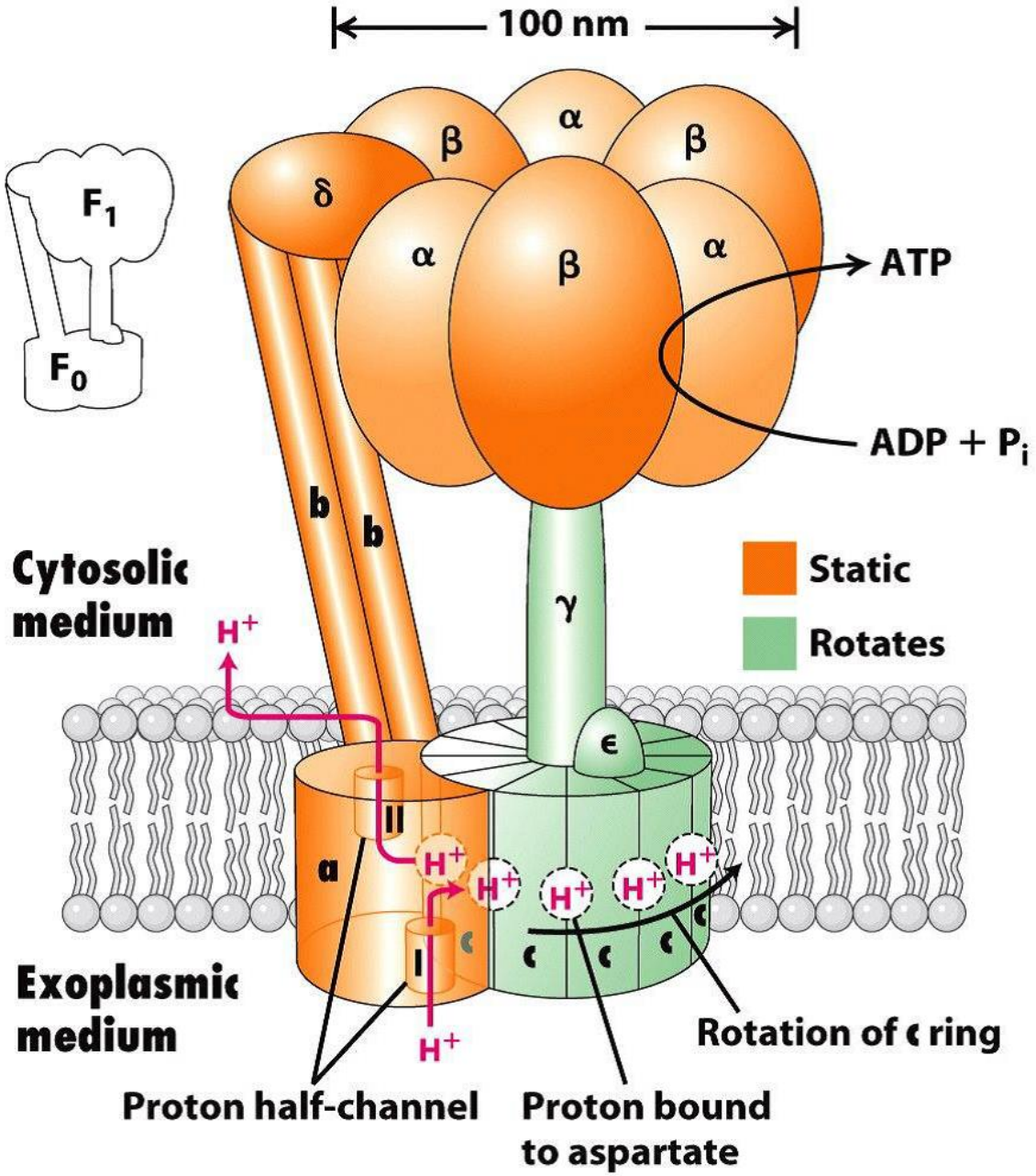


Figure 12-24
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