# 17 Fatty Acid Catabolism

# The Oxidation of Long-Chain Fatty Acids to Acetyl-CoA

- serves as a central energy-yielding pathway in many organisms and tissues
  - provides as much as 80% of the energetic needs in mammalian heart and liver
  - provides >40% of the daily energy requirement

- electrons removed from fatty acids during oxidation pass through the respiratory chain, driving ATP synthesis

- acetyl-CoA produced from the fatty acids may be completely oxidized to $CO_2$ in the citric acid cycle

# *β* Oxidation

- ***β* oxidation** = oxidation of the fatty acyl group at the C-3, or *β*, position—hence the name
  - occurs after the carboxyl group at C-1 is activated by attachment to coenzyme A

# P1 Principle 1 (1 of 5)

**Metabolites of diverse origin funnel into a few central pathways.** Fatty acid catabolism and glycolysis convert quite different starting materials into the same product (acetyl-CoA). The electrons from the oxidative reactions of these pathways and of the citric acid cycle are carried by common cofactors (NAD and FAD) to the mitochondrial respiratory chain leading to oxygen, providing the energy for ATP synthesis by oxidative phosphorylation.

# P2 Principle 2 (1 of 5)

**Evolution selects for chemical mechanisms that make useful reactions more energetically favorable, and those same mechanisms are used in different pathways.** In the breakdown of fatty acids, we see the activation of a carboxylic acid by its conversion to a thioester, as we saw with acetyl-CoA in the citric acid cycle. To break the C–C bonds in the long chain of relatively inert $–CH_2–CH_2–$ groups in fatty acids, a carbonyl group is created adjacent to the $–CH_2–$ group, as we saw in the reactions of the citric acid cycle.

# P3 Principle 3 (1 of 4)

**Allosteric mechanisms and posttranslational regulation (protein phosphorylation) coordinate metabolic processes within a cell. Hormones and growth factors coordinate metabolic activities among tissues and organs.** Reciprocal regulation of catabolic and anabolic pathways prevents the inefficiency of futile cycling.

# P4 Principle 4 (1 of 6)

**When a process lacks a critical component—an enzyme, a cofactor, or a regulatory agent—the resulting loss of homeostasis may cause disease across a spectrum of severity.** Defects in fatty acid breakdown are no exception.

# P5 Principle 5 (1 of 4)

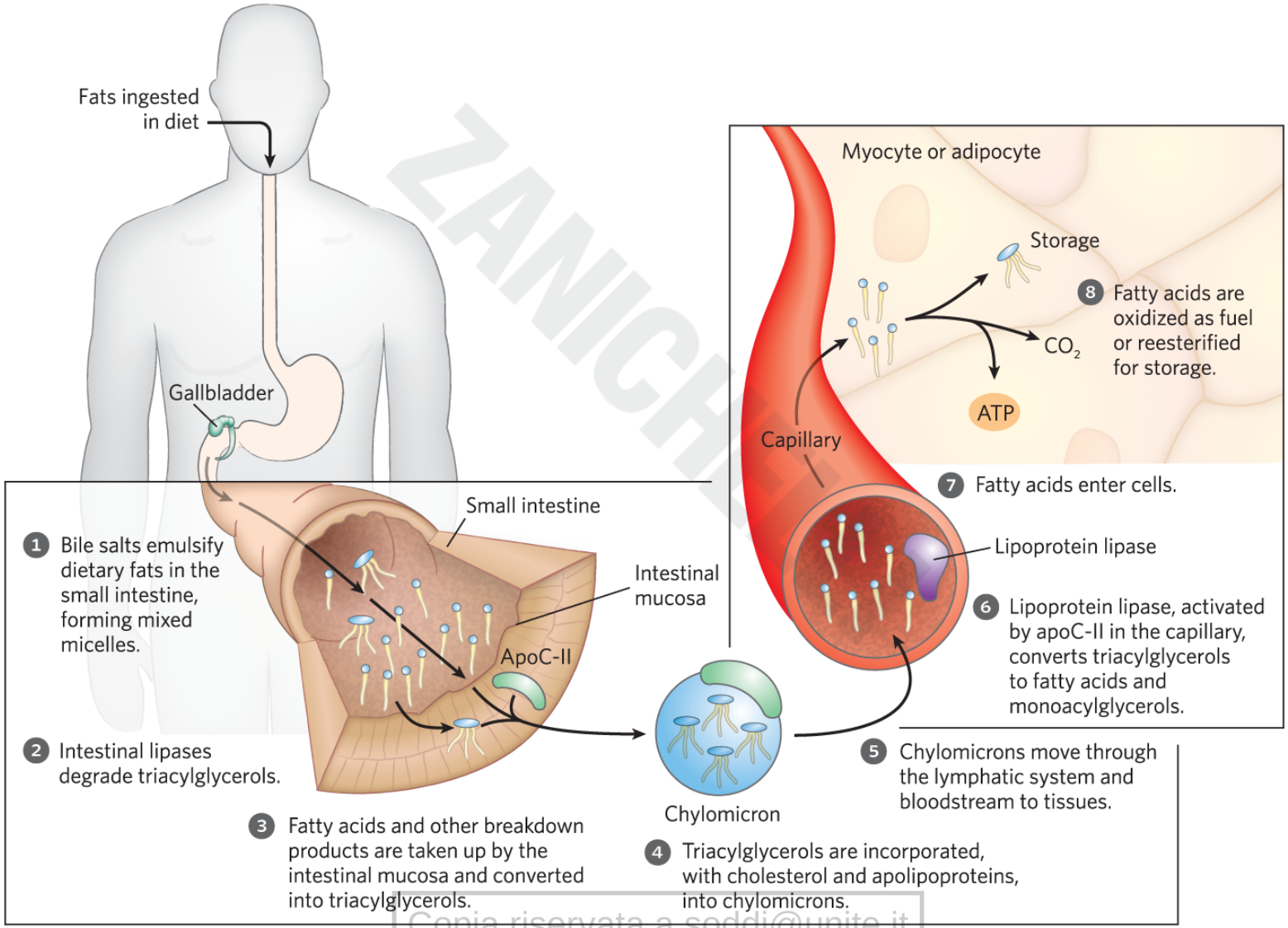
**The liver plays a unique role in whole-body metabolism.** When glucose is unavailable, the liver makes glucose by gluconeogenesis and releases it to the blood for distribution to other tissues, including the brain. During starvation, the liver processes fatty acids into ketone bodies, which, unlike fatty acids, can cross the blood brain barrier and fuel the brain.

# 17.1 Digestion, Mobilization, and Transport of Fats

# Sources of Fatty Acid Fuels

- cells can obtain fatty acid fuels from four sources:
  - fats consumed in the diet
  - fats stored in cells as lipid droplets
  - fats synthesized in one organ for export to another
  - fats obtained by autophagy

# Dietary Fats Are Absorbed in the Small Intestine

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# Chylomicron Formation

- **apolipoproteins** = proteins in their lipid-free form that bind lipids to form lipoproteins
  - target triacylglycerols, phospholipids, cholesterol, and cholesteryl esters for transport between organs

- **chylomicrons** = particles consisting of triacylglycerols, cholesterol, and apolipoproteins

# Lipoprotein Particles

- **lipoprotein particles** = spherical aggregates of apolipoproteins and lipids
  - arranged with hydrophobic lipids at the core and hydrophilic protein side chains and lipid head groups at the surface
  - various in densities depending on combinations of lipid and protein
    - range from chylomicrons and very-low-density lipoproteins (VLDL) to very-high-density lipoproteins (VHDL)

# Apolipoprotein B-48 (apoB-48) and Apolipoprotein C-II (apoC-II)

- **apolipoprotein B-48 (apoB-48)** = primary protein component of chylomicrons

- **apolipoprotein C-II (apoC-II)** = protein picked up in the blood by chylomicrons from **high-density lipoprotein (HDL)** particles

# Lipoprotein Lipase

- **lipoprotein lipase** = extracellular enzyme in the capillaries of muscle and adipose tissue that hydrolyzes triacylglycerols to free fatty acids and monoacylglycerols
  - activated by apoC-II

# P3 Principle 3 (2 of 4)

**Allosteric mechanisms and posttranslational regulation (protein phosphorylation) coordinate metabolic processes within a cell. Hormones and growth factors coordinate metabolic activities among tissues and organs.** Reciprocal regulation of catabolic and anabolic pathways prevents the inefficiency of futile cycling.

# Storage of Excess Fatty Acids

- fatty acids are converted to triacylglycerols in the liver
- triacylglycerols are packaged with specific apolipoproteins into VLDLs
- VLDLs are secreted and transported in the blood to adipose tissue
- triacylglycerols are removed and stored in lipid droplets within adipocytes in the adipose tissue

# Hormones Trigger Mobilization of Stored Triacylglycerols

- **lipid droplets** = organelles stored in adipocytes and steroid-synthesizing cells that contain neutral lipids
  - contain a core of triacylglycerols and sterol esters surrounded by a monolayer of phospholipids

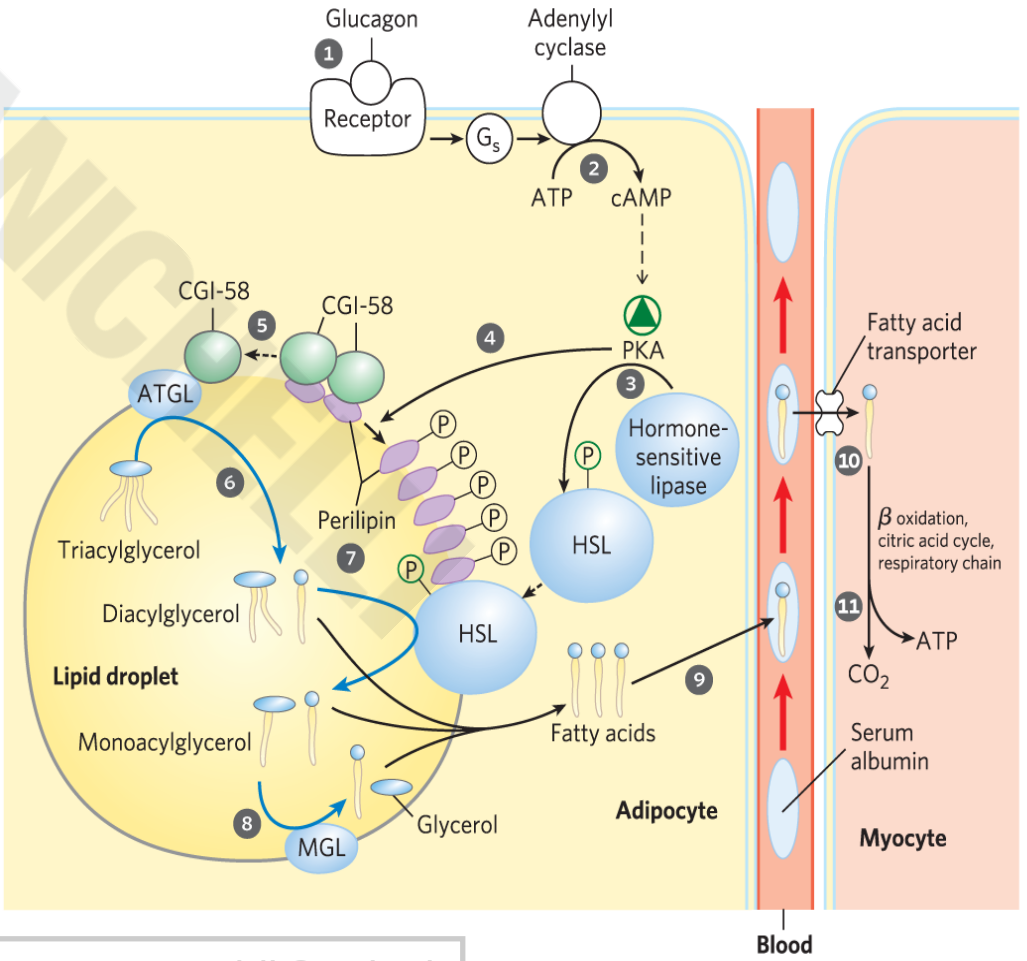
- **perilipins** = family of proteins that coats the surface of lipid droplets to restrict access to lipid droplets
  - prevent untimely lipid mobilization

# P1 Principle 1 (2 of 5)

**Metabolites of diverse origin funnel into a few central pathways.** Fatty acid catabolism and glycolysis convert quite different starting materials into the same product (acetyl-CoA). The electrons from the oxidative reactions of these pathways and of the citric acid cycle are carried by common cofactors (NAD and FAD) to the mitochondrial respiratory chain leading to oxygen, providing the energy for ATP synthesis by oxidative phosphorylation.

