21 Lipid Biosynthesis

P1 Principle 1 (1 of 3)

Lipids are the principal form of stored energy in most higher organisms, as well as the major constituents of membranes.

P2 Principle 2 (1 of 4)

Anabolism is not simply the reverse of catabolism. Biosynthetic pathways typically diverge from breakdown pathways to overcome irreversible steps in catabolism.

P3 Principle 3 (1 of 5)

Like other anabolic pathways, the reaction sequences in lipid biosynthesis are endergonic and reductive. They use ATP as a source of metabolic energy and a reduced electron carrier (usually NADPH) as a reductant.

P4 Principle 4 (1 of 5)

Lipid biosynthesis, like other anabolic pathways, is subject to regulation to respond to cellular and organismal requirements. The places where catabolic and anabolic pathways diverge (Principle 2) provide opportunities to impose metabolic regulation to conserve resources and avoid futile cycles.

P5 Principle 5 (1 of 7)

Like other major classes of biological molecules, lipids have a plethora of cellular functions. Specialized lipids serve as pigments (retinal, carotene), cofactors (vitamin K), detergents (bile salts), transporters (dolichols), hormones (vitamin D derivatives, sex hormones), extracellular and intracellular messengers (eicosanoids, phosphatidylinositol derivatives), and anchors for membrane proteins (covalently attached fatty acids, prenyl groups, phosphatidylinositol). The ability to synthesize a variety of lipids is essential to all organisms.

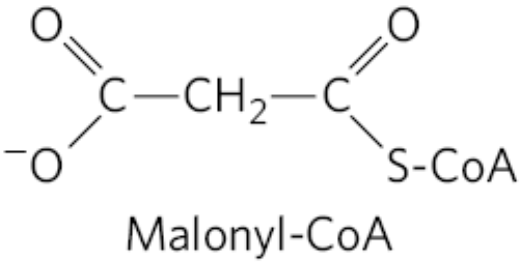
21.1 Biosynthesis of Fatty Acids and Eicosanoids

P2 Principle 2 (2 of 4)

Anabolism is not simply the reverse of catabolism. Biosynthetic pathways typically diverge from breakdown pathways to overcome irreversible steps in catabolism.

Differences between Fatty Acid Breakdown and Biosynthesis

- occur by different pathways
  - biosynthesis requires **malonyl-CoA**



Malonyl-CoA

- catalyzed by different sets of enzymes

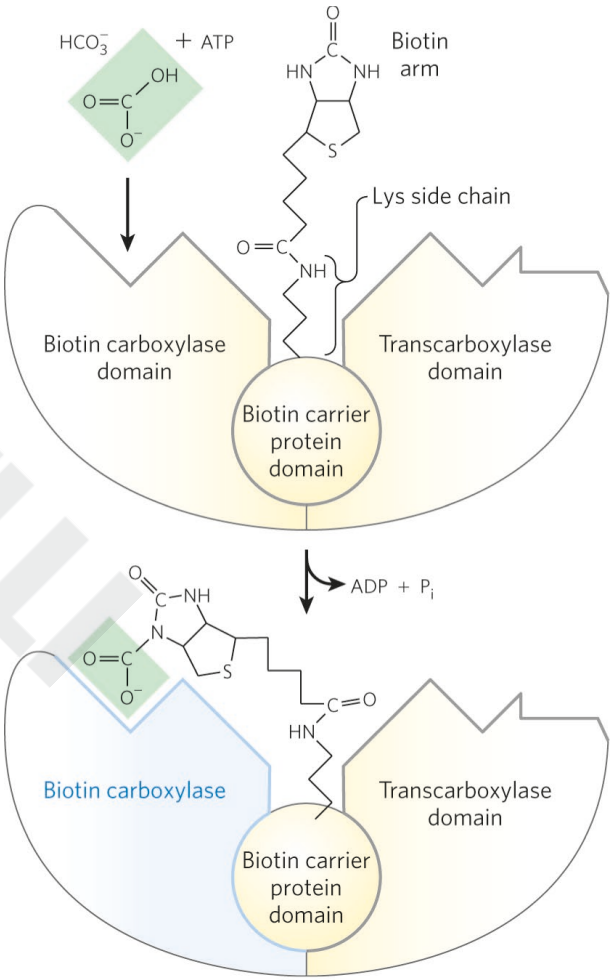
- occur in different cellular compartments (in eukaryotes)
  - breakdown occurs in the mitochondria
  - biosynthesis occurs in the cytosol

Malonyl-CoA Is Formed from Acetyl-CoA and Bicarbonate

- **acetyl-CoA carboxylase** = catalyzes the irreversible formation of malonyl-CoA from acetyl-CoA
  - reaction occurs in the cytoplasm
  - contains a biotin prosthetic group covalently bound in amide linkage to the *ε*-amino group of a Lys residue

The Acetyl-CoA Carboxylase Reaction

- this reaction is similar to other biotin-dependent carboxylation reactions
- the carboxyl group from HCO_3^- is transferred to biotin in an ATP-dependent reaction



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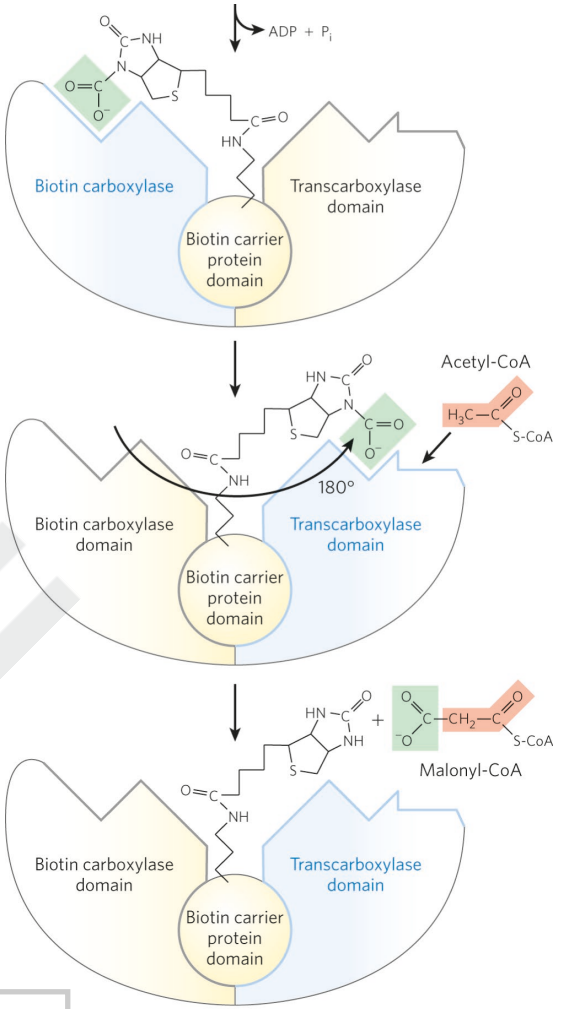
The Acetyl-CoA Carboxylase Reaction, Continued

- the carboxyl group is carried by the biotin to a different active site, where the CO_2 is transferred to acetyl-CoA to yield malonyl-CoA
  - functions to make subsequent steps more thermodynamically favorable



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Bacterial and Plant Acetyl-CoA Carboxylase

- bacterial acetyl-CoA carboxylase has three separate polypeptide subunits

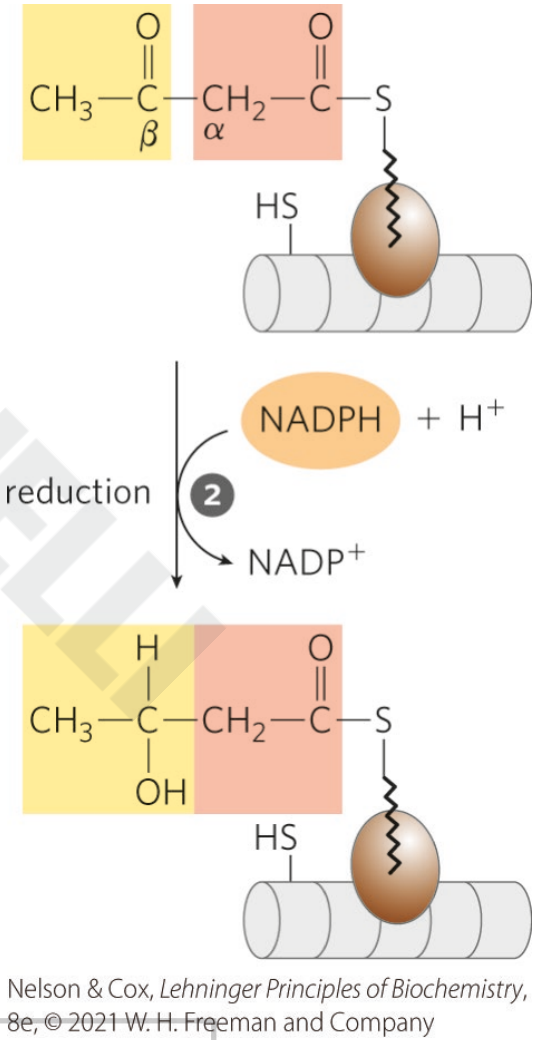
- plant cells contain both types of acetyl-CoA carboxylase

Fatty Acid Synthesis Proceeds in a Repeating Reaction Sequence

- **fatty acid synthase** = catalyzes assembly of long carbon chains of fatty acids in the cytosol through a repeating four-step sequence
  - begins with malonyl-CoA and acetyl-CoA
  - each sequence elongates chain by two carbons

Step 1 of Fatty Acid Synthesis: Condensation

- an activated acyl group and two carbons from malonyl-CoA undergo condensation to form a β-keto product
  - CO_2 from the malonyl group is eliminated
  - the acyl chain is extended by two carbons