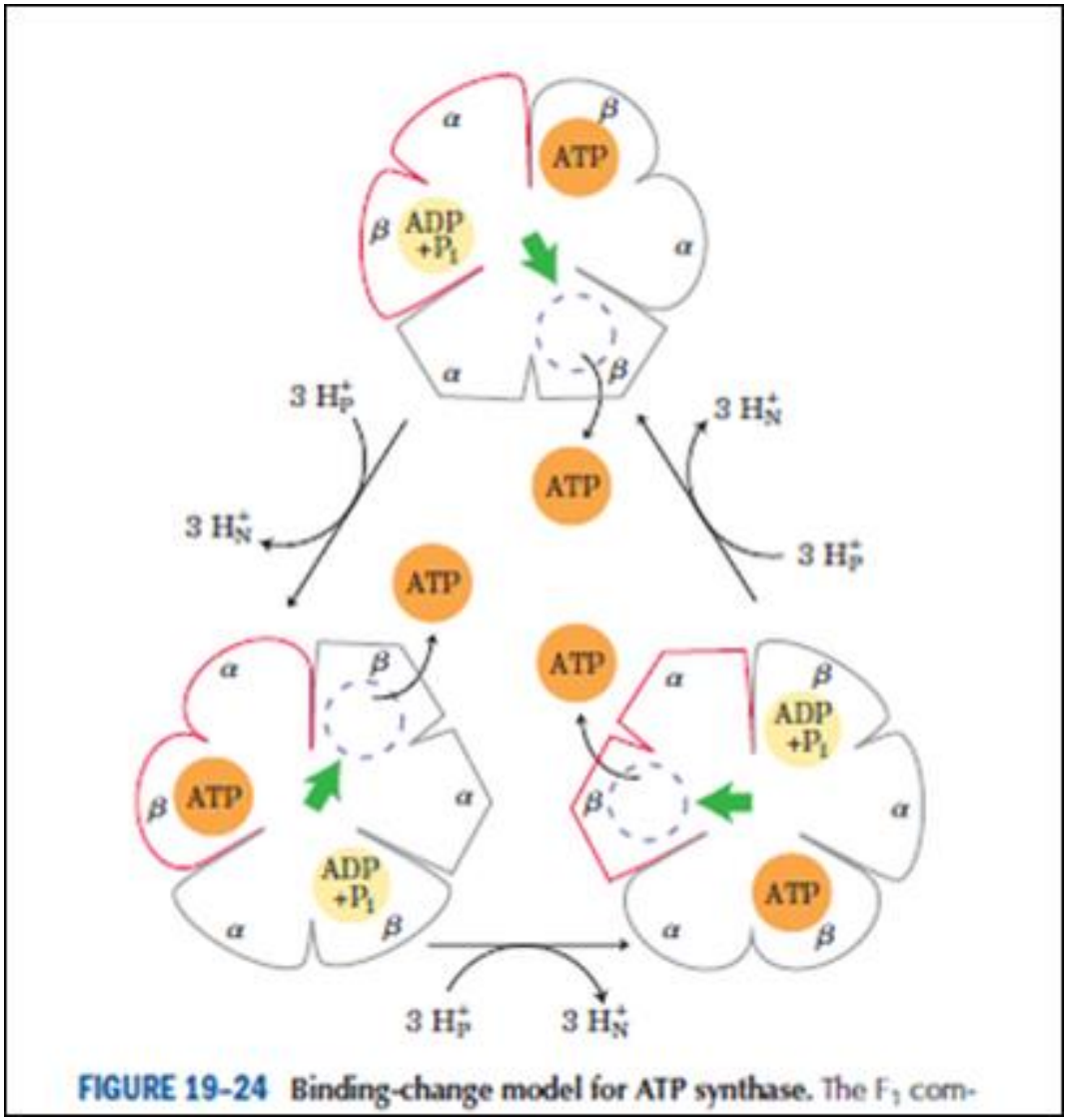

FIGURE 19–24 Binding-change model for ATP synthase. The F_1 com-

O->L->T