# Mobilization of Triacylglycerols Stored in Adipose Tissue

- mobilization occurs when hormones (glucagon and epinepherine) signal the need for metabolic energy
- PKA triggers changes that open the lipid droplet to the action of three cytosolic lipases

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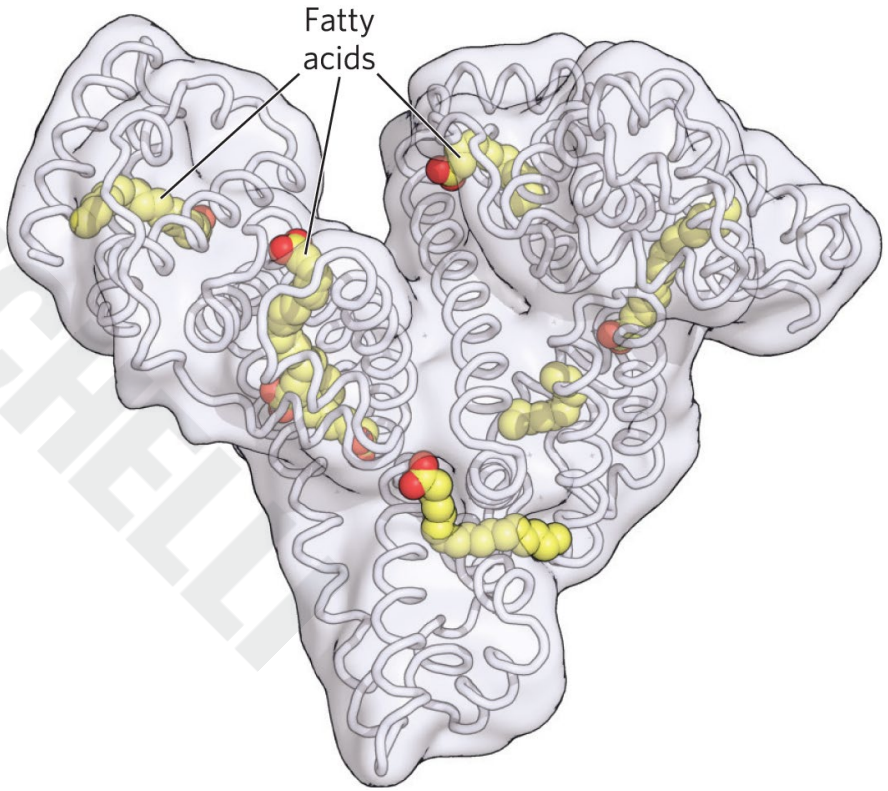
# Human Serum Albumin

- **free fatty acids, FFAs** = fatty acids released by lipases

- **serum albumin** = blood protein that noncovalently binds and transports FFAs to target tissues
  - makes up ~½ of the total serum protein

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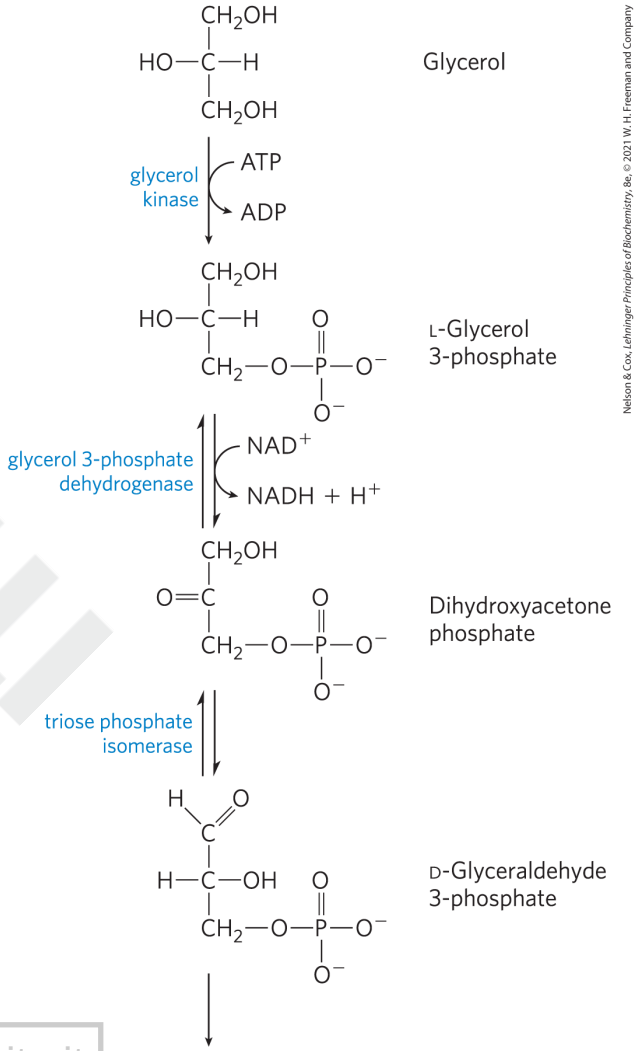
# Entry of Glycerol into the Glycolytic Pathway

- most of the biologically available energy of triacylglycerols resides in their three long-chain fatty acids
- **glycerol kinase** = phosphorylates glycerol to form glycerol 3-phosphate
- glyceraldehyde 3-phosphate can enter glycolysis

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# Fatty Acids Are Activated and Transported into Mitochondria

- small (< 12 carbons) fatty acids diffuse freely across mitochondrial membranes

- **carnitine shuttle** = transports long-chain fatty acids (containing 14+ carbons) through the mitochondrial membrane
  - requires activation to a fatty acyl-CoA and attachment to carnitine

# Fatty Acyl-CoA Synthetase

- **fatty acyl-CoA synthetase** = isozymes present in the outer mitochondrial membrane that activate the fatty acid by conversion to fatty acyl-CoA thioesters

fatty acid + CoA + ATP ⇄

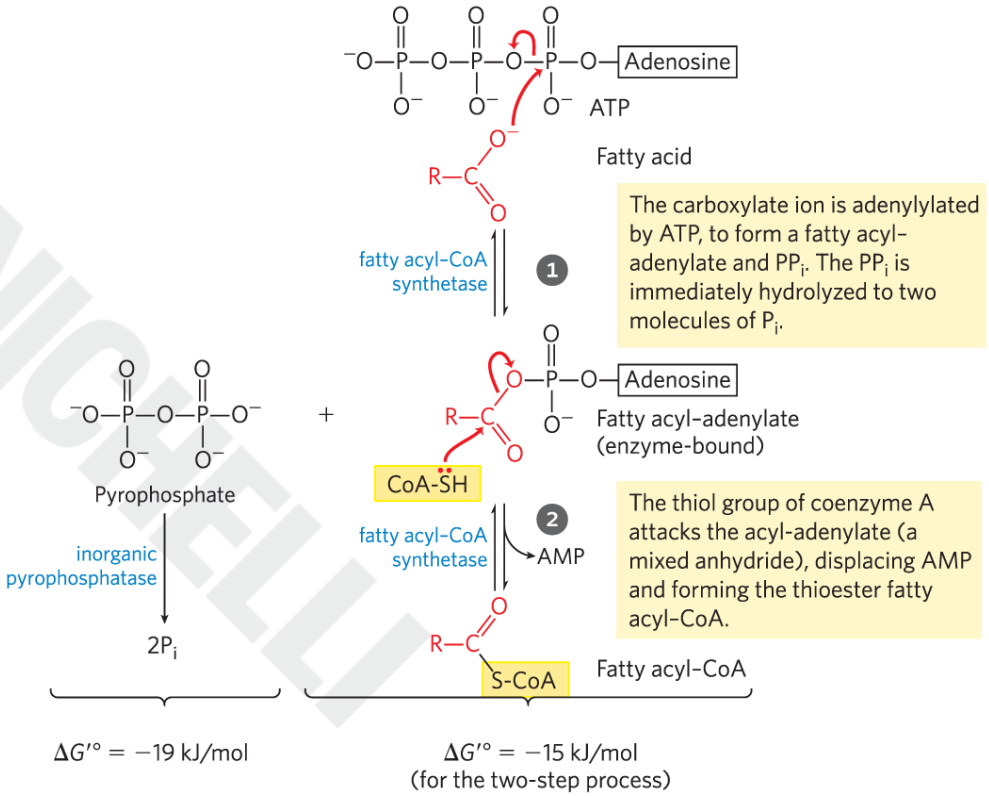
fatty acyl-CoA + AMP + $PP_i$

# P2 Principle 2 (2 of 5)

**Evolution selects for chemical mechanisms that make useful reactions more energetically favorable, and those same mechanisms are used in different pathways.** In the breakdown of fatty acids, we see the activation of a carboxylic acid by its conversion to a thioester, as we saw with acetyl-CoA in the citric acid cycle. To break the C–C bonds in the long chain of relatively inert $–CH_2–CH_2–$ groups in fatty acids, a carbonyl group is created adjacent to the $–CH_2–$ group, as we saw in the reactions of the citric acid cycle.

# Formation of a Fatty Acyl-CoA

- **fatty acyl-CoA** = contains a thioester linkage between the fatty acid carboxyl group and the thiol group of coenzyme A
  - high energy compound
  - formation is made more favorable by the hydrolysis of *two* ATP bonds

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# The Overall Reaction for Fatty Acyl-CoA Formation

- involves three steps:
  - the two-step formation of the fatty acyl-CoA derivative
  - the hydrolysis of the pyrophosphate created

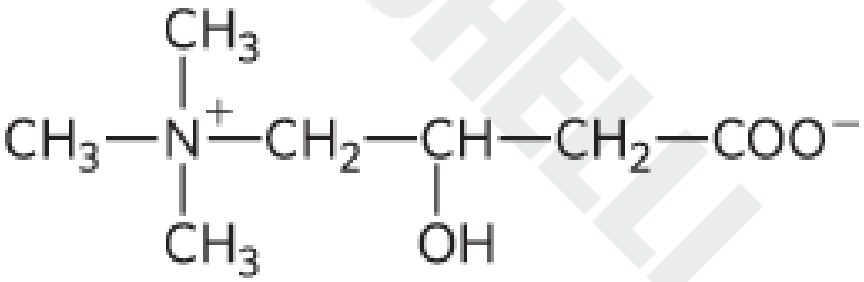
- the overall reaction is:

$$\text{fatty acid} + \text{CoA} + \text{ATP} \rightleftharpoons \text{fatty acyl-CoA} + \text{AMP} + 2P_i \qquad (17\text{-}1)$$

$$\Delta G'^{\circ} = -34 \text{ kJ/mol}$$

# Carnitine

- **carnitine** = compound that transports fatty acyl-CoAs destined for mitochondrial oxidation across the inner mitochondrial membrane



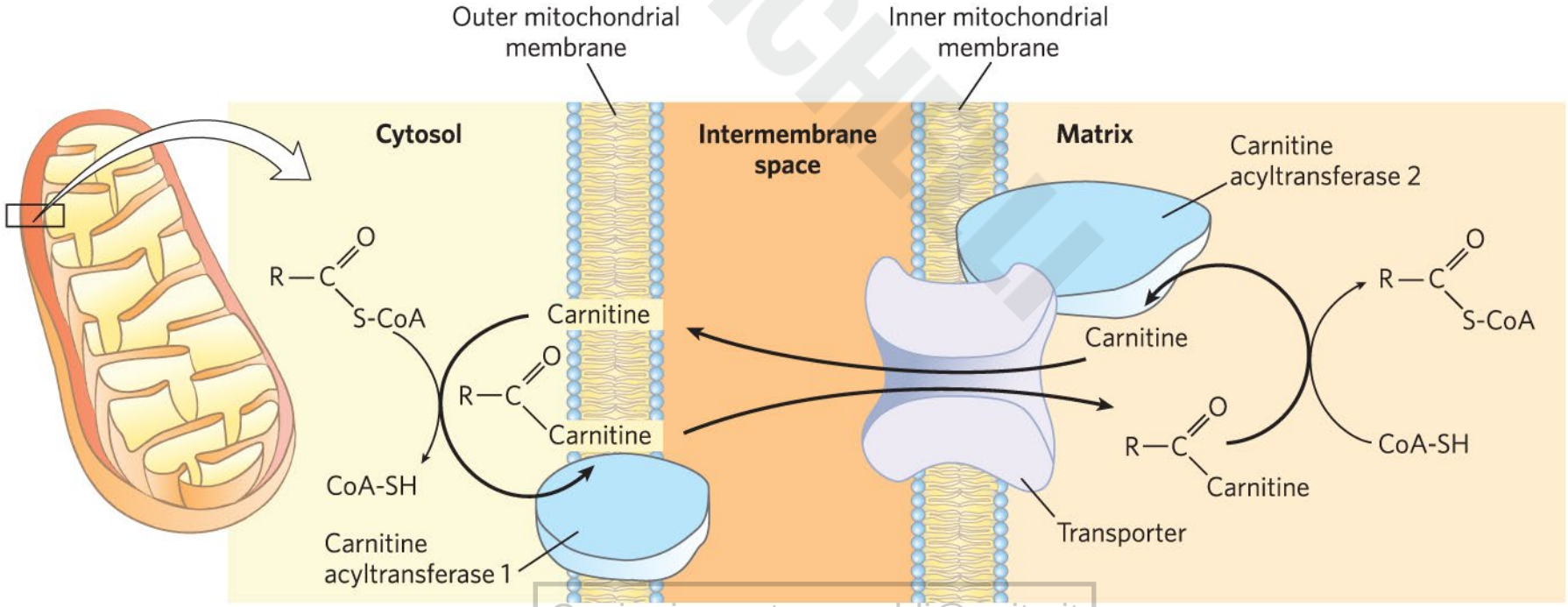

Carnitine

# Attachment of Carnitine to the Fatty Acyl-CoA

- **carnitine acyl-transferase 1, CAT1 (carnitine palmitoyltransferase 1, CPT1)** = catalyzes a transesterification reaction to transiently attach a fatty acyl-CoA to the hydroxyl group of carnitine to form fatty acyl-carnitine