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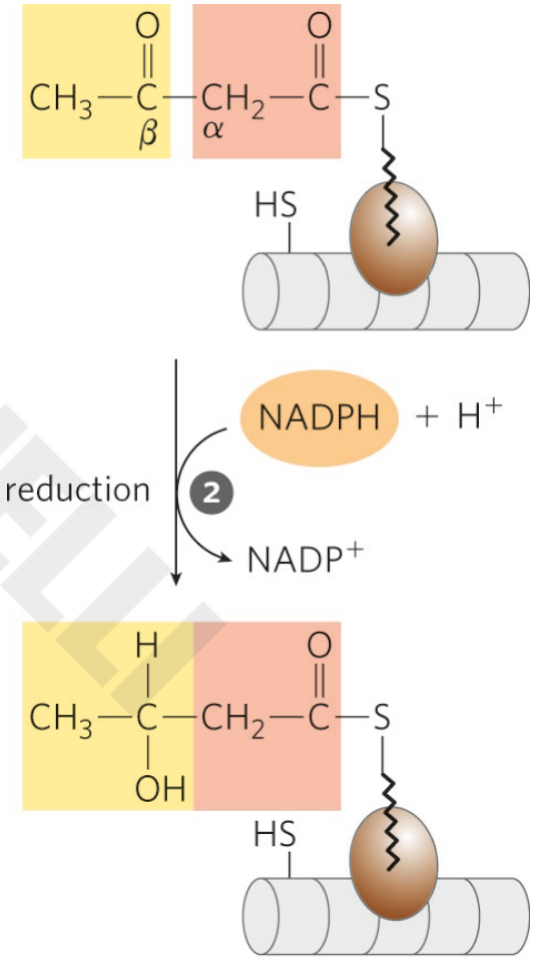
Step 2 of Fatty Acid Synthesis: Reduction of the β-Keto Product

- the β-keto product is reduced to an alcohol
  - requires NADPH



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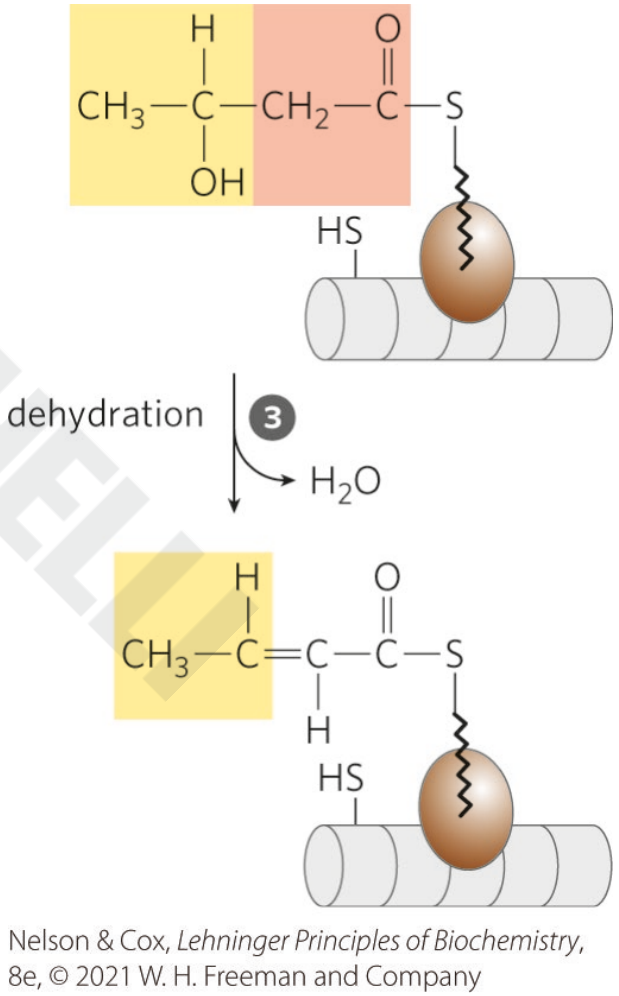
Step 3 of Fatty Acid Synthesis: Dehydration

- H_2O is eliminated to form a double bond



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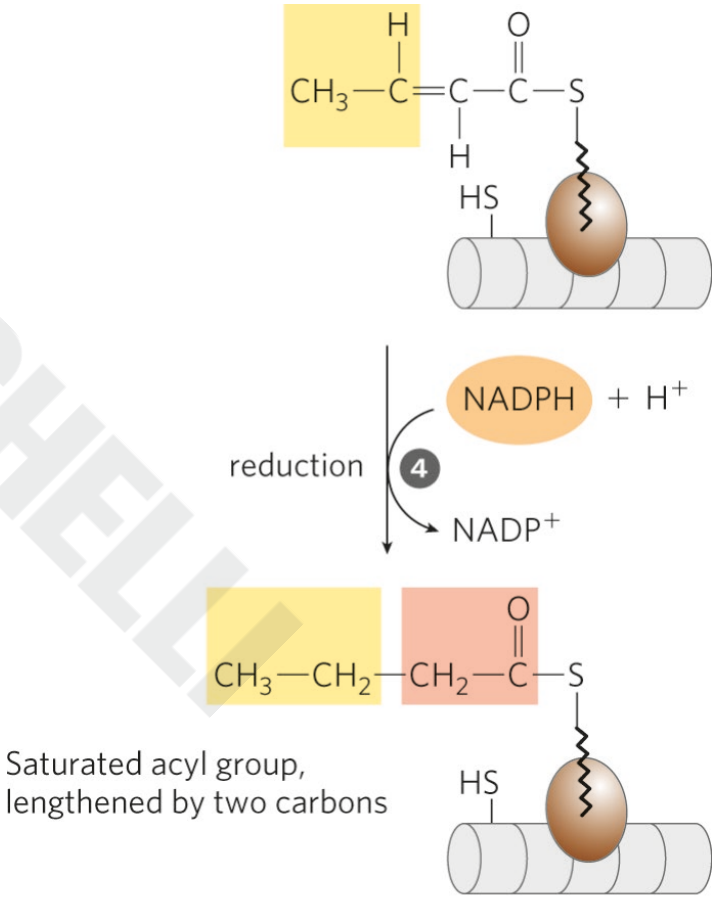
Step 4 of Fatty Acid Synthesis: Reduction of the Double Bond

- the double bond is reduced to form the corresponding saturated fatty acyl group
  - requires NADPH



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P2 Principle 2 (3 of 4)

Anabolism is not simply the reverse of catabolism. Biosynthetic pathways typically diverge from breakdown pathways to overcome irreversible steps in catabolism.

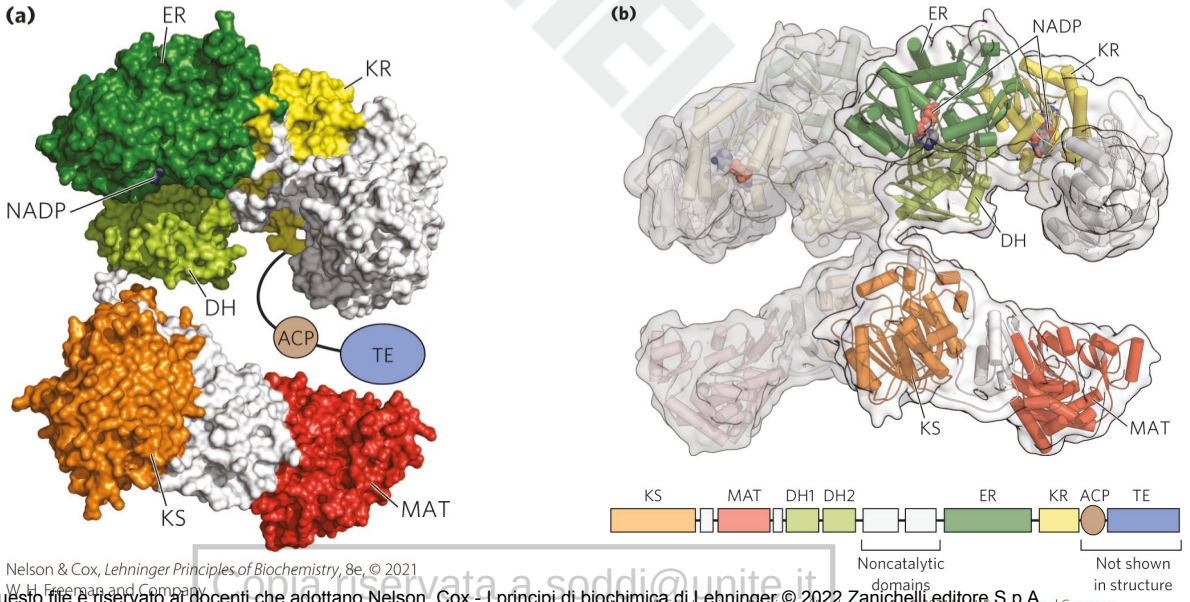
The Cofactor and Activating Groups in Fatty Acid Breakdown and Biosynthesis

- in β oxidation:
  - NAD and FAD serve as electron acceptors
  - the activating group is the thiol (–SH) group of coenzyme A

- in fatty acid synthesis:
  - the reducing agent is NADPH
  - the activating groups are two different enzyme-bound –SH groups

Fatty Acid Synthase I (FAS I)

- FAS I = found in mammals
  - seven active sites are in separate domains within a single multifunctional polypeptide chain
  - two polypeptide chains function independently, but as a homodimer
  - forms a single product



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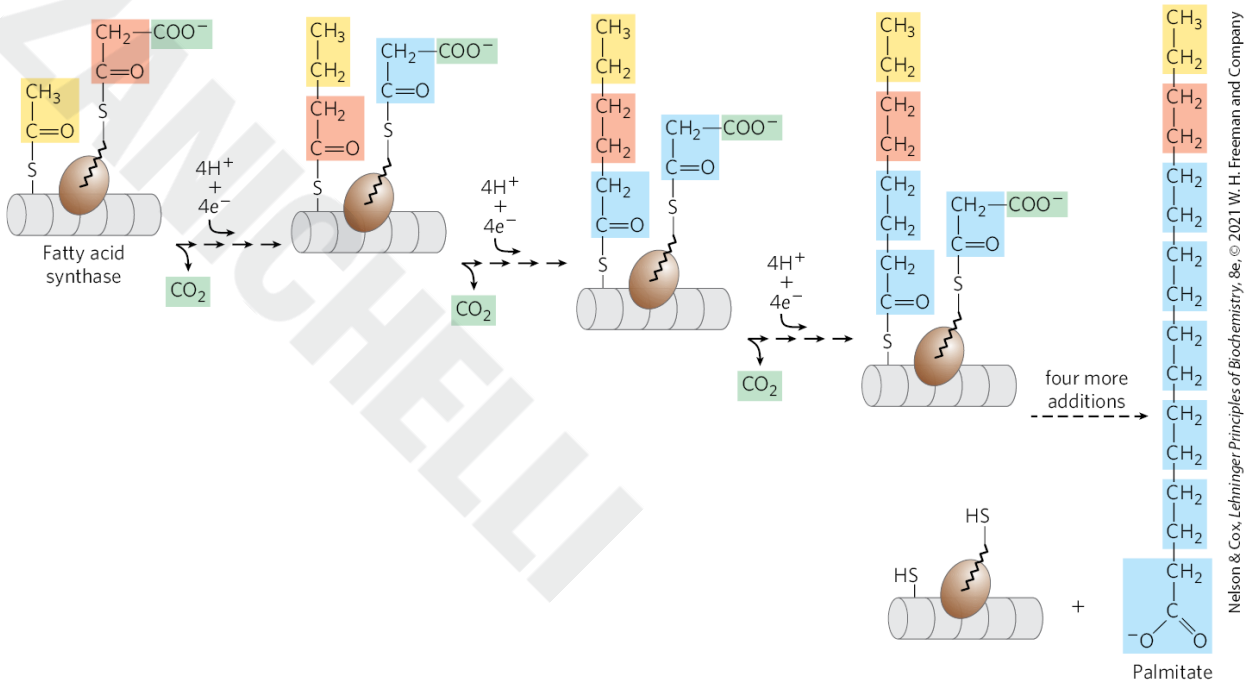
Acyl Carrier Protein (ACP)

- **acyl carrier protein (ACP)** = shuttles the acyl group from one active site to another in sequence
  - is covalently linked to the acyl group
  - is part of the single FAS I polypeptide

The Overall Process of Palmitate Synthesis

- carbons C-16 and C-15 of the palmitate are derived from the methyl and carboxyl carbon atoms, respectively, of an acetyl-CoA used to prime the system at the outset



Fatty Acid Synthase II (FAS II)

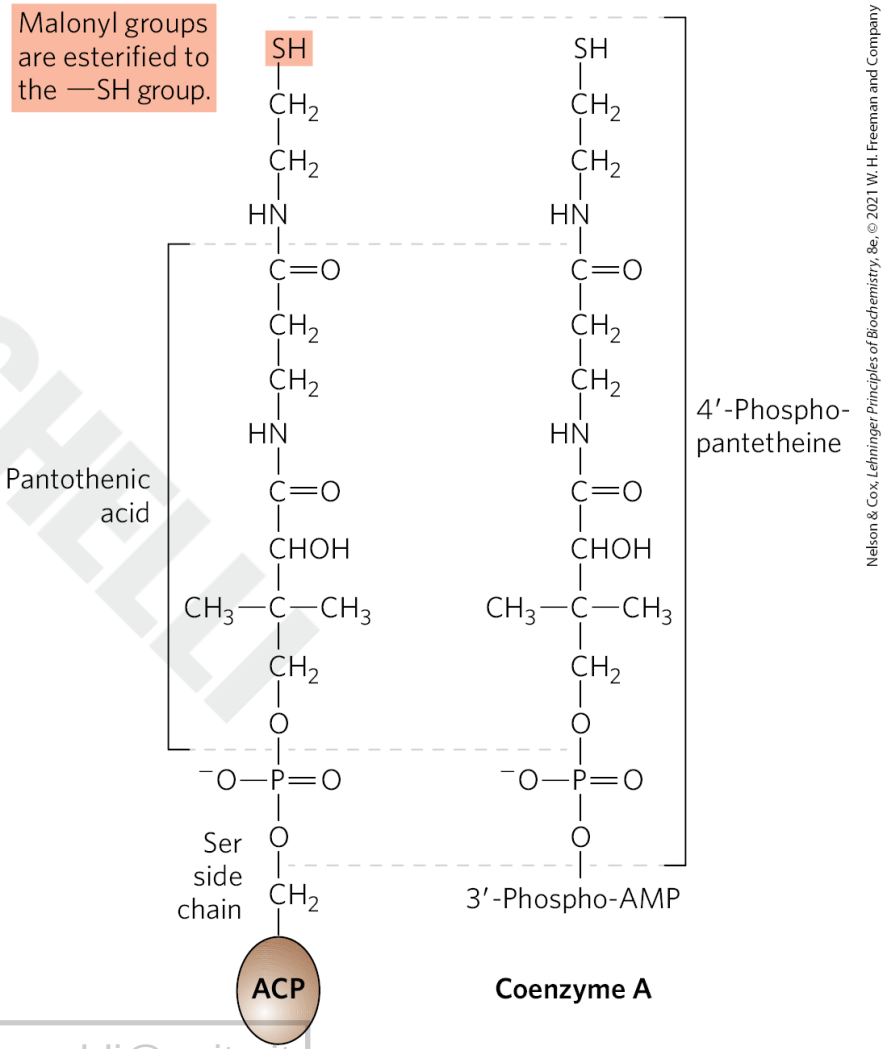
- FAS II = found in plants, most bacteria, and vertebrate mitochondria
  - is a dissociated system
  - each step in the synthesis catalyzed by a separate enzyme
  - generates a variety of products

The Mammalian Fatty Acid Synthase Has Multiple Active Sites

- the intermediates remain covalently attached as thioesters to one of two thiol groups:
  - the —SH group of a Cys residue in *β*-ketoacyl-ACP synthase
  - the —SH group of acyl carrier protein

Acyl Carrier Protein (ACP) Contains 4′-Phosphopantetheine

- **4′-phosphopantetheine** = a prosthetic group of ACP that serves as a flexible arm
  - also in coenzyme A
  - tethers the fatty acyl chain to the surface of the FAS complex
  - carries reaction intermediates from one active site to the next

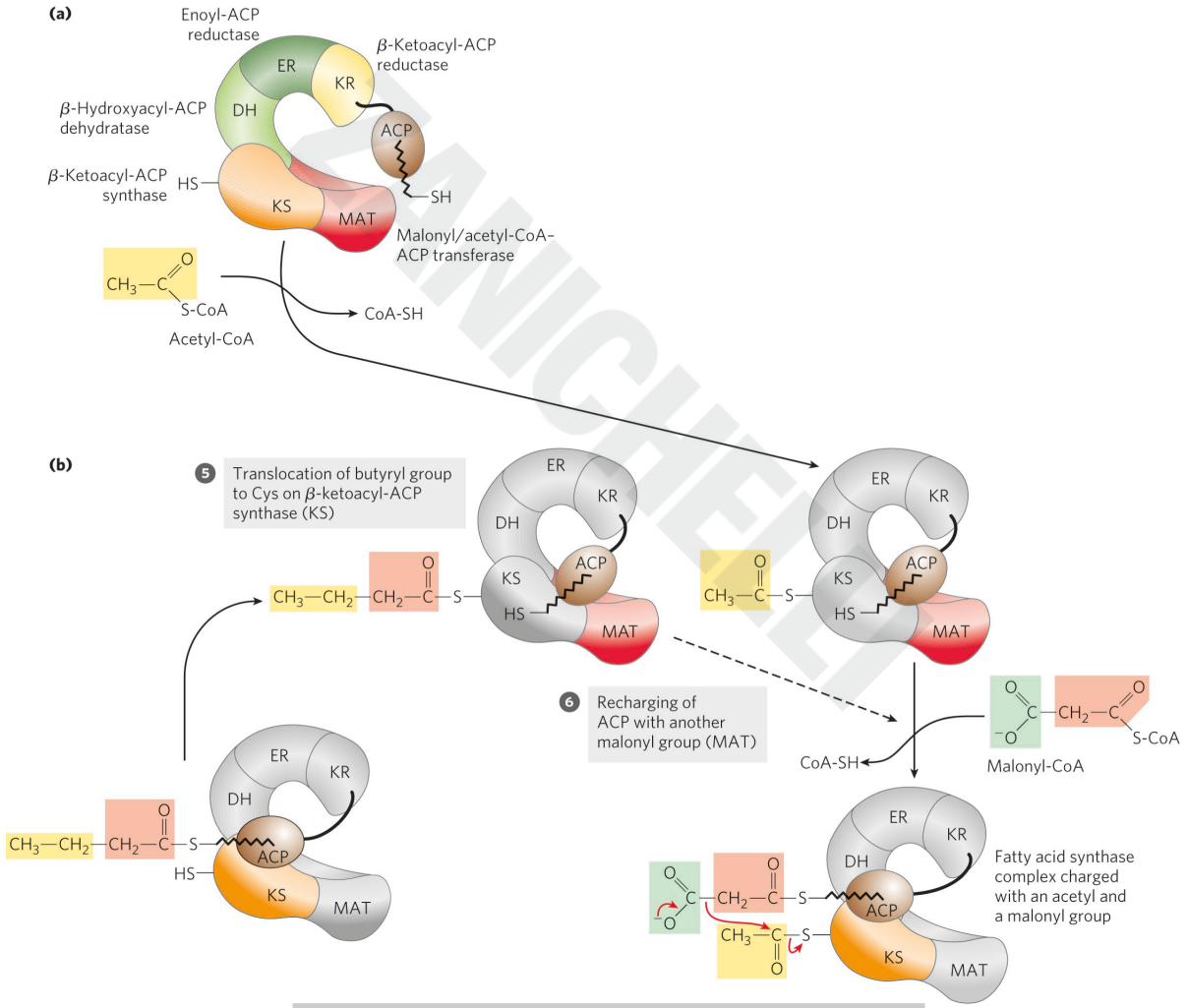


Fatty Acid Synthase Receives the Acetyl and Malonyl Groups

- the two thiol groups on the enzyme complex must first be charged with the correct acyl groups