# The Acyl-Carnitine/Carnitine Cotransporter

- **acyl-carnitine/carnitine cotransporter** = allows the passive transport of the fatty acyl-carnitine ester
  - moves one carnitine into the intermembrane space as one fatty acyl-carnitine moves into the matrix

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# Carnitine Acyltransferase 2 (CAT2)

- **carnitine acyltransferase 2 (CAT2, CPT2)** = transfers the fatty acyl group from carnitine back to coenzyme A to regenerate fatty acyl-CoA and free carnitine
  - located on the inner face of the inner mitochondrial membrane

# The Two Pools of Coenzyme A

- one pool is in the cytosol and the other is in mitochondria
- coenzyme A in the mitochondrial matrix is largely used in oxidative degradation of pyruvate, fatty acids, and some amino acids
- coenzyme A in the cytosol is used in the biosynthesis of fatty acids

# The Two Pools of Fatty Acyl-CoA

- one pool is in the cytosol and the other is in mitochondria
- fatty acyl-CoA in the mitochondrial matrix can be used for oxidation and ATP production
  - conversion to the carnitine ester commits it to oxidation
- fatty acyl–CoA in the cytosolic pool can be used for membrane lipid synthesis

# The Carnitine Shuttle Is a Major Control Point

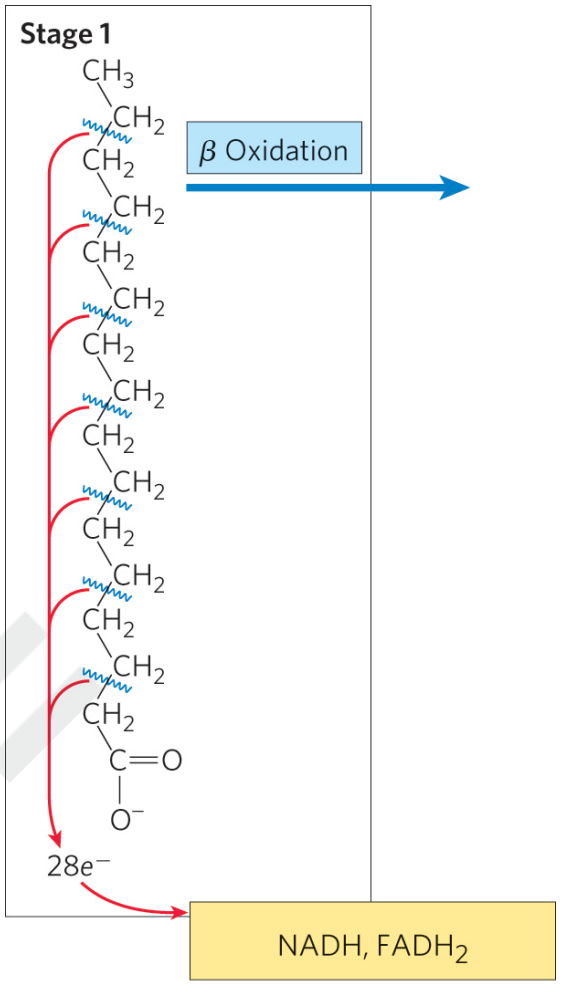
- carnitine-mediated entry is the rate-limiting step for oxidation of fatty acids in mitochondria

- carnitine acyltransferase 1 is inhibited by malonyl-CoA, the first intermediate in fatty acid synthesis
  - prevents the simultaneous synthesis and degradation of fatty acids

# 17.2 Oxidation of Fatty Acids

# Stage 1 of Fatty Acid Oxidation

- Stage 1: $\beta$ oxidation
  - fatty acids undergo oxidative removal of successive two-carbon units in the form of acetyl-CoA

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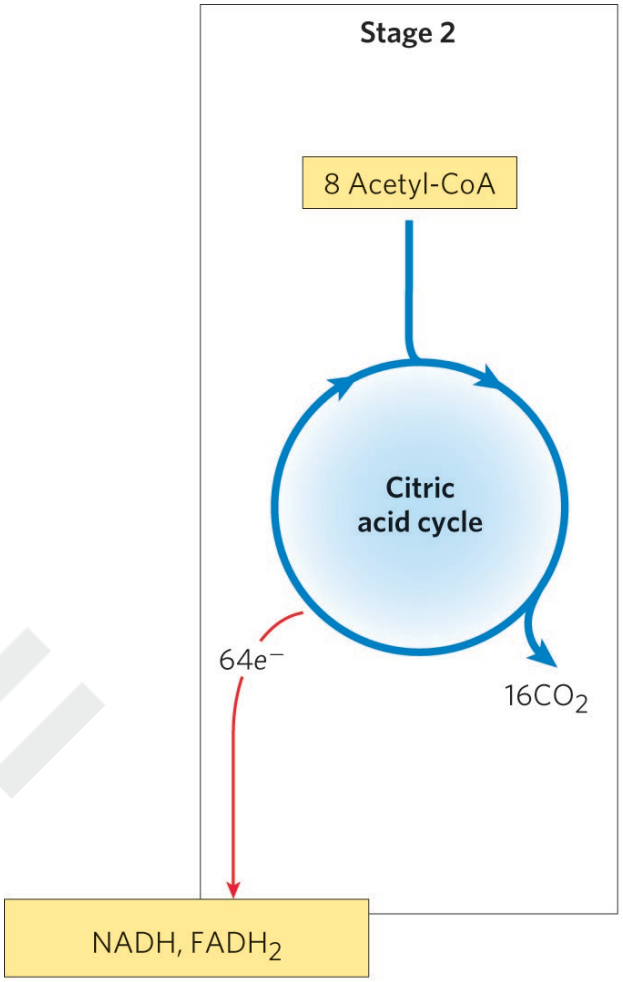
# Stage 2 of Fatty Acid Oxidation

- Stage 2: oxidation of acetyl-CoA groups to $CO_2$ in the citric acid cycle
  - occurs in the mitochondrial matrix
  - generates NADH, $FADH_2$, and one GTP

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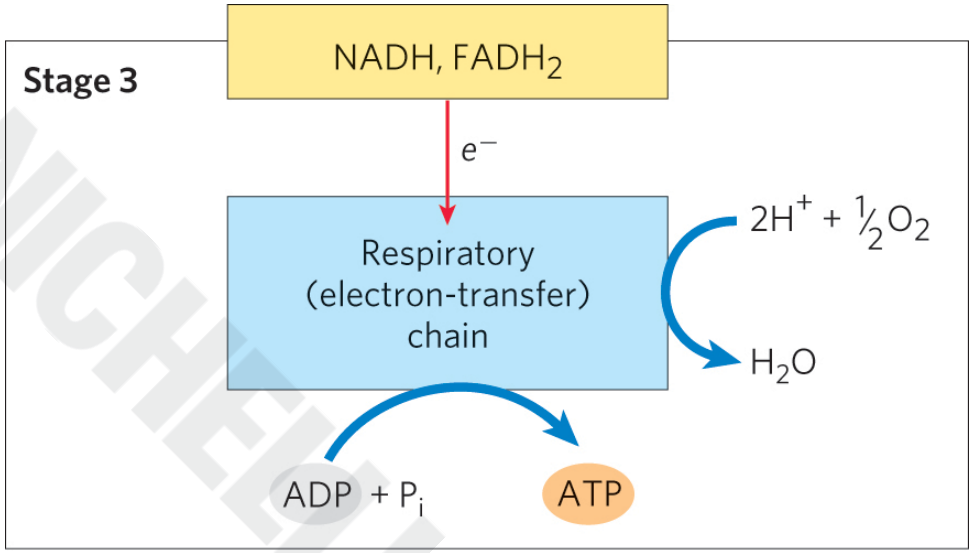
# Stage 3 of Fatty Acid Oxidation

- Stage 3: electron transfer chain and oxidative phosphorylation
  - generates ATP from NADH and $FADH_2$

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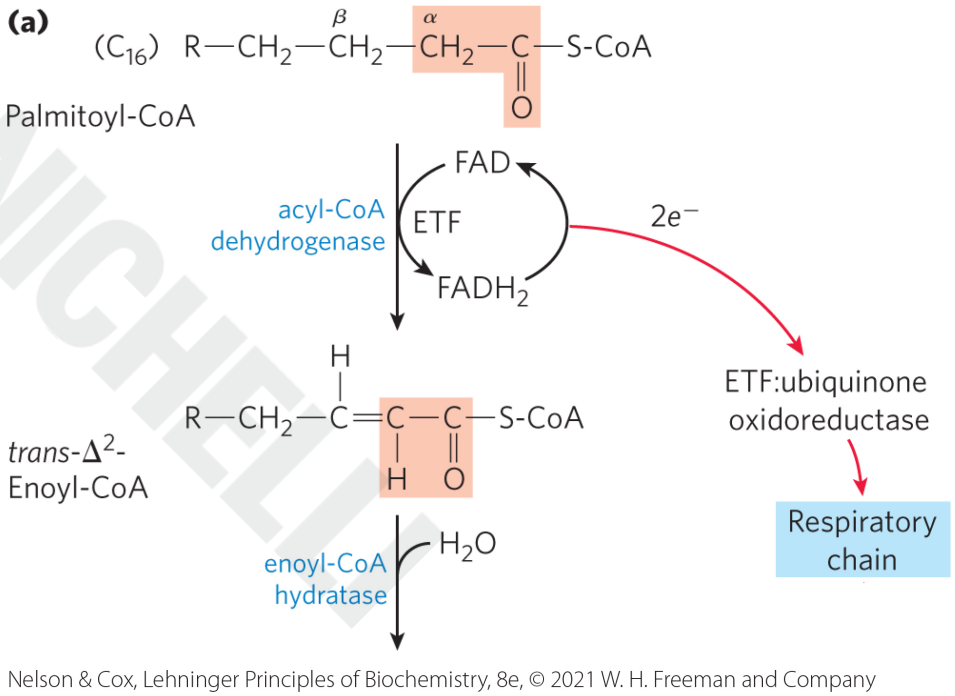
# The β Oxidation of Saturated Fatty Acids Has Four Basic Steps

- **acyl-CoA dehydrogenase** = flavoprotein with tightly bound FAD that catalyzes the dehydrogenation of fatty acyl-CoA to yield a ***trans*-$\Delta^2$-enoyl-CoA**

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# Acyl-CoA Dehydrogenase Isozymes

- isozymes are specific for fatty-acyl chain lengths:
  - VLCAD (inner mitochondrial matrix): 12-18 carbons
  - MCAD (matrix): 4-14 carbons
  - SCAD (matrix): 4-8 carbons

# Electrons from Fatty Acyl-CoA Enter the Mitochondrial Respiratory Chain

- **electron transfer flavoprotein (ETF)** = electron carrier that accepts electrons from $FADH_2$

- **ETF:ubiquinone oxidoreductase** = flavoprotein that accepts electrons from ETF
  - passes electrons through ubiquinone into the mitochondrial respiratory chain

# P2 Principle 2 (3 of 5)

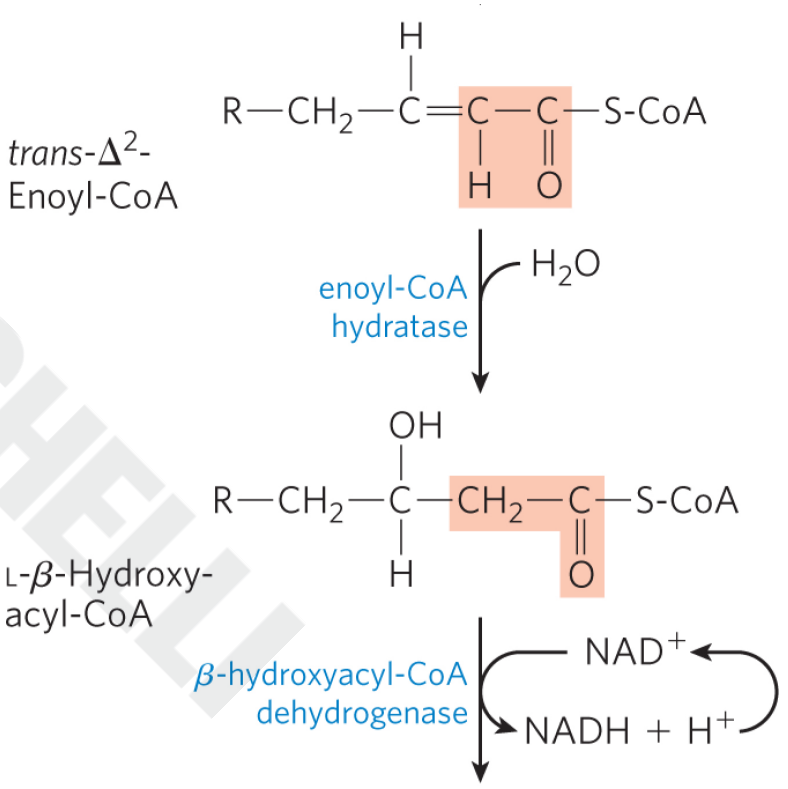
**Evolution selects for chemical mechanisms that make useful reactions more energetically favorable, and those same mechanisms are used in different pathways.** In the breakdown of fatty acids, we see the activation of a carboxylic acid by its conversion to a thioester, as we saw with acetyl-CoA in the citric acid cycle. To break the C–C bonds in the long chain of relatively inert $–CH_2–CH_2–$ groups in fatty acids, a carbonyl group is created adjacent to the $–CH_2–$ group, as we saw in the reactions of the citric acid cycle.