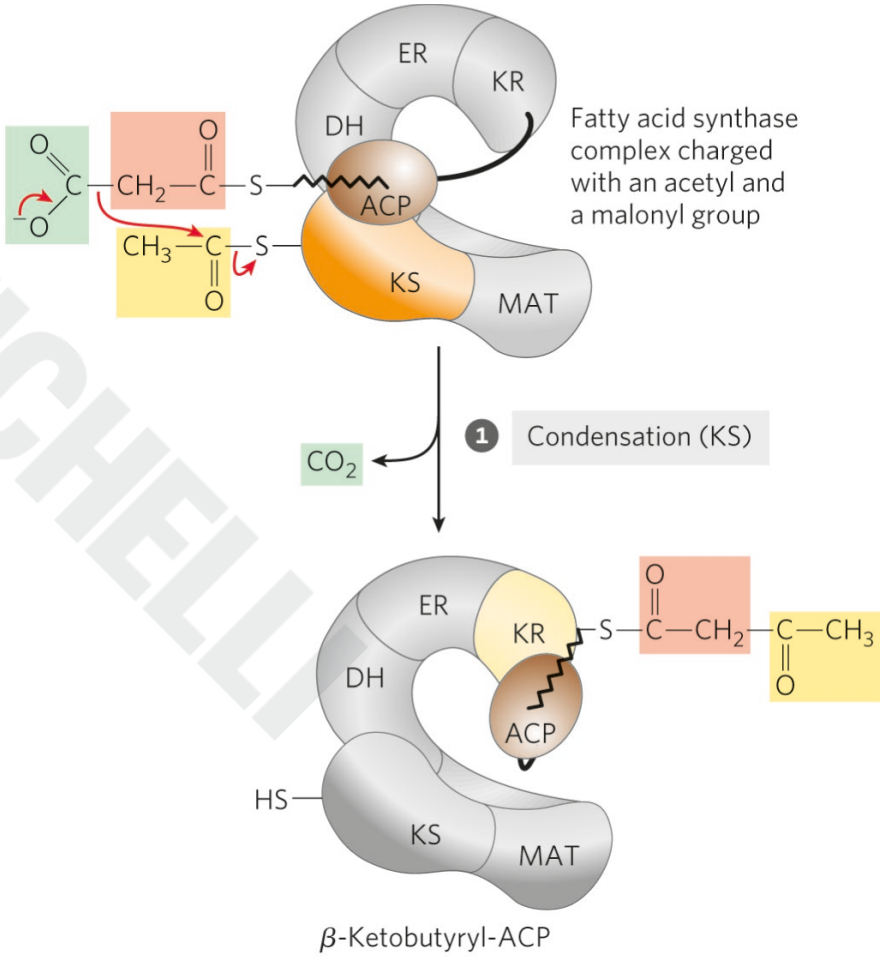
- **malonyl/acetyl-CoA–ACP transferase** (MAT) domain = catalyzes two reactions:
  - the transfer of the acetyl group of acetyl-CoA to ACP (which is then transferred to ***β*-ketoacyl-ACP synthase** (KS))
  - the transfer of the malonyl group from malonyl-CoA to the —SH group of ACP

Activation of the Acetyl and Malonyl Groups



Step 1: Condensation

- a formal Claisen condensation of the activated acetyl and malonyl groups yields **acetoacetyl-ACP** and CO_2



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P2 Principle 2 (4 of 4)

Anabolism is not simply the reverse of catabolism. Biosynthetic pathways typically diverge from breakdown pathways to overcome irreversible steps in catabolism.

P3 Principle 3 (2 of 5)

Like other anabolic pathways, the reaction sequences in lipid biosynthesis are endergonic and reductive. They use ATP as a source of metabolic energy and a reduced electron carrier (usually NADPH) as a reductant.

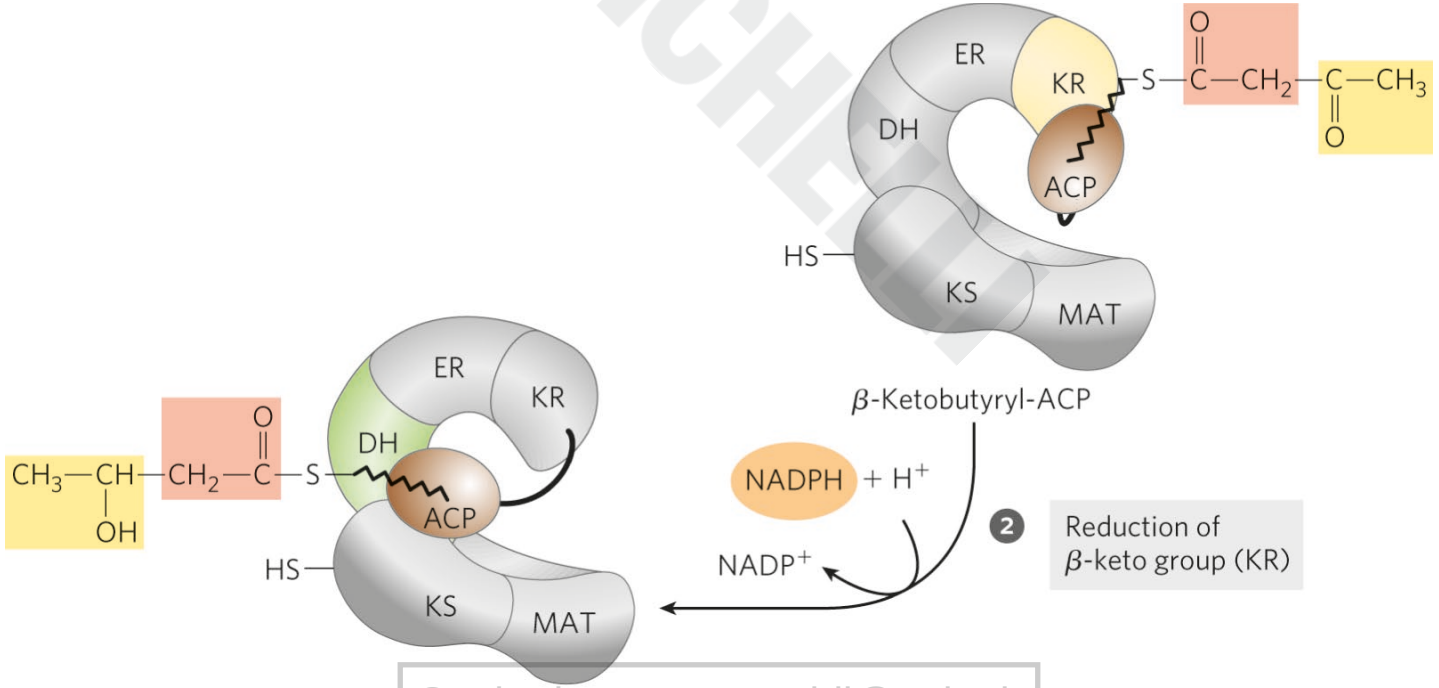
The Use of Activated Malonyl Groups Makes Condensation Thermodynamically Favorable

- coupling the condensation to the decarboxylation of the malonyl group renders the overall process highly exergonic

- by using activated malonyl groups in the synthesis of fatty acids and activated acetate in their degradation, the cell makes both processes energetically favorable

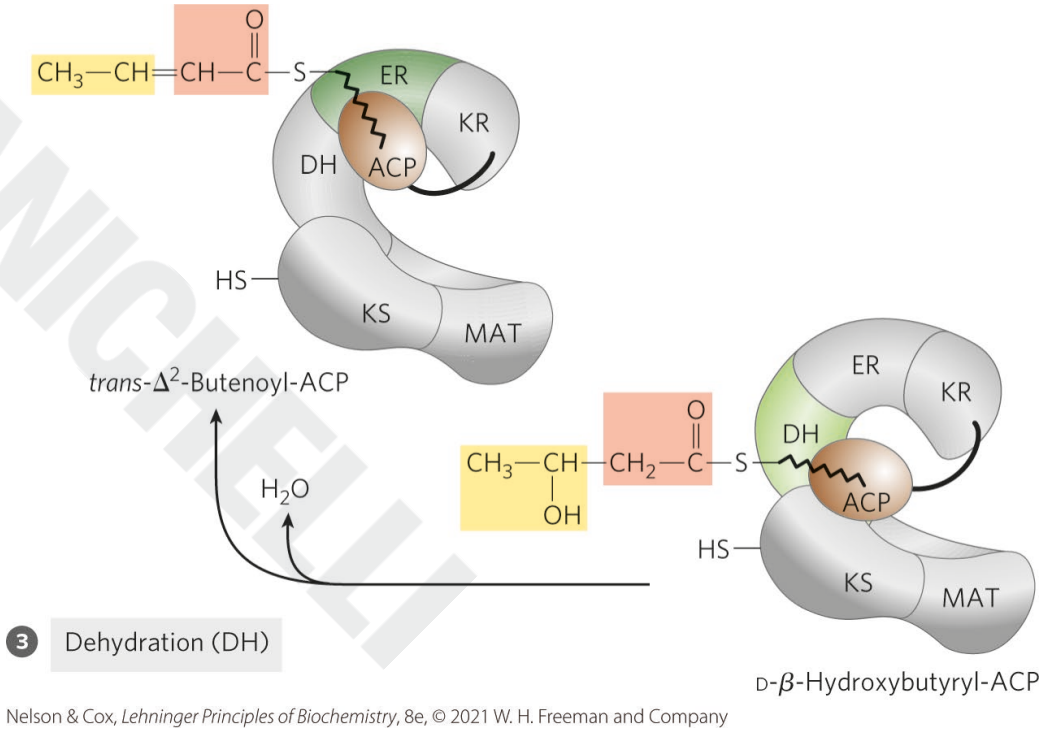
Step 2: Reduction of the Carbonyl Group

- **β-ketoacyl-ACP reductase** (KR) = catalyzes the reduction of the carbonyl group at C-3 of acetoacetyl-CoA to form D-β-hydroxybutyryl-ACP
  - uses NADPH as the electron donor



Step 3: Dehydration

- ***β*-hydroxyacyl-ACP dehydratase** (DH) = catalyzes the formation of ***trans*-Δ^2-butenoyl-ACP**
  - elements of H_2O are removed from C-2 and C-3 of D-*β*-hydroxybutyryl-ACP