# The Oxidation Catalyzed by Acyl-CoA Dehydrogenase Is Analogous to Succinate Dehydrogenation

- in both reactions:
  - the enzyme is bound to the inner membrane
  - a double bond is introduced into a carboxylic acid between the *α* and *β* carbons
  - FAD is the electron acceptor
  - electrons from the reaction ultimately enter the respiratory chain and pass to $O_2$

# Hydration of the *Trans*-$\Delta^2$-Enoyl-CoA

- **enoyl-CoA hydratase** = catalyzes the addition of water to the double bond of the *trans*-$\Delta^2$-enoyl-CoA to form L-$\beta$-**hydroxyacyl-CoA (3-hydroxyacyl-CoA)**
  - formally analogous to the fumarase reaction in the citric acid cycle

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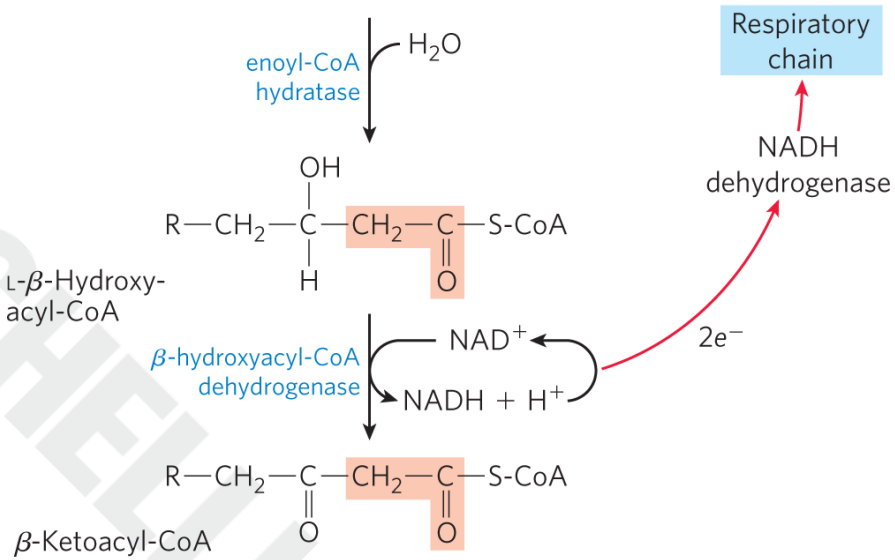
# Dehydration of L-β-Hydroxyacyl-CoA

- **β-hydroxyacyl-CoA dehydrogenase** = catalyzes the dehydrogenation of L-**β-hydroxyacyl-CoA** to form **β-ketoacyl-CoA**
  - enzyme is specific for the L stereoisomer
  - closely analogous to the malate dehydrogenase reaction of the citric acid cycle

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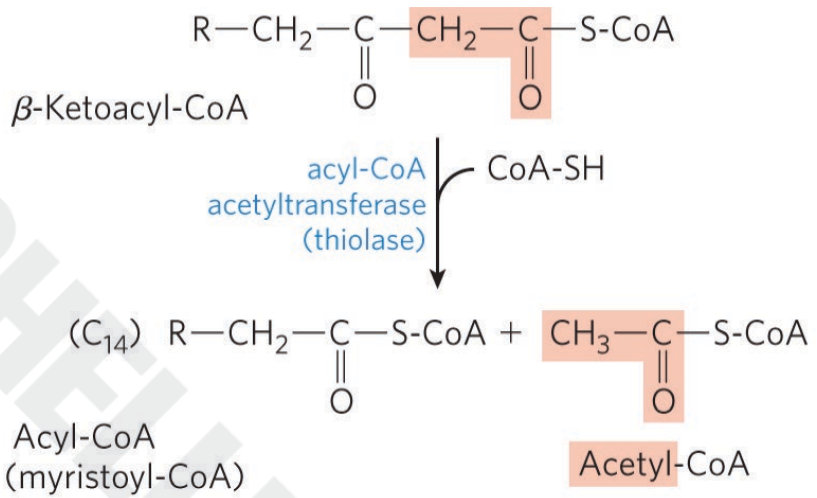
# Electrons from NADH Enter the Mitochondrial Respiratory Chain

- **NADH dehydrogenase (Complex I)** = electron carrier of the respiratory chain
  - accepts electrons from the NADH formed in the *β*-hydroxyacyl-CoA dehydrogenase reaction

# Cleavage of the β-Ketoacyl-CoA

- **acyl-CoA acetyl-transferase (thiolase) =** catalyzes the reaction of β-ketoacyl-CoA with free coenzyme A to yield acetyl CoA and a fatty acyl-CoA shortened by two carbons
  - reverse Claisen condensation

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# Trifunctional Protein (TFP)

- **trifunctional protein (TFP)** = a multienzyme complex associated with the inner mitochondrial membrane that catalyzes steps 2-4 of the *β*-oxidation pathway for fatty acyl chains of 12+ carbons
  - allows efficient substrate channeling

- TFP is a heterooctamer of $\alpha_4\beta_4$ subunits:
  - *α* subunits contain enoyl-CoA hydratase and β-hydroxyacyl-CoA dehydrogenase activity
  - *β* subunits contain thiolase activity

# P2 Principle 2 (5 of 5)

**Evolution selects for chemical mechanisms that make useful reactions more energetically favorable, and those same mechanisms are used in different pathways.** In the breakdown of fatty acids, we see the activation of a carboxylic acid by its conversion to a thioester, as we saw with acetyl-CoA in the citric acid cycle. To break the C–C bonds in the long chain of relatively inert $–CH_2–CH_2–$ groups in fatty acids, a carbonyl group is created adjacent to the $–CH_2–$ group, as we saw in the reactions of the citric acid cycle.

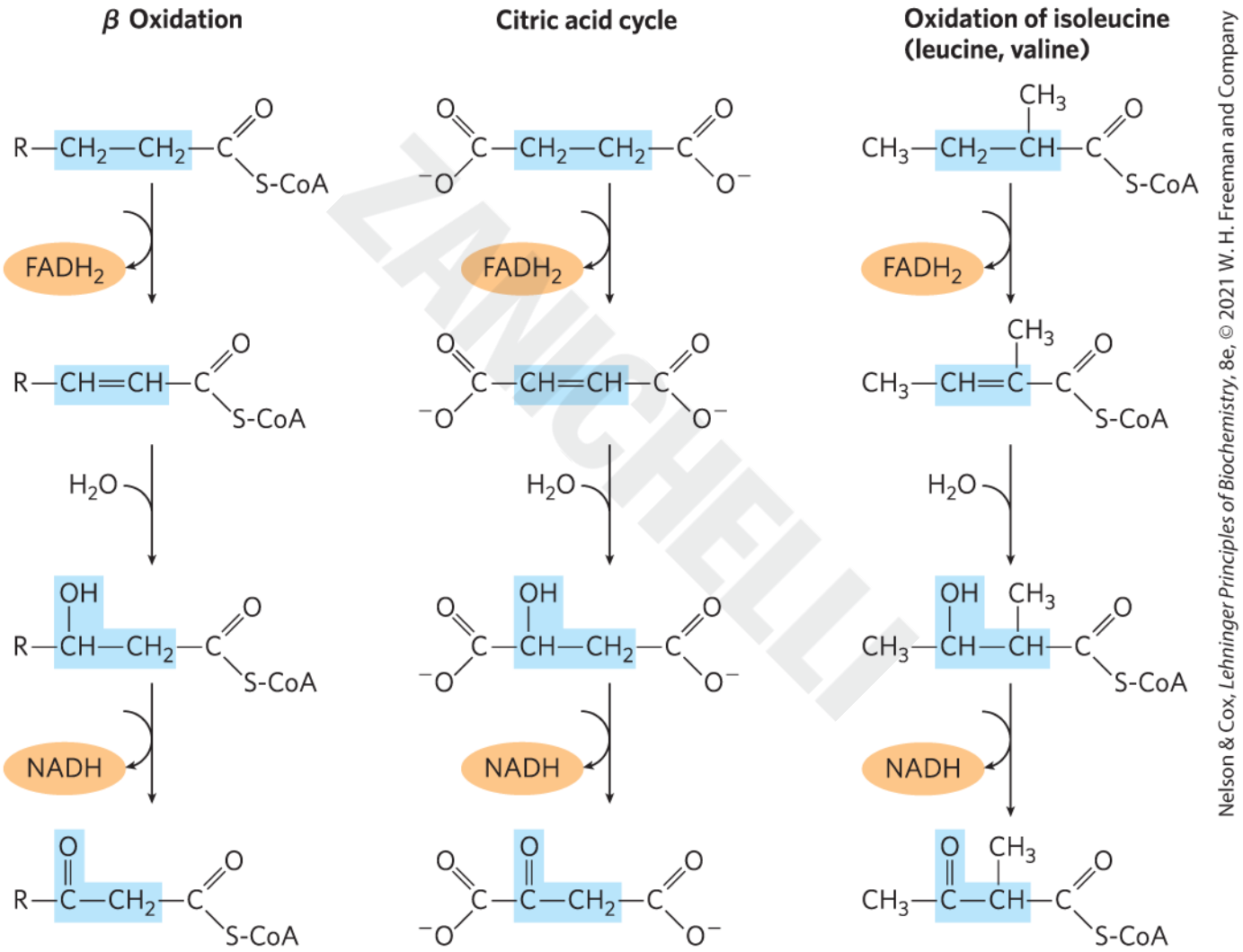
# The Chemical Logic of the β-Oxidation Sequence

- the first three reactions convert the stable single bond between methylene groups to a much less stable C–C bond

- the ketone function on the β carbon (C-3) makes it a good target for nucleophilic attack

- the terminal $–CH_2–CO–S$-CoA is a good leaving group, facilitating breakage of the α–β bond

# A Conserved Reaction Sequence

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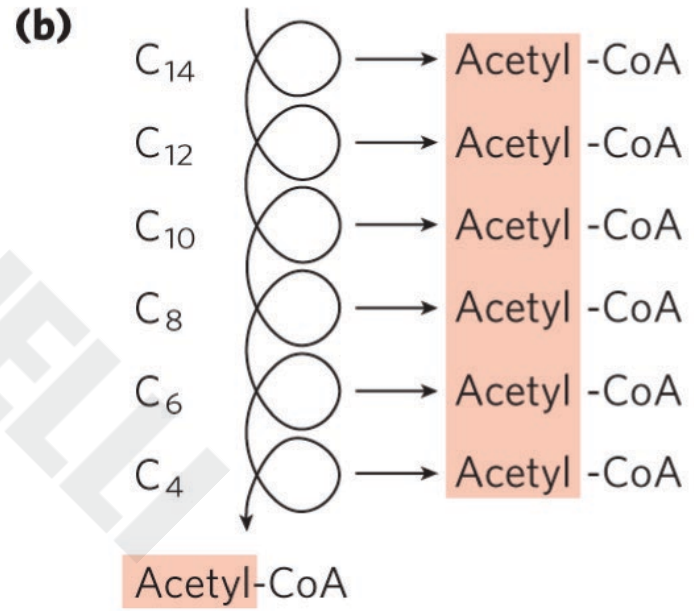
# The Four β-Oxidation Steps Are Repeated to Yield Acetyl-CoA and ATP

- the shortened fatty acyl–CoA reenters the β-oxidation sequence for removal of another, and then another, acetyl-CoA

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# The Overall Reaction for One Pass Through Stage 1 of β Oxidation

- each pass removes:
  - one molecule of acetyl-CoA
  - two pairs of electrons
  - four protons ($H^+$)

- the overall reaction (beginning with palmitoyl-CoA) is:

$$\text{palmitoyl-CoA} + \text{CoA} + \text{FAD} + \text{NAD}^+ + \text{H}_2\text{O} \longrightarrow \text{myristoyl-CoA} + \text{acetyl-CoA} + \text{FADH}_2 + \text{NADH} + \text{H}^+ \quad (17\text{-}2)$$

# The Overall Reaction for Stage 1 of β Oxidation

- the overall reaction (beginning with palmitoyl-CoA) is:

$$\text{palmitoyl-CoA} + 7\text{CoA} + 7\text{FAD} + 7\text{NAD}^+ + 7\text{H}_2\text{O} \longrightarrow 8\ \text{acetyl-CoA} + 7\text{FADH}_2 + 7\text{NADH} + 7\text{H}^+ \qquad (17\text{-}3)$$

# P1 Principle 1 (3 of 5)

**Metabolites of diverse origin funnel into a few central pathways.** Fatty acid catabolism and glycolysis convert quite different starting materials into the same product (acetyl-CoA). The electrons from the oxidative reactions of these pathways and of the citric acid cycle are carried by common cofactors (NAD and FAD) to the mitochondrial respiratory chain leading to oxygen, providing the energy for ATP synthesis by oxidative phosphorylation.