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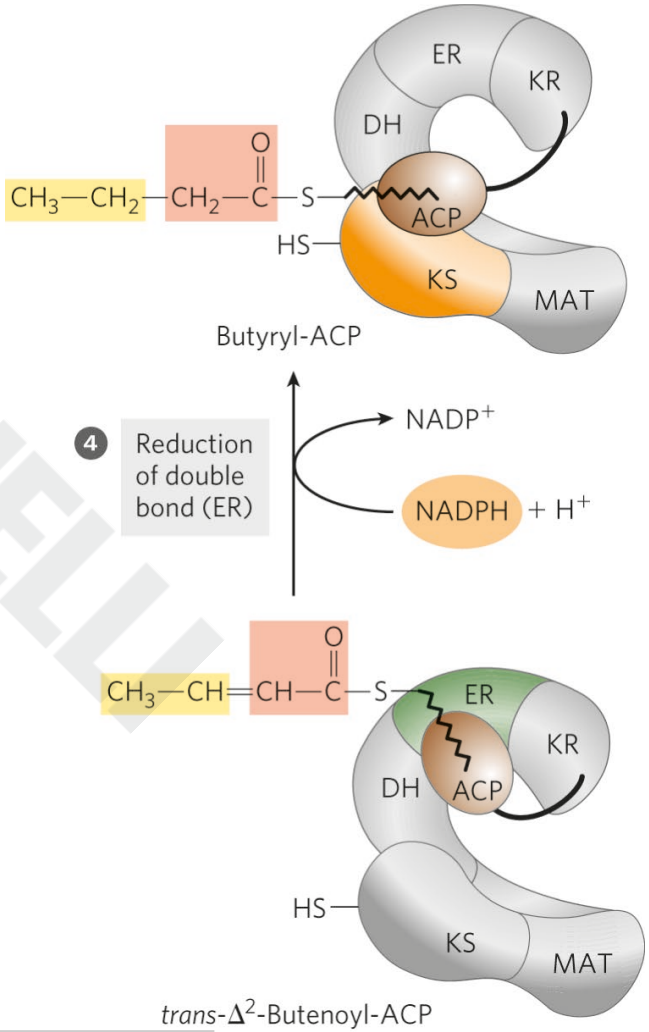
Step 4: Reduction of the Double Bond

- **enoyl-ACP reductase** (ER) = catalyzes the reduction of the double bond of *trans*-Δ^2-butenoyl-ACP to form **butyryl-ACP**
  - uses NADPH as the electron donor



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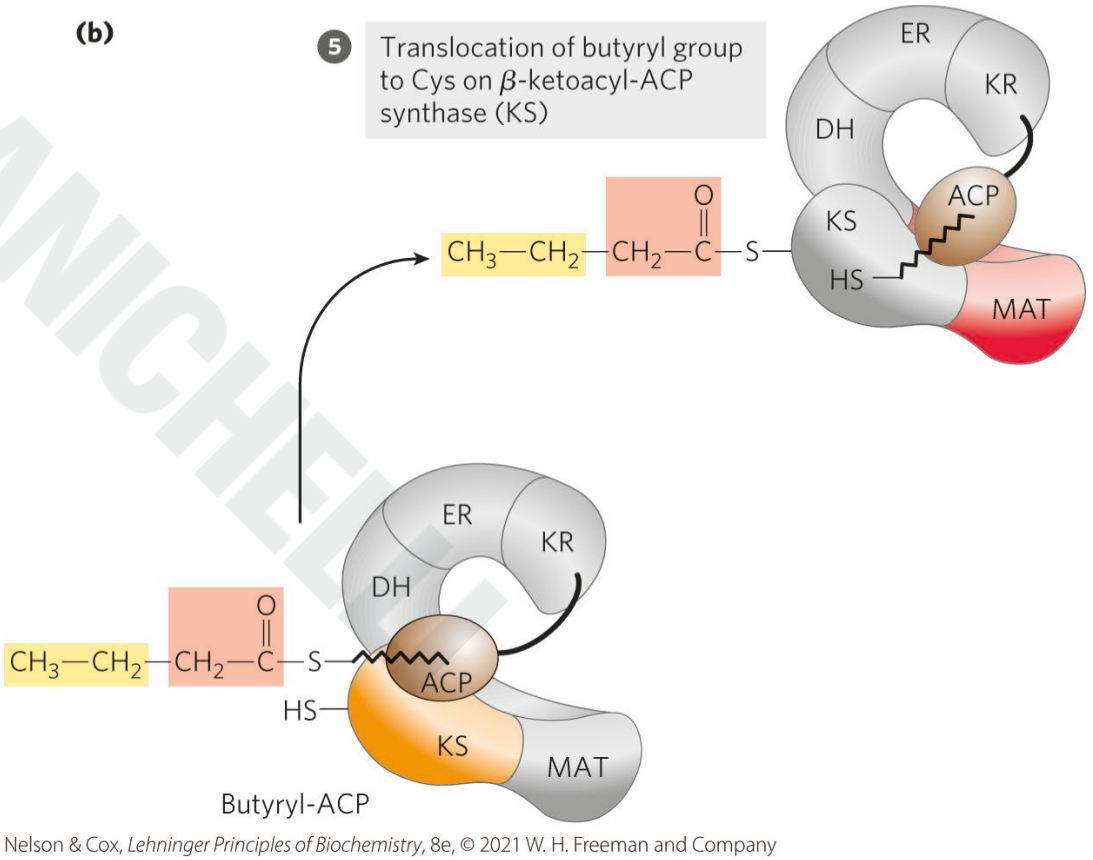
The Fatty Acid Synthase Reactions Are Repeated to Form Palmitate

- production of butyryl-ACP marks completion of one pass through the fatty acid synthase complex

Step 5: Transfer of the Butyryl Group

- the butyryl group is transferred from the phosphopantetheine —SH group of ACP to the Cys —SH group of *β*-ketoacyl-ACP synthase



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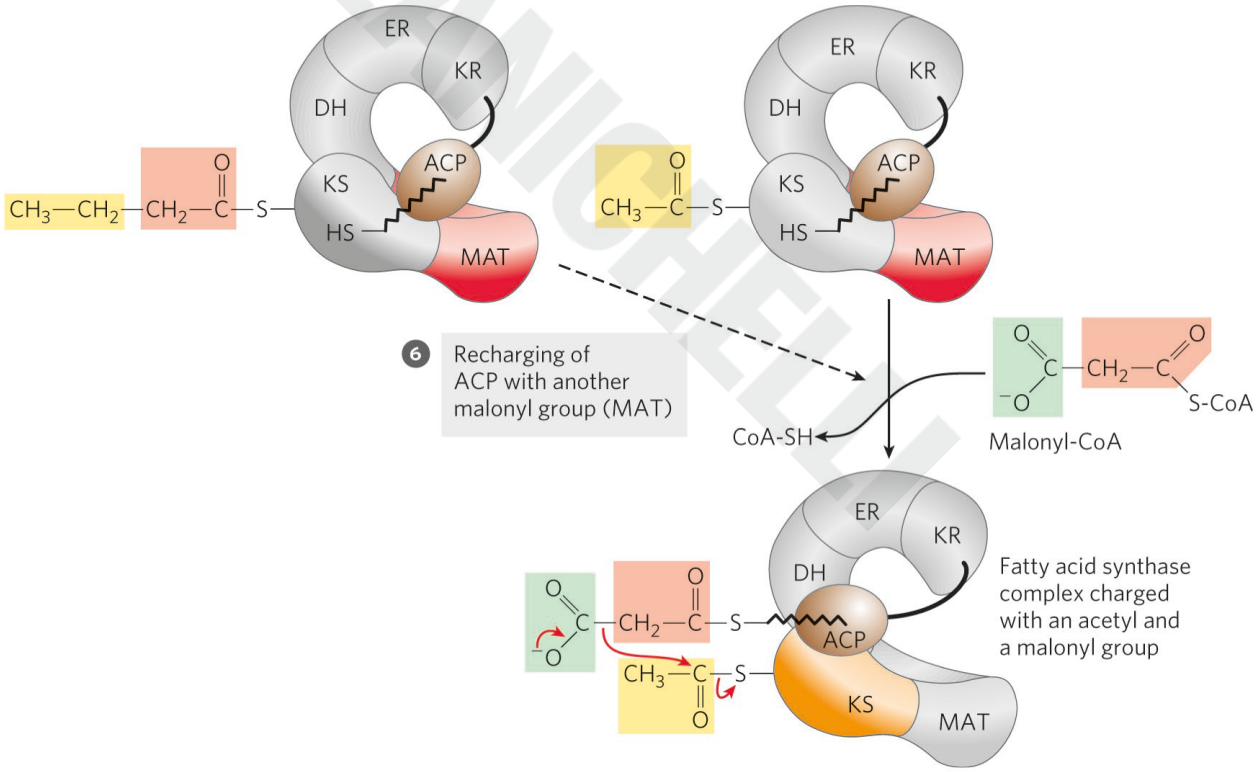
Step 6: Recharging ACP

- ACP is recharged by the linkage of another malonyl group to the unoccupied phosphopantetheine —SH group



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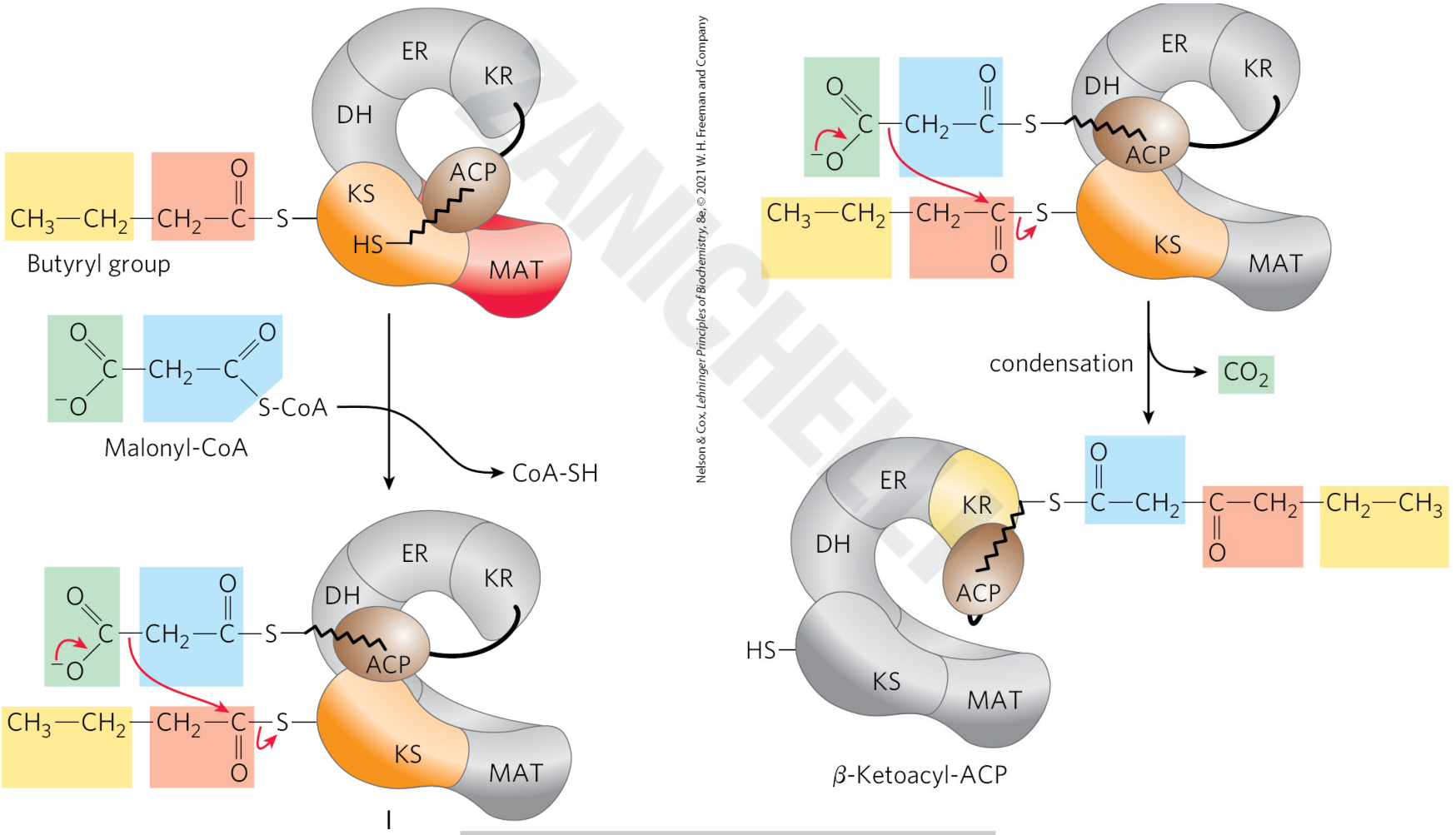
Beginning of the Second Round of the Fatty Acid Synthesis Cycle



Thioesterase Releases Palmitate from ACP

- **thioesterase** (TE) = hydrolyzes the thioester linkage between palmitate and ACP to release free palmitate

The Reaction for the Formation of Seven Malonyl-CoA Molecules

- the overall reaction is:

$$7 \text{ acetyl-CoA} + 7CO_2 + 7ATP \rightarrow 7 \text{ malonyl-CoA} + 7ADP + 7P_i \qquad (21\text{-}1)$$

The Reaction for the Seven Cycles of Condensation and Reduction

- the overall reaction is:

$$\text{acetyl-CoA} + 7\ \text{malonyl-CoA} + 14\ \text{NADPH} + 14H^+ \rightarrow \text{palmitate} + 7CO_2 + 8\text{CoA} + 14\text{NADP}^+ + 6H_2O \quad (21\text{-}2)$$

- one H_2O is used to hydrolyze the thioester linking the palmitate product to the enzyme

The Overall Reaction for the Synthesis of Palmitate

- the overall reaction is:

$$8\ \text{acetyl-CoA} + 7\text{ATP} + 14\text{NADPH} + 14\text{H}^+ \rightarrow \text{palmitate} + 8\text{CoA} + 7\text{ADP} + 7\text{P}_i + 14\text{NADP}^+ + 6\text{H}_2\text{O}$$

(21-3)

P3 Principle 3 (3 of 5)

Like other anabolic pathways, the reaction sequences in lipid biosynthesis are endergonic and reductive. They use ATP as a source of metabolic energy and a reduced electron carrier (usually NADPH) as a reductant.

Biosynthesis of Fatty Acids Requires Acetyl-CoA and Two Forms of Chemical Energy

- biosynthesis of fatty acids requires:
  - acetyl-CoA
  - the group transfer potential of ATP to make malonyl-CoA
  - the reducing power of NADPH to reduce the *β*-keto group and the double bond

P3 Principle 3 (4 of 5)

Like other anabolic pathways, the reaction sequences in lipid biosynthesis are endergonic and reductive. They use ATP as a source of metabolic energy and a reduced electron carrier (usually NADPH) as a reductant.

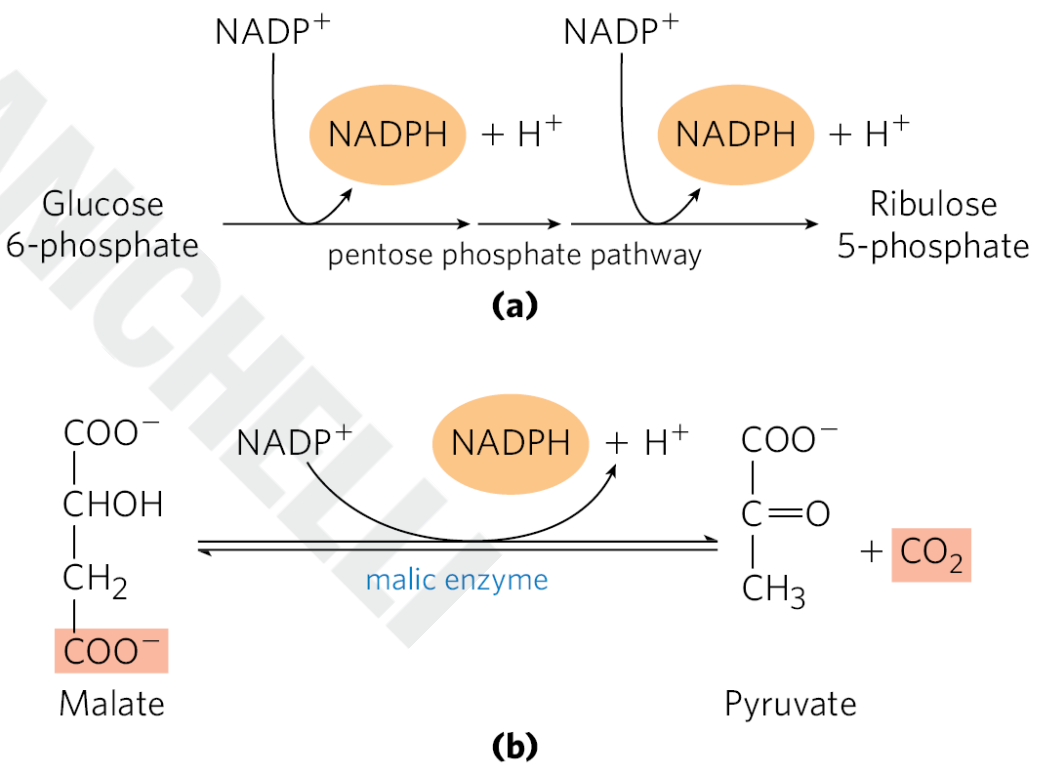
Fatty Acid Synthesis Is a Cytosolic Process in Most Eukaryotes but Takes Place in the Chloroplasts in Plants

- electron-carrying cofactors for anabolism and catabolism are segregated

- fatty acid synthesis occurs where NADPH levels are high:
  - cytosol for animals and yeast
  - chloroplasts for plants

Production of NADPH in Hepatocytes and Adipocytes

- fatty acid synthesis occurs in the cytosol
- **malic enzyme** = catalyzes the reversible formation of pyruvate and CO_2 from malate



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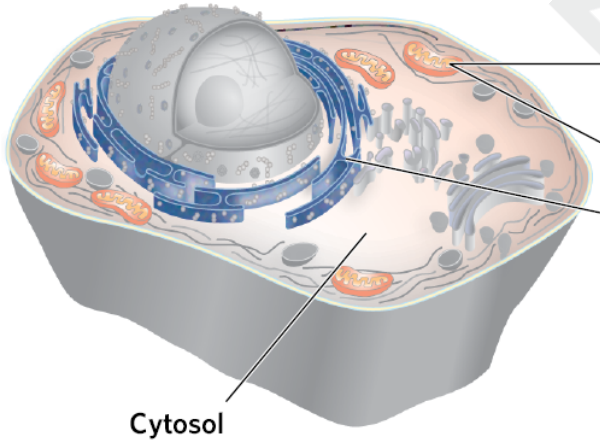
Production of NADPH in Photosynthetic Cells

- fatty acid synthesis occurs in the chloroplast stroma
- NADPH is produced in chloroplasts by the light-dependent reactions of photosynthesis:

Subcellular Localization of Lipid Metabolism

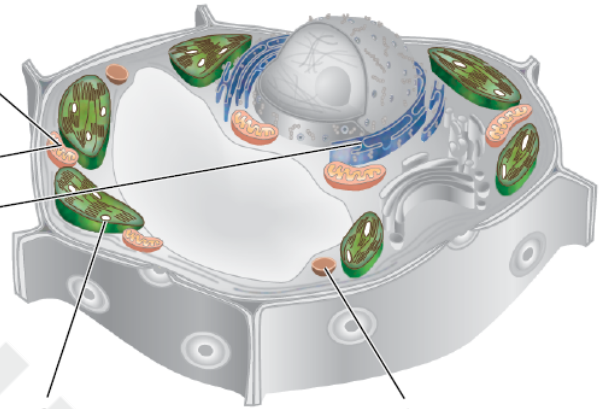


Animal cells, yeast cells

Mitochondria
- No fatty acid oxidation
- Fatty acid oxidation
- Ketone body synthesis
- Fatty acid elongation
- Acetyl-CoA production

Endoplasmic reticulum
- Phospholipid synthesis
- Sterol synthesis (late stages)
- Fatty acid elongation
- Fatty acid desaturation

Cytosol
- NADPH production (pentose phosphate pathway; malic enzyme)
- [NADPH]/[$NADP^+$] high
- Isoprenoid and sterol synthesis (early stages)
- Fatty acid synthesis



Plant cells

Chloroplasts
- NADPH, ATP production
- [NADPH]/[$NADP^+$] high
- Fatty acid synthesis

Peroxisomes
- Fatty acid oxidation (producing H_2O_2)
- Catalase, peroxidase: $H_2O_2 \longrightarrow H_2O$