# $FADH_2$ and NADH Donate Electrons to the Respiratory Chain

- each $FADH_2$ donates a pair of electrons to ETF
  - generates 1.5 molecules of ATP
- each NADH donates a pair of electrons to the mitochondrial NADH dehydrogenase
  - generates 2.5 molecules of ATP
- in total, 4 ATP are formed for each pass through $\beta$ oxidation

# “Metabolic Water”

- each pair of electrons transferred from NADH or $FADH_2$ to $O_2$ yields one $H_2O$ (“metabolic water”)
- reduction of $O_2$ by NADH also consumes one $H^+$ per NADH molecule: $NADH + H^+ + ½O_2 \rightarrow NAD^+ + H_2O$
- important in hibernating animals and camels

Stouffer Productions/Animals Animals

# The Overall Reaction for Stage 1 of β Oxidation, Including Electron Transfers and Oxidative Phosphorylations

- the overall reaction is:

$$\text{palmitoyl-CoA} + 7\text{CoA} + 7\text{O}_2 + 28\text{P}_i + 28\text{ADP} \longrightarrow 8\ \text{acetyl-CoA} + 28\text{ATP} + 7\text{H}_2\text{O} \qquad (17\text{-}4)$$

# P1 Principle 1 (4 of 5)

**Metabolites of diverse origin funnel into a few central pathways.** Fatty acid catabolism and glycolysis convert quite different starting materials into the same product (acetyl-CoA). The electrons from the oxidative reactions of these pathways and of the citric acid cycle are carried by common cofactors (NAD and FAD) to the mitochondrial respiratory chain leading to oxygen, providing the energy for ATP synthesis by oxidative phosphorylation.

# Acetyl-CoA Can Be Further Oxidized in the Citric Acid Cycle

- acetyl-CoA produced from the oxidation of fatty acids can be oxidized to $CO_2$ and $H_2O$ by the citric acid cycle

- the overall reaction for the second and third stages of fatty acid oxidation (in the oxidation of palmitoyl-CoA) is:

$$8\ \text{acetyl-CoA} + 16O_2 + 80P_i + 80\text{ADP} \longrightarrow 8\text{CoA} + 80\text{ATP} + 16CO_2 + 16H_2O \qquad (17\text{-}5)$$

# The Overall Reaction for the Complete Oxidation of Palmitoyl-CoA to $CO_2$ and $H_2O$

- the overall reaction is:

$$\text{palmitoyl-CoA} + 23O_2 + 108P_i + 108\text{ADP} \longrightarrow \text{CoA} + 108\text{ATP} + 16CO_2 + 23H_2O \qquad (17\text{-}6)$$

# ATP Yield During Complete Oxidation of Palmitoyl-CoA

**Table 17-1 Yield of ATP during Oxidation of One Molecule of Palmitoyl-CoA to $CO_2$ and $H_2O$**

| Enzyme catalyzing the oxidation step | Number of NADH or $FADH_2$ formed | Number of ATP ultimately formed |
|---|---|---|
| ***β* Oxidation** | | |
| Acyl-CoA dehydrogenase | 7 $FADH_2$ | 10.5 |
| *β*-Hydroxyacyl-CoA dehydrogenase | 7 NADH | 17.5 |
| **Citric acid cycle** | | |
| Isocitrate dehydrogenase | 8 NADH | 20 |
| *α*-Ketoglutarate dehydrogenase | 8 NADH | 20 |
| Succinyl-CoA synthetase | | 8 |
| Succinate dehydrogenase | 8 $FADH_2$ | 12 |
| Malate dehydrogenase | 8 NADH | 20 |
| Total | | 108 |

# P1 Principle 1 (5 of 5)

**Metabolites of diverse origin funnel into a few central pathways.** Fatty acid catabolism and glycolysis convert quite different starting materials into the same product (acetyl-CoA). The electrons from the oxidative reactions of these pathways and of the citric acid cycle are carried by common cofactors (NAD and FAD) to the mitochondrial respiratory chain leading to oxygen, providing the energy for ATP synthesis by oxidative phosphorylation.

# Oxidation of Unsaturated Fatty Acids Requires Two Additional Reactions

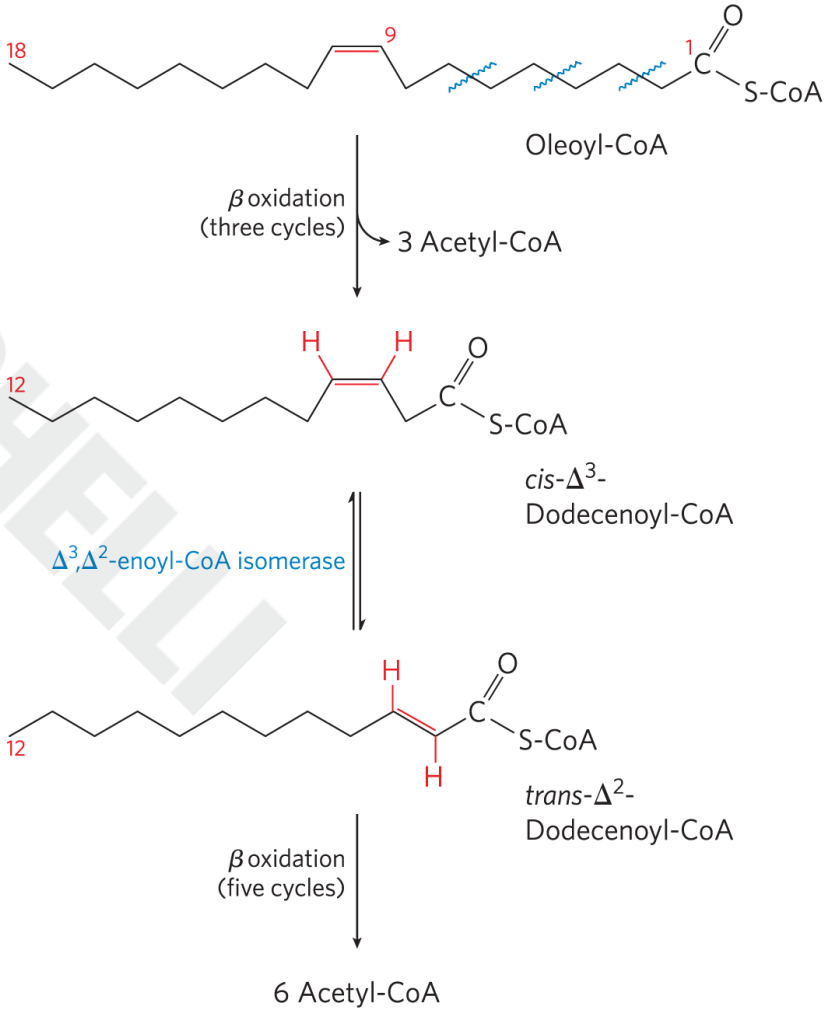
- enoyl-CoA hydratase cannot catalyze the addition of $H_2O$ to a cis double bond

- oxidation of unsaturated fatty acids requires two additional enzymes:
  - enoyl-CoA isomerase (converts cis double bonds to trans)
  - 2,4-dienoyl-CoA reductase (reduces cis double bonds)

# Oxidation of a Monounsaturated Fatty Acid

- oxidation of a monounsaturated fatty acid requires an enoyl-CoA isomerase

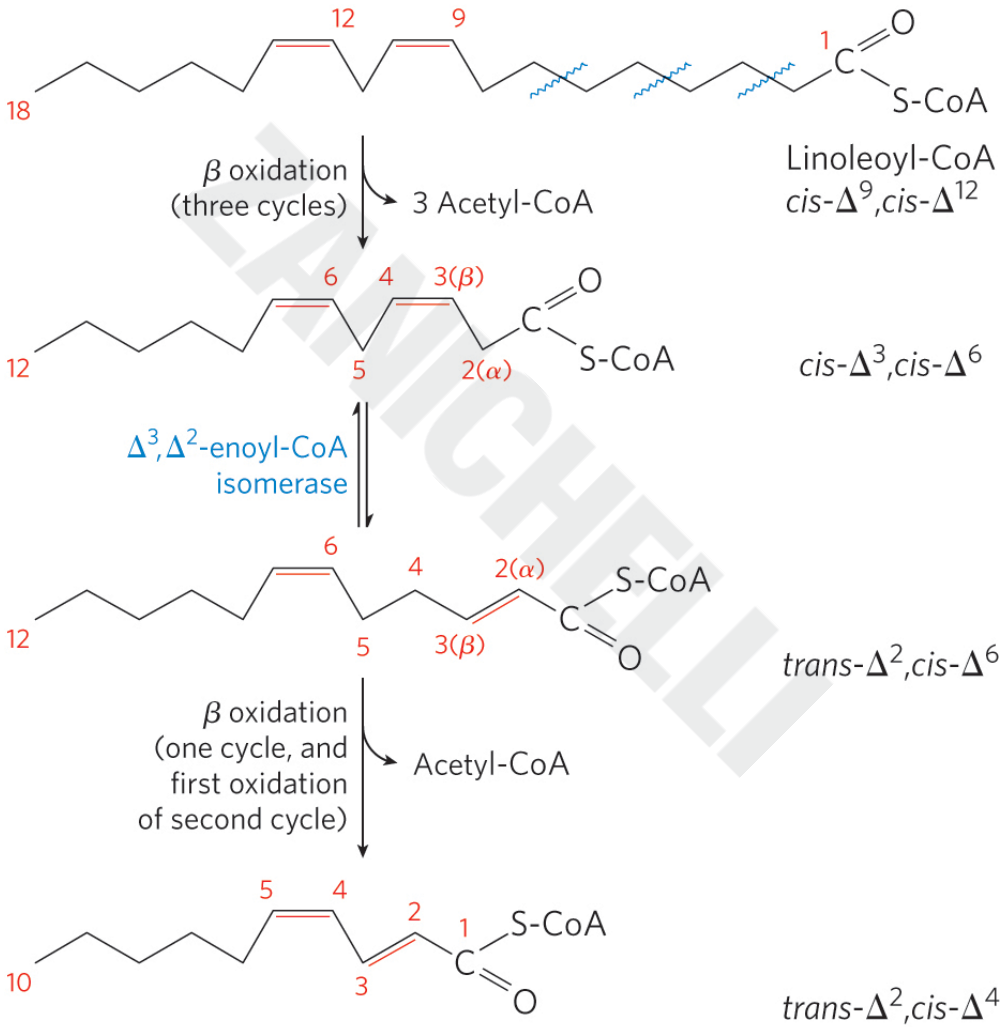
- **$\Delta^3,\Delta^2$- enoyl-CoA isomerase** = isomerizes the *cis*-$\Delta^3$-enoyl-CoA to the *trans*-$\Delta^2$-enoyl-CoA



# Oxidation of a Polyunsaturated Fatty Acid

- requires both enoyl-CoA isomerase and **2,4-dienoyl-CoA reductase** to transform the *cis*-$\Delta^3$,*cis*-$\Delta^6$ intermediate into one that can enter the $\beta$-oxidation pathway

# Oxidation of Linoleoyl-CoA ($\Delta^{9,12}$)

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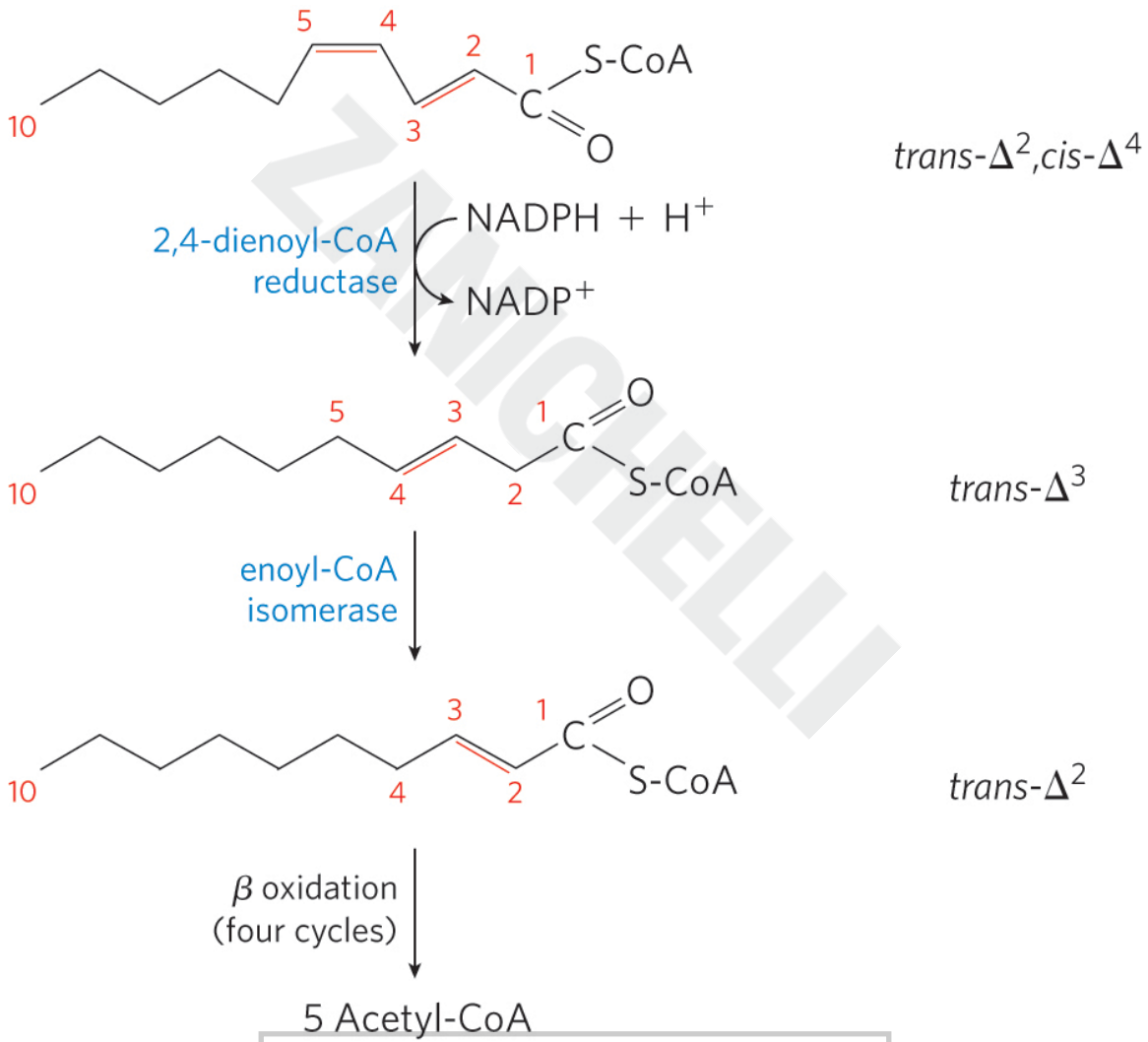
# Oxidation of Linoleoyl-CoA ($\Delta^{9,12}$), Continued



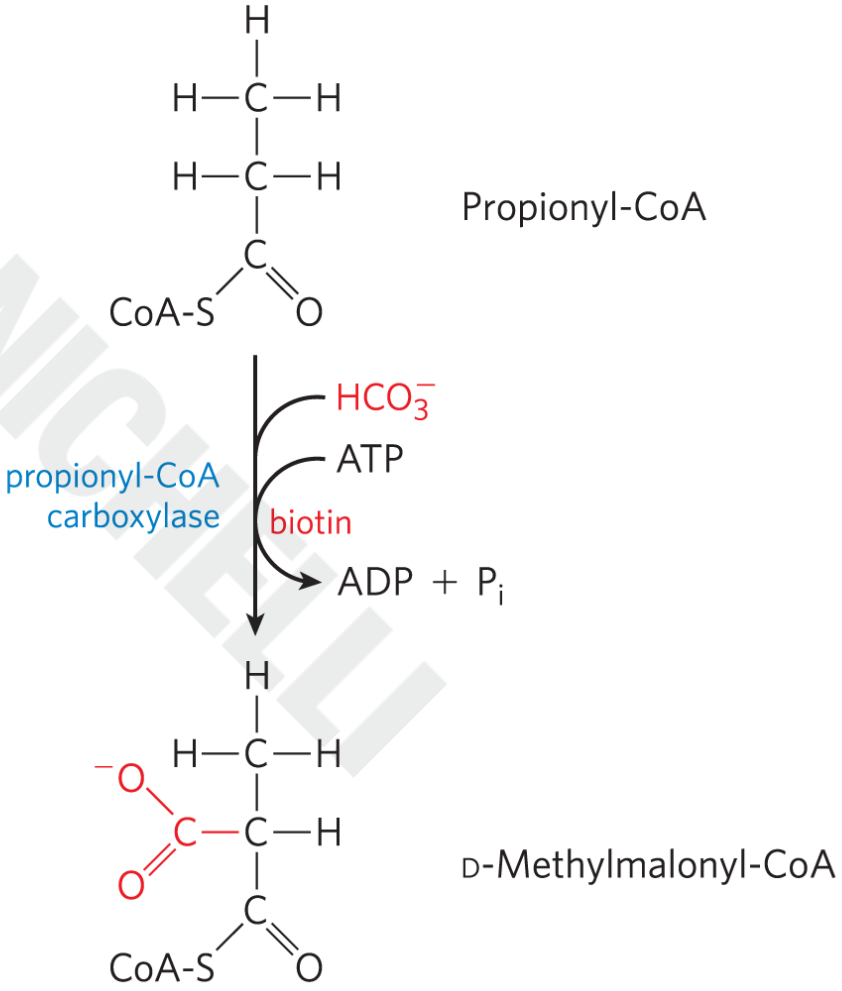
# Complete Oxidation of Odd-Number Fatty Acids Requires Three Extra Reactions

- **propionate** ($CH_3–CH_2–COO^-$) = three-carbon compounds formed by cattle and other ruminant animals during carbohydrate fermentation

- odd-number fatty acids are oxidized by the *β*-oxidation pathway to yield acetyl-CoA and a molecule of **propionyl-CoA**

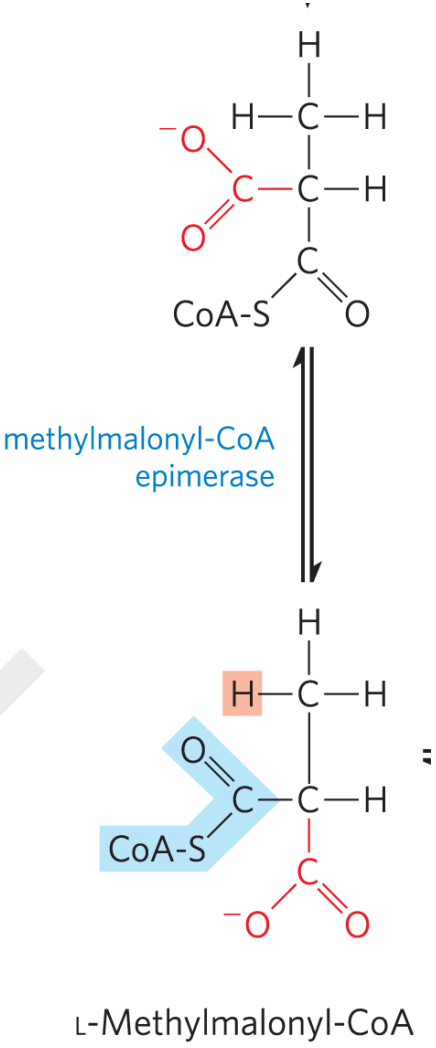
# Oxidation of Propionyl-CoA – Step 1

- **propionyl-CoA carboxylase** = catalyzes the carboxylation of propionyl-CoA to form **D-methylmalonyl-CoA**
  - requires the cofactor biotin



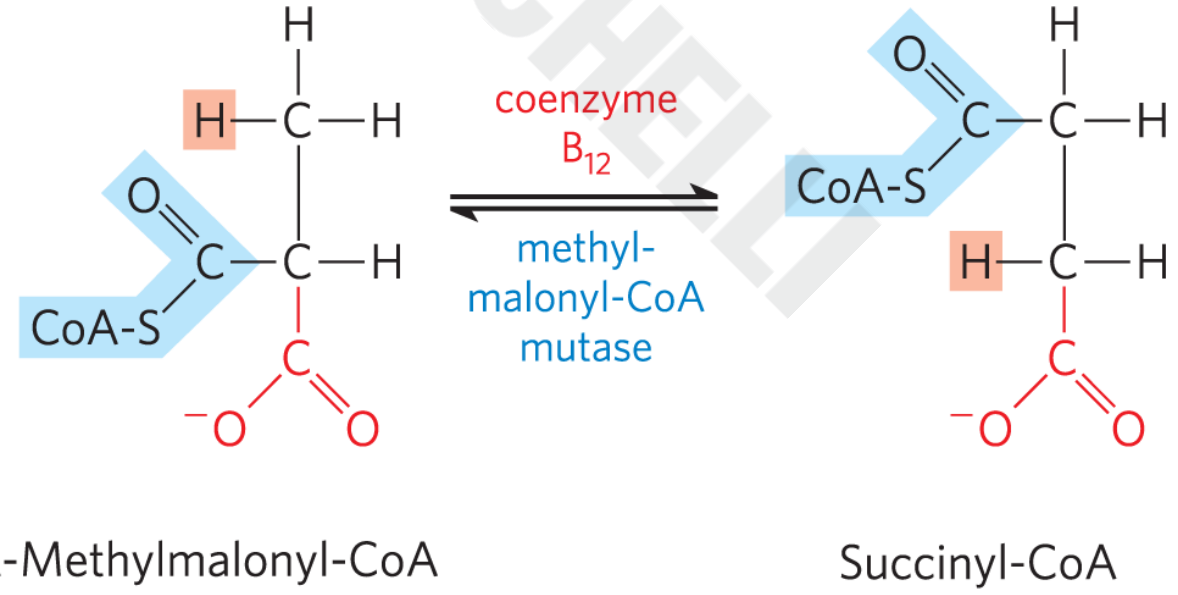
# Oxidation of Propionyl-CoA – Step 2

- **methylmalonyl-CoA epimerase** = catalyzes the epimerization of D-methylmalonyl-CoA to its L stereoisomer



# Oxidation of Propionyl-CoA – Step 3

- **methylmalonyl-CoA mutase** = catalyzes the intramolecular rearrangement of L-methylmalonyl-CoA to form succinyl-CoA (which can enter the citric acid cycle)
  - requires **5′-deoxyadenosylcobalamin**, or **coenzyme $B_{12}$**, as its coenzyme



# P4 Principle 4 (2 of 6)

**When a process lacks a critical component—an enzyme, a cofactor, or a regulatory agent—the resulting loss of homeostasis may cause disease across a spectrum of severity.** Defects in fatty acid breakdown are no exception.

# Deficiencies in Propionyl-CoA Carboxylase

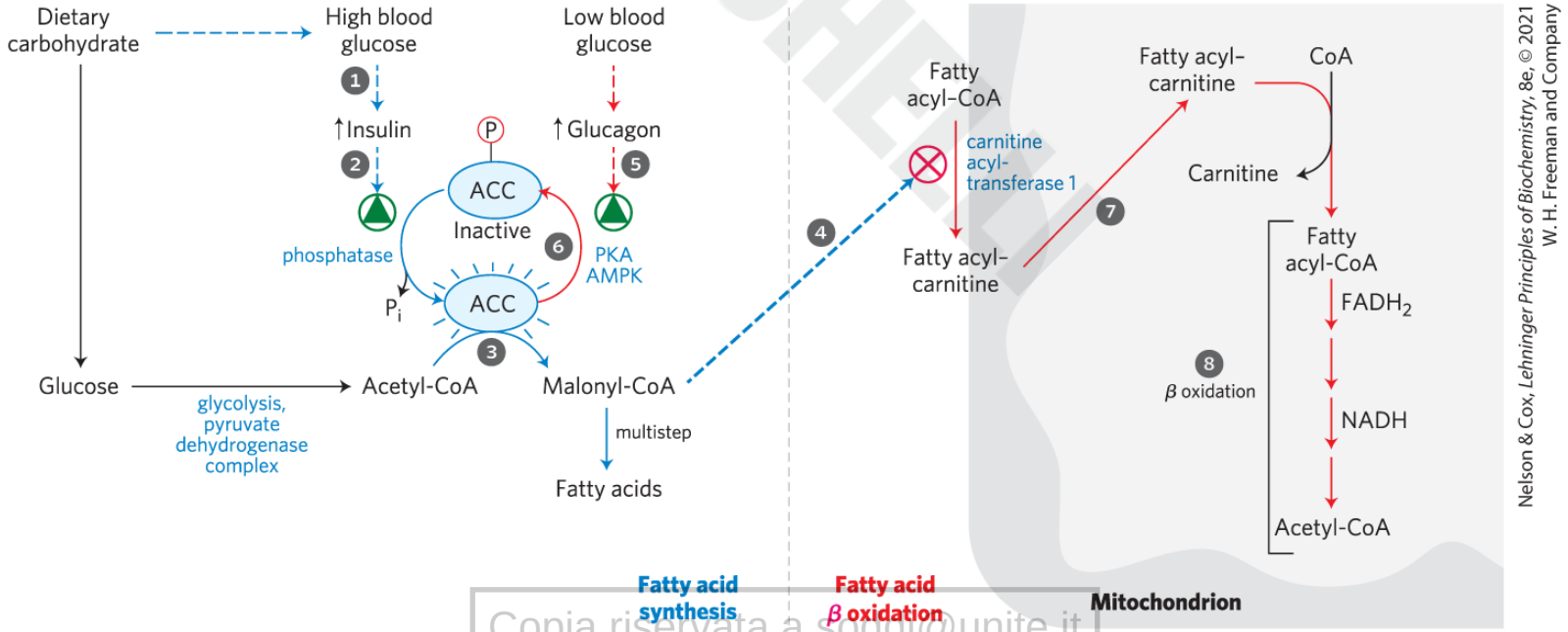
- occurs in ~ 1 in 100,000 babies
- propionic acidemia = severe acidification of the blood and urine resulting from accumulated propionyl-CoA in the mitochondria being released to the blood as propionate
  - uses the carnitine shuttle

# P3 Principle 3 (3 of 4)

**Allosteric mechanisms and posttranslational regulation (protein phosphorylation) coordinate metabolic processes within a cell. Hormones and growth factors coordinate metabolic activities among tissues and organs.** Reciprocal regulation of catabolic and anabolic pathways prevents the inefficiency of futile cycling.