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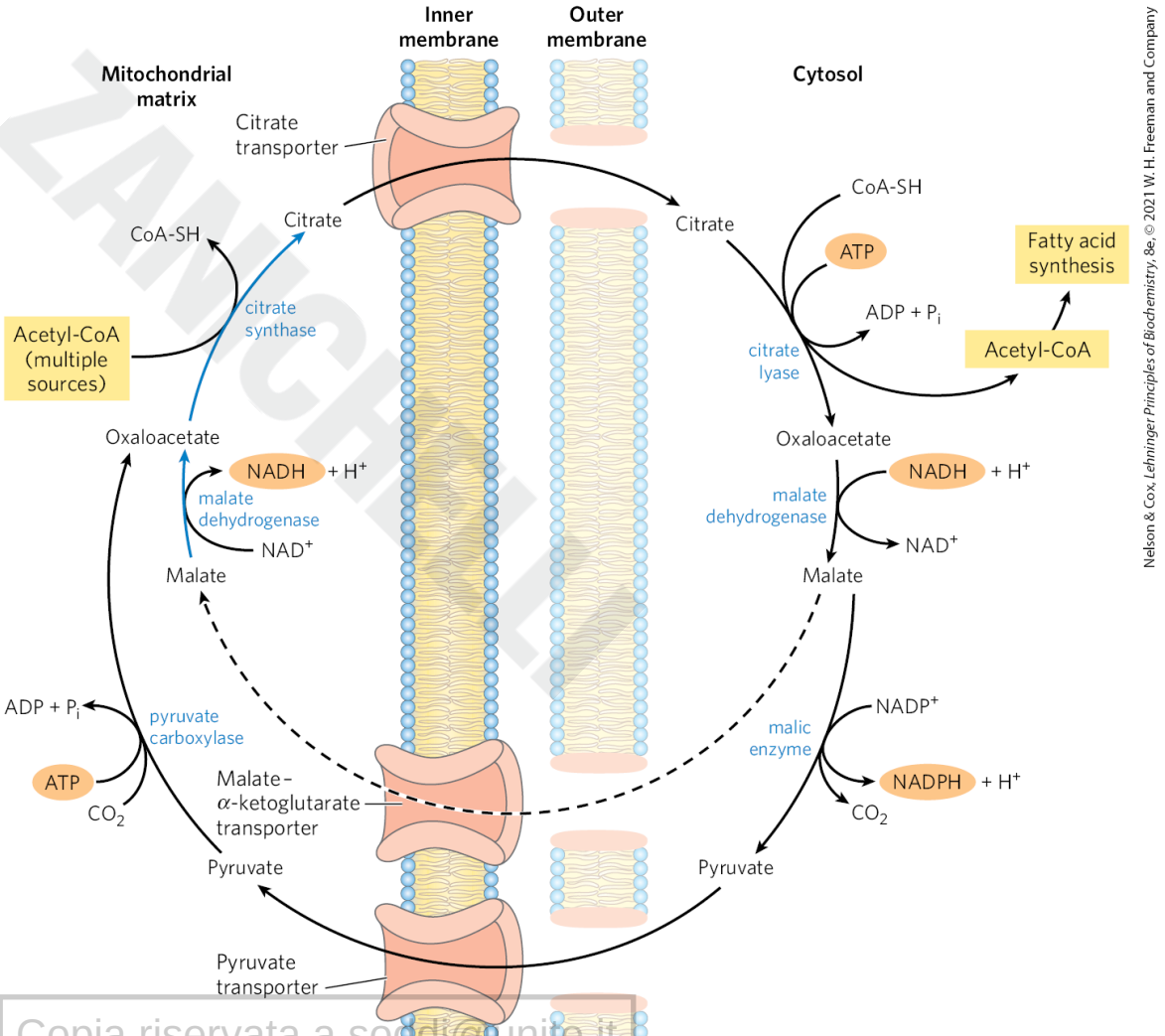
Acetate is Shuttled Out of Mitochondria as Citrate

- in nonphotosynthetic eukaryotes, acetyl CoA is formed in mitochondria from:
  - pyruvate oxidation
  - catabolism of the carbon skeletons of amino acids

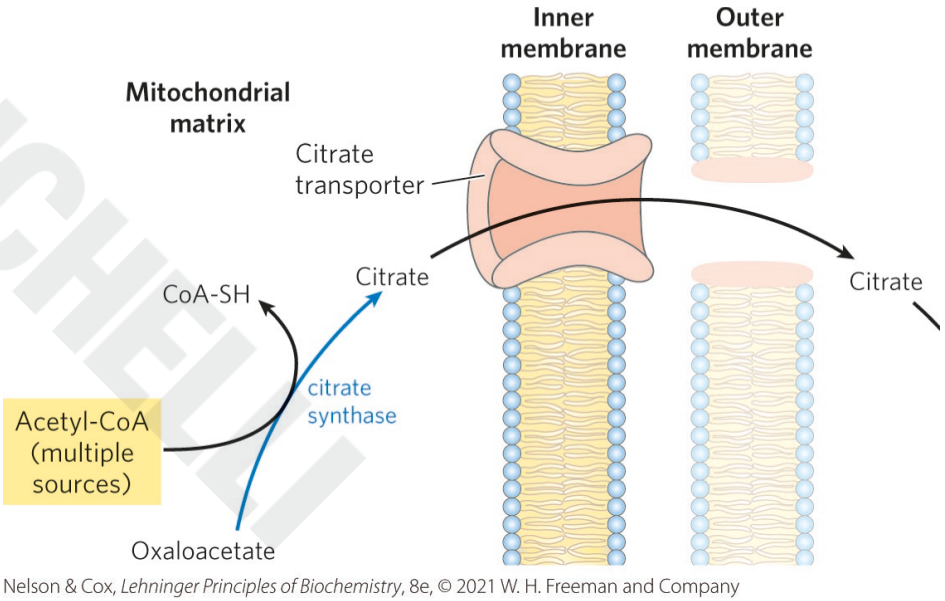
Shuttle for Transfer of Acetyl Groups from Mitochondria to the Cytosol

- the energy cost is two ATP per acetyl-CoA transported into the cytosol



Citrate Passes Through the Inner Membrane on the Citrate Transporter

- **citrate synthase** = catalyzes the formation of citrate from acetyl-CoA and oxaloacetate
  - occurs in the mitochondrial matrix
- **citrate transporter** = transports citrate through the inner mitochondrial membrane



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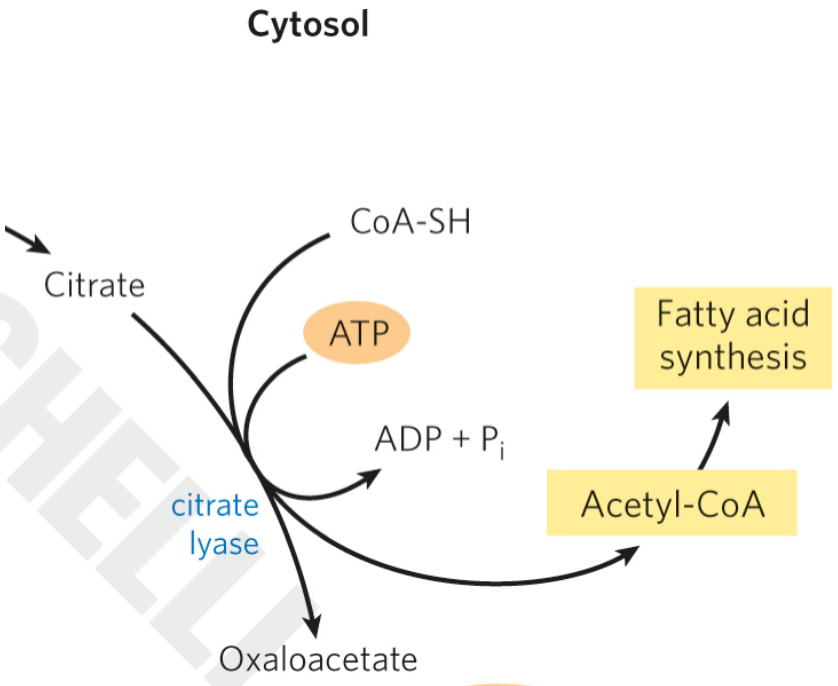
Citrate Is Cleaved in the Cytosol

- **citrate lyase** = catalyzes cleavage of citrate to regenerate acetyl-CoA and oxaloacetate
  - requires ATP



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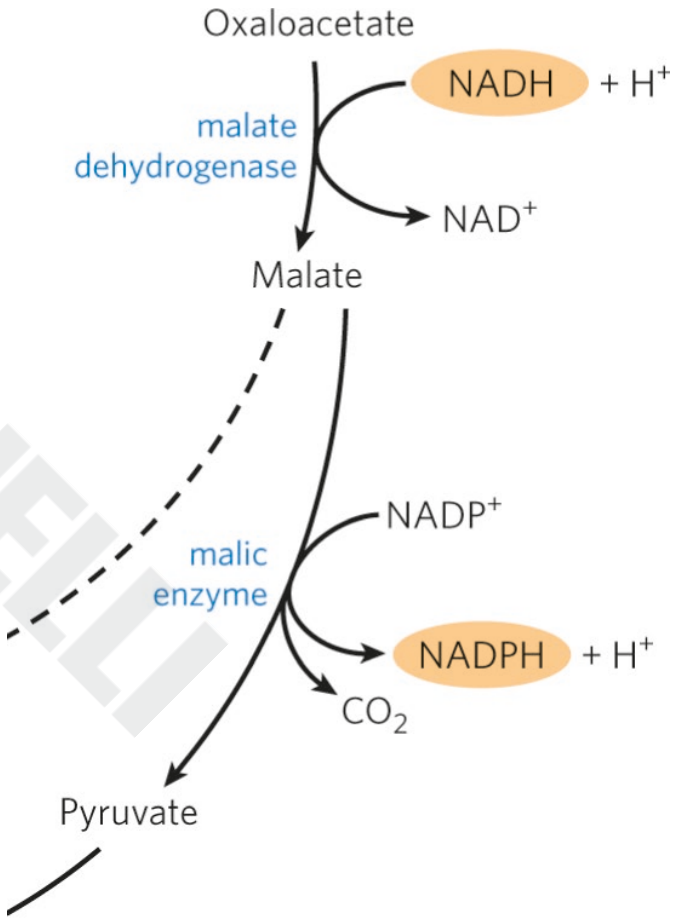
The Fate of Malate in the Cytosol

- there is no oxaloacetate transporter in the mitochondrial membrane
- malate dehydrogenase = reduces oxaloacetate to malate
- malic enzyme = oxidizes malate to pyruvate



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The Malate-*α*-Ketoglutarate Transporter and the Pyruvate Transporter

- **malate-*α*-ketoglutarate transporter** = transports malate into the matrix where it is reoxidized to oxaloacetate by malate dehydrogenase

- pyruvate transporter = transports pyruvate into the matrix where it is converted to oxaloacetate by pyruvate carboxylase

P1 Principle 1 (2 of 3)

Lipids are the principal form of stored energy in most higher organisms, as well as the major constituents of membranes.