# Fatty Acid Oxidation Is Tightly Regulated

- **malonyl-CoA** = the first intermediate of cytosolic fatty acid synthesis
  - blocks entry of fatty acids into mitochondria to prevent futile cycling



# P3 Principle 3 (4 of 4)

**Allosteric mechanisms and posttranslational regulation (protein phosphorylation) coordinate metabolic processes within a cell. Hormones and growth factors coordinate metabolic activities among tissues and organs.** Reciprocal regulation of catabolic and anabolic pathways prevents the inefficiency of futile cycling.

# Transcription Factors Turn on the Synthesis of Proteins for Lipid Catabolism

- **PPAR** family of nuclear receptors = transcription factors that affect many metabolic processes in response to a variety of fatty acid–like ligands

- PPAR*α* stimulates the synthesis of enzymes required in *β* oxidation when there is an increased demand for energy from fat catabolism

# P4 Principle 4 (3 of 6)

**When a process lacks a critical component—an enzyme, a cofactor, or a regulatory agent—the resulting loss of homeostasis may cause disease across a spectrum of severity.** Defects in fatty acid breakdown are no exception.

# Genetic Defects in Fatty Acyl-CoA Dehydrogenases Cause Serious Disease

- **medium-chain acyl-CoA dehydrogenase (MCAD)** = acyl-CoA dehydrogenase isozyme that acts on fatty acids of 4-14 carbons

- individuals with two mutant MCAD alleles cannot oxidize fatty acids of 6-12 carbons
  - symptoms include fatty liver, high blood levels of octanoic acid (8:0), coma, and death

# P4 Principle 4 (4 of 6)

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# Other Genetic Defects in Fatty Acid Transport or Oxidation

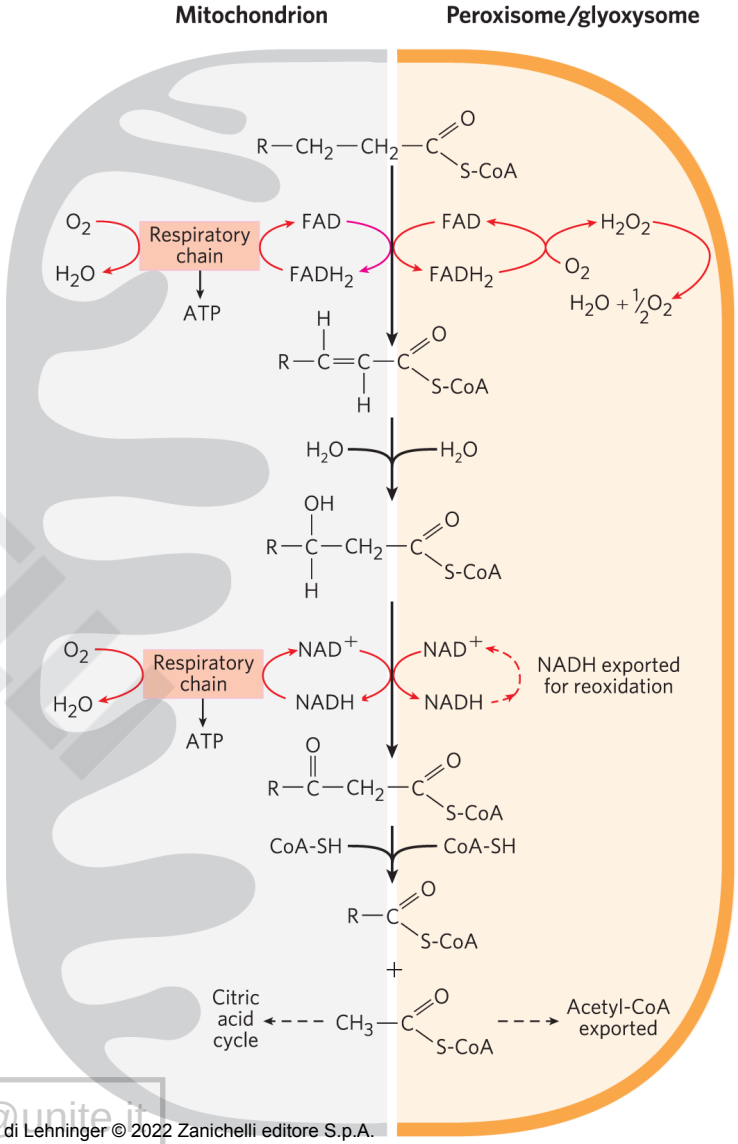
- loss of the long-chain *β*-hydroxyacyl-CoA dehydrogenase activity of the trifunctional protein, TFP

- defects in the *α* or *β* subunits that affect all three activities of TFP

# Peroxisomes Also Carry Out β Oxidation

- **peroxisomes** = organelles found in plants and animals

- β oxidation in peroxisomes has four steps:
  - dehydrogenation
  - addition of water to the resulting double bond
  - oxidation of the β-hydroxyacyl-CoA to a ketone
  - thiolytic cleavage by coenzyme A



# Differences Between the Peroxisomal and Mitochondrial Pathways

- in peroxisomes, the flavoprotein acyl-CoA oxidase that introduces the double bond passes electrons directly to $O_2$, producing $H_2O_2$
  - the enzyme **catalase** cleaves $H_2O_2$ to $H_2O$ and $O_2$

- the peroxisomal system is much more active on very-long-chain fatty acids and branched-chain fatty acids

# P4 Principle 4 (5 of 6)

**When a process lacks a critical component—an enzyme, a cofactor, or a regulatory agent—the resulting loss of homeostasis may cause disease across a spectrum of severity.** Defects in fatty acid breakdown are no exception.

# Genetic Defects in Peroxisomal Oxidation

- **Zellwger syndrome** = characterized by an inability to make peroxisomes
  - individuals lack all metabolism related to peroxisomes

- **X-linked adrenoleukodystrophy (XALD)** = characterized by the inability of peroxisomes to oxidize very-long-chain fatty acids
  - due to the lack of a functional transporter in the peroxisomal membrane

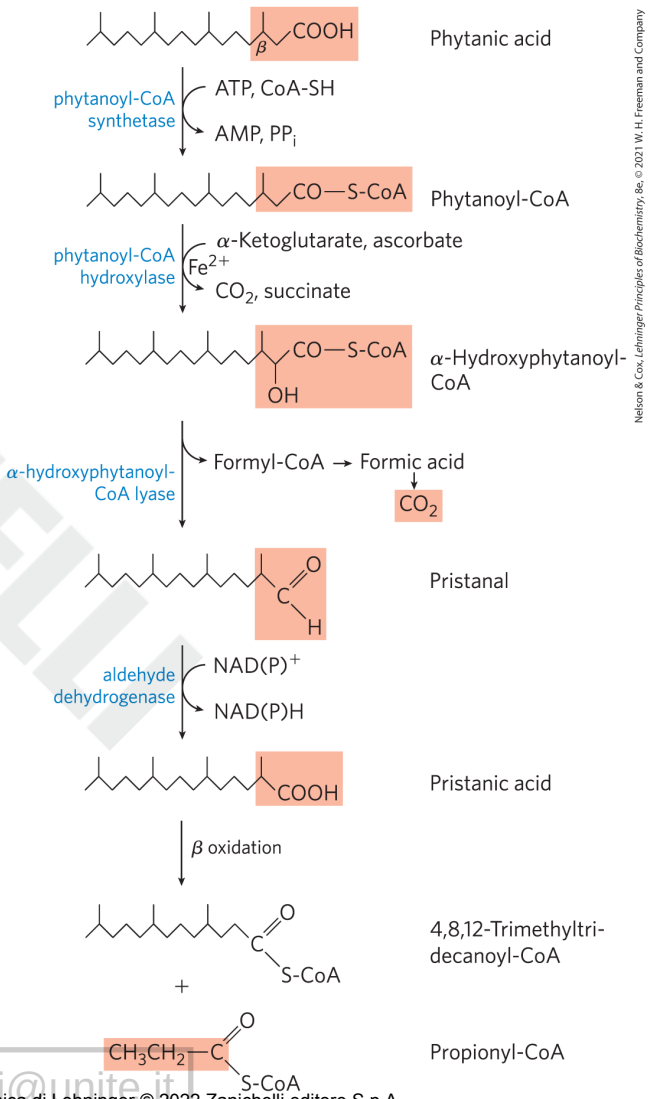
# Phytanic Acid Undergoes α Oxidation in Peroxisomes

- phytanic acid = a long-chain fatty acid with methyl branches that is derived from the phytol side chain of chlorophyll
  - the methyl group on the β carbon makes β oxidation impossible

# *α* Oxidation of Phytanic Acid

- ***α* oxidation** = removes a single carbon from the carboxyl end of the fatty acid
  - converts branched fatty acids to products that can undergo *β* oxidation to yield acetyl-CoA and propionyl-CoA

- **Refsum disease** = results from a genetic defect in phytanoyl-CoA hydroxylase



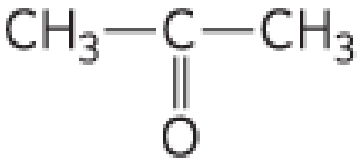
# 17.3 Ketone Bodies

# P5 Principle 5 (2 of 4)

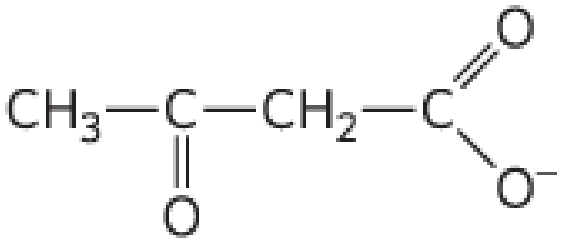
**The liver plays a unique role in whole-body metabolism.** When glucose is unavailable, the liver makes glucose by gluconeogenesis and releases it to the blood for distribution to other tissues, including the brain. During starvation, the liver processes fatty acids into ketone bodies, which, unlike fatty acids, can cross the blood brain barrier and fuel the brain.

# The “Ketone Bodies”

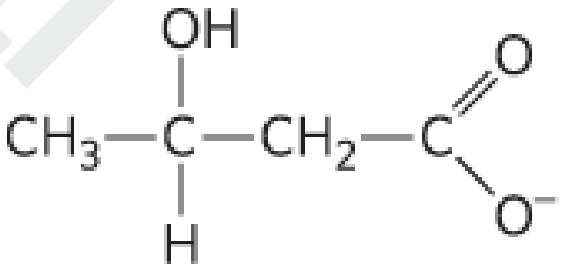
- **“ketone bodies” = acetone, acetoacetate**, and **D-β-hydroxybutyrate**
  - formed from acetyl-CoA in the liver
- acetone is exhaled
- acetoacetate and D-β-hydroxybutyrate are transported to extrahepatic tissues and converted to acetyl-CoA to be oxidized in the citric acid cycle



Acetone



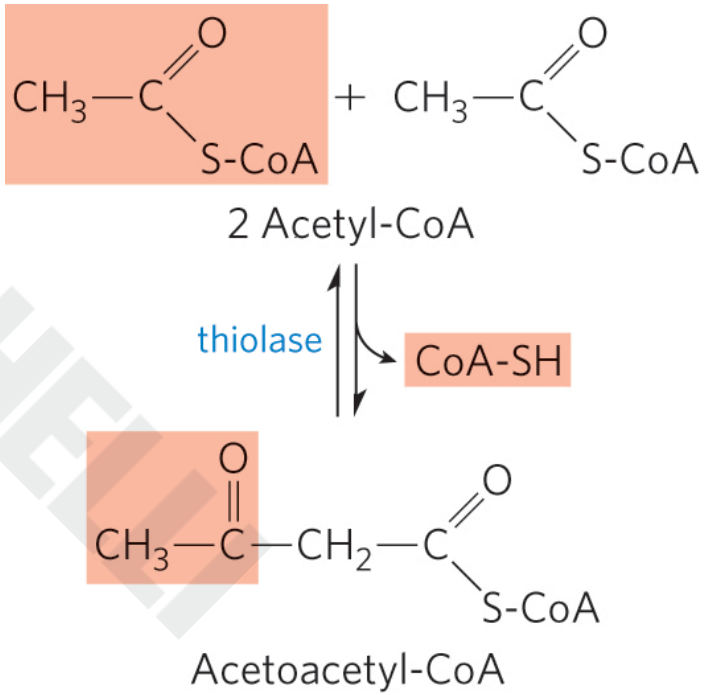
Acetoacetate



D-β-Hydroxybutyrate

# Ketone Bodies, Formed in the Liver, Are Exported to Other Organs as Fuel

- thiolase = catalyzes the enzymatic condensation of two acetyl-CoA molecules to form acetoacetyl-CoA
  - reversal of the last step of $\beta$ oxidation

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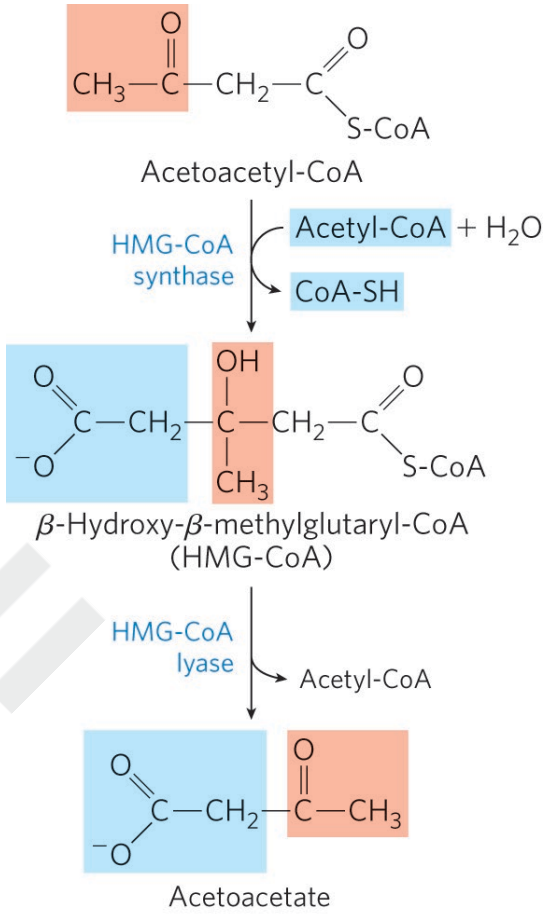
# The HMG-CoA Synthase and HMG-CoA Lyase Reactions

- HMG-CoA synthase = catalyzes the condensation of acetoacetyl-CoA with acetyl-CoA to form β-**hydroxy-β-methylglutaryl-CoA (HMG-CoA)**

- HMG-CoA lyase = catalyzes the cleavage of HMG-CoA to free acetoacetate and acetyl-CoA

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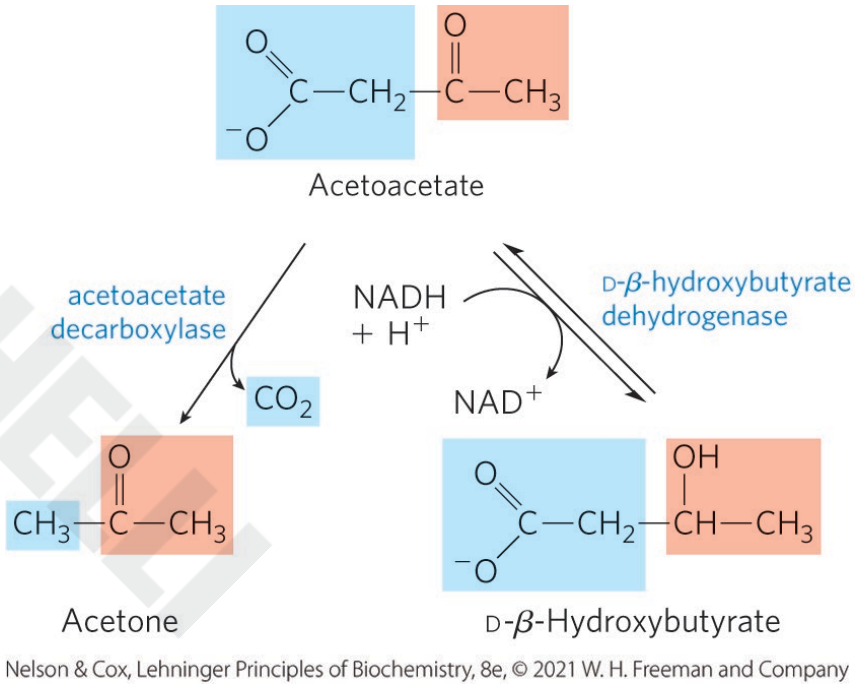
# The Decarboxylation and Reduction of Acetoacetate

- acetoacetate decarboxylase = catalyzes the decarboxylation of acetoacetate to acetone
- D-$\beta$-hydroxybutyrate dehydrogenase = catalyzes the reversible reduction of acetoacetate to D-$\beta$-hydroxybutyrate

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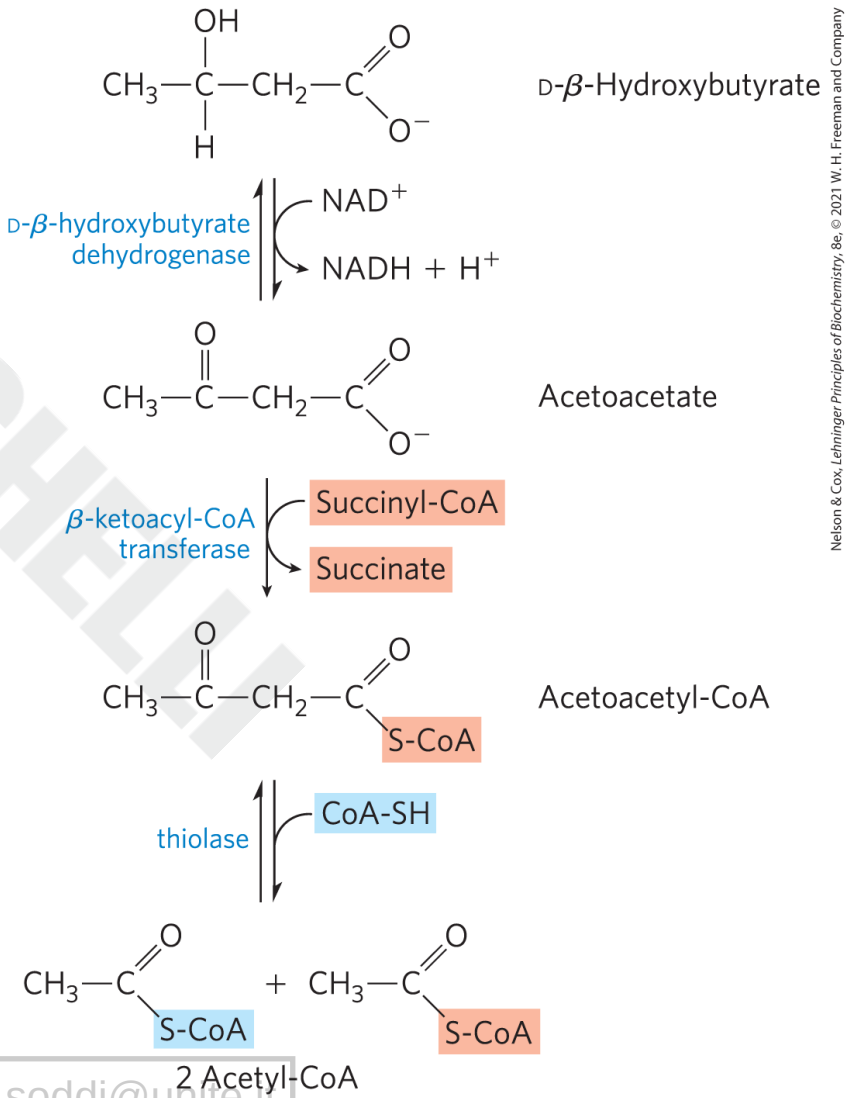
# D-β-Hydroxybutyrate as Fuel

- D-β-hydroxybutyrate dehydrogenase = catalyzes the oxidation of D-β-hydroxybutyrate to acetoacetate in extrahepatic tissue
- **β-ketoacyl-CoA transferase** = catalyzes the activation of acetoacetate
- acetyl-CoA enters the citric acid cycle

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# P5 Principle 5 (3 of 4)

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# Ketone Bodies Are Used as Fuels in all Tissues Except Liver

- the liver lacks *β*-ketoacyl-CoA transferase
- the liver is a producer of ketone bodies, not a consumer

# P4 Principle 4 (6 of 6)

**When a process lacks a critical component—an enzyme, a cofactor, or a regulatory agent—the resulting loss of homeostasis may cause disease across a spectrum of severity.** Defects in fatty acid breakdown are no exception.

# P5 Principle 5 (4 of 4)

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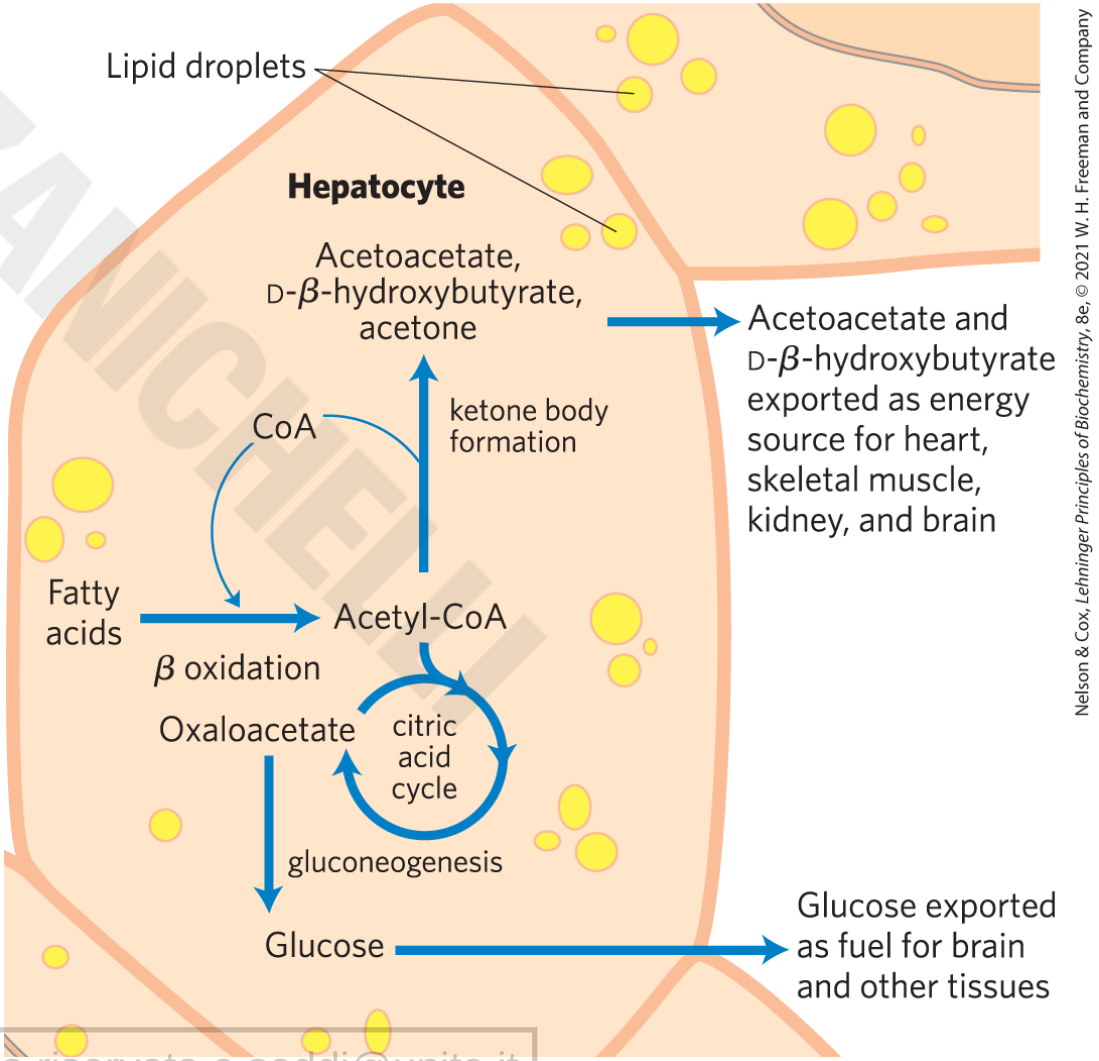
# Ketone Bodies Are Overproduced in Diabetes and during Starvation

- the accumulation of acetyl-CoA accelerates formation of ketone bodies
  - extrahepatic tissues do not have the capacity to oxidize them all



# Acidosis, Ketosis, and Ketoacidosis

- **acidosis** = lowered blood pH
  - can be caused by increased levels of acetoacetate, and D-$\beta$-hydroxybutyrate

- **ketosis** = high levels of ketone bodies in the blood and urine

- **ketoacidosis** = condition when ketosis and acidosis are combined

# Individuals with Untreated Diabetes Have High Acetone Levels

- **acetoacetate decarboxylase** = catalyzes the decarboxylation of acetoacetate to acetone
- individuals with untreated diabetes produce large quantities of acetoacetate
- acetone formed from the decarboxylation of acetoacetate is volatile
  - imparts a characteristic odor to the breath