P4 Principle 4 (2 of 5)

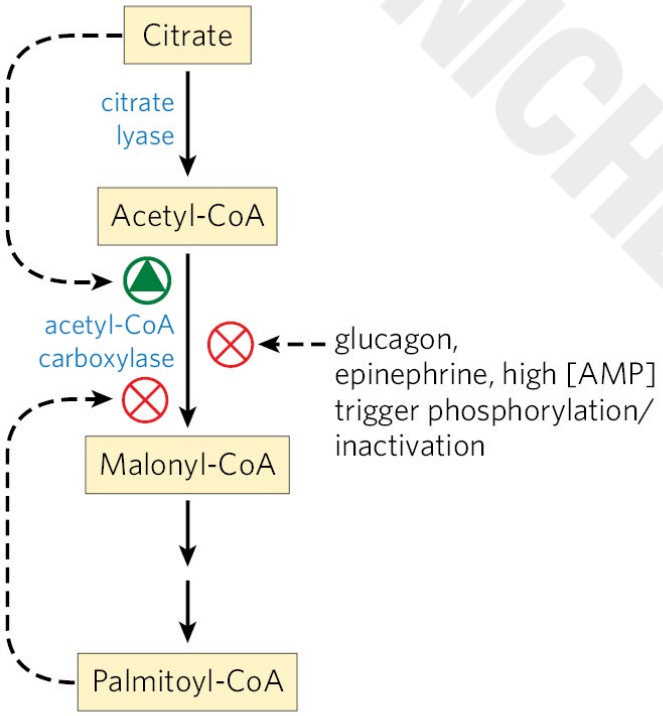
Lipid biosynthesis, like other anabolic pathways, is subject to regulation to respond to cellular and organismal requirements. The places where catabolic and anabolic pathways diverge (Principle 2) provide opportunities to impose metabolic regulation to conserve resources and avoid futile cycles.

Fatty Acid Biosynthesis Is Tightly Regulated

- excess metabolic fuel is generally converted to fatty acids and stored as lipids, such as triacylglycerols

- the reaction catalyzed by acetyl-CoA carboxylase is the rate-limiting step in the biosynthesis of fatty acids

Regulation of Fatty Acid Synthesis



(b) Courtesy James M. Ntambi, PhD, Professor of Biochemistry, Steenbock Professor of Nutritional Sciences, University of Wisconsin–Madison.

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(b)

P4 Principle 4 (3 of 5)

Lipid biosynthesis, like other anabolic pathways, is subject to regulation to respond to cellular and organismal requirements. The places where catabolic and anabolic pathways diverge (Principle 2) provide opportunities to impose metabolic regulation to conserve resources and avoid futile cycles.

Regulation of Acetyl-CoA Carboxylase By Covalent Modification

- phosphorylation inactivates the enzyme
  - triggered by the hormones glucagon and epinephrine or by high [AMP]
  - reduces sensitivity of citrate activation and slows fatty acid synthesis
  - causes polymerization of ACC into long, inactive filaments

P4 Principle 4 (4 of 5)

Lipid biosynthesis, like other anabolic pathways, is subject to regulation to respond to cellular and organismal requirements. The places where catabolic and anabolic pathways diverge (Principle 2) provide opportunities to impose metabolic regulation to conserve resources and avoid futile cycles.

Regulation of Acetyl-CoA in Plants and Bacteria

- the plant enzyme is activated by an increase in stromal pH and [Mg^{2+}]
  - occurs during illumination

- bacterial regulation employs guanine nucleotides to coordinate cell growth with membrane formation

P4 Principle 4 (5 of 5)

Lipid biosynthesis, like other anabolic pathways, is subject to regulation to respond to cellular and organismal requirements. The places where catabolic and anabolic pathways diverge (Principle 2) provide opportunities to impose metabolic regulation to conserve resources and avoid futile cycles.

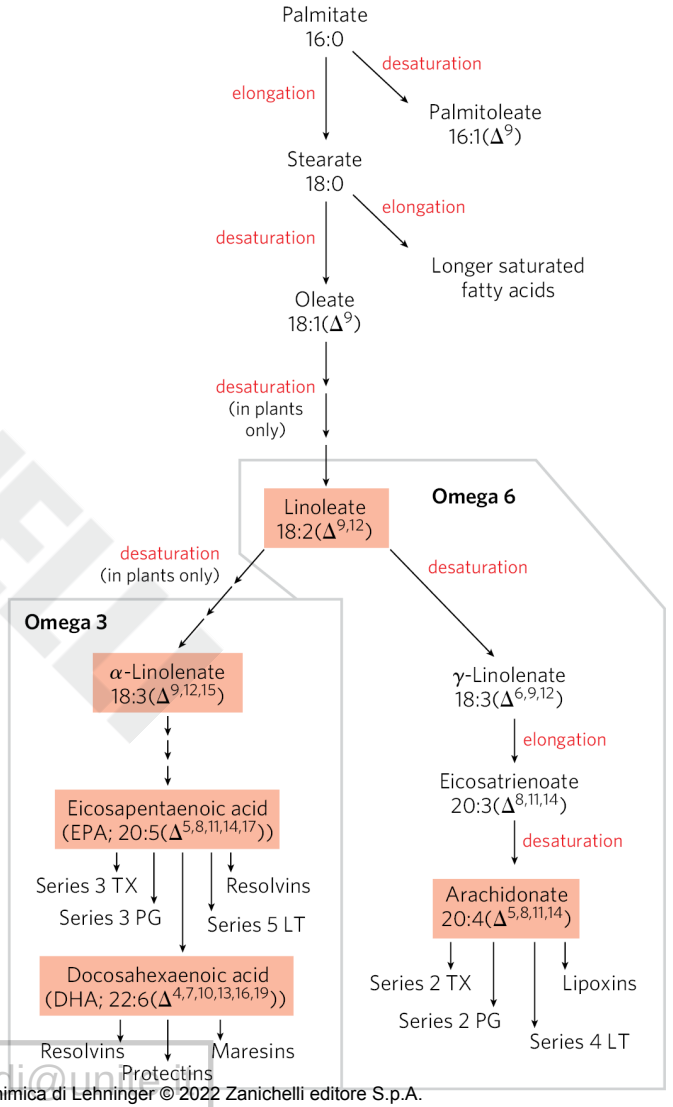
Additional Regulation of Fatty Acid Pathways

- pathways are also regulated at the level of gene expression
  - example: fatty acids bind PPARs (nuclear receptor proteins).

- fatty acid synthesis and β oxidation do not occur simultaneously
  - during fatty acid synthesis, malonyl-CoA inhibits fatty acid import into the mitochondria
    - shuts down β oxidation

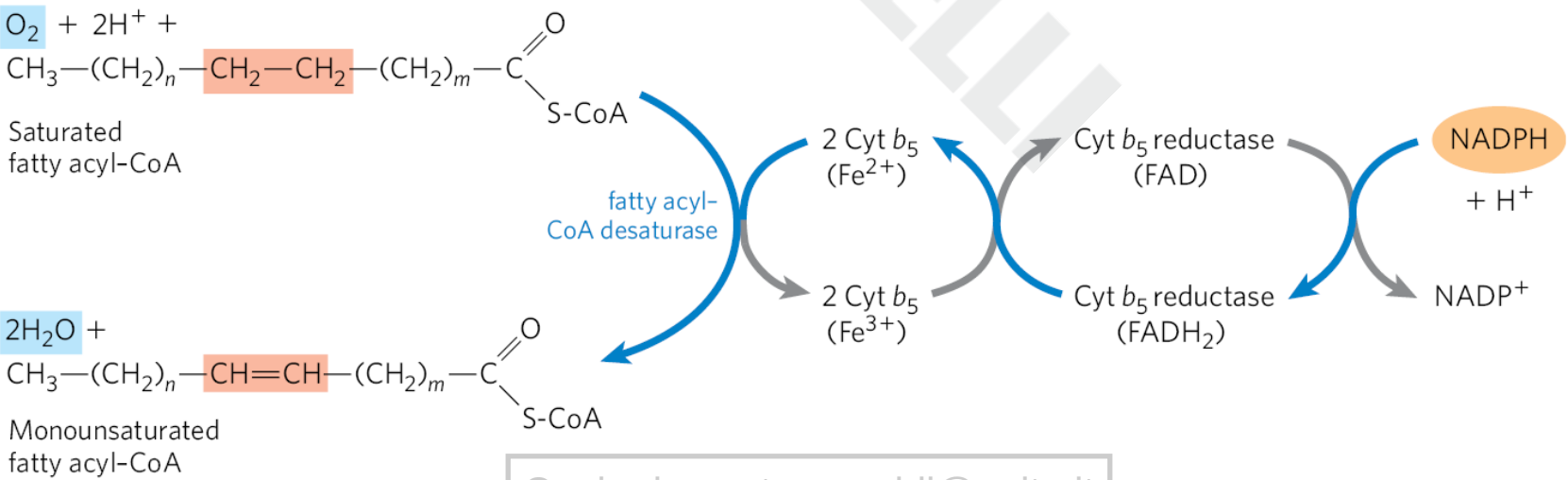
Long-Chain Saturated Fatty Acids Are Synthesized from Palmitate

- palmitate is the precursor of other long-chain fatty acids.
- **fatty acid elongation systems** = lengthen palmitate to form long saturated fatty acids
  - present in smooth ER and mitochondria
  - stearate (18:0) is the most common product



Desaturation of Fatty Acids Requires a Mixed-Function Oxidase

- **fatty acyl-CoA desaturase** = catalyzes an oxidative reaction that introduces a double bond into a fatty acid chain
  - is a mixed-function oxidase
  - requires NADPH, cytochrome b_5, and cytochrome b_5 reductase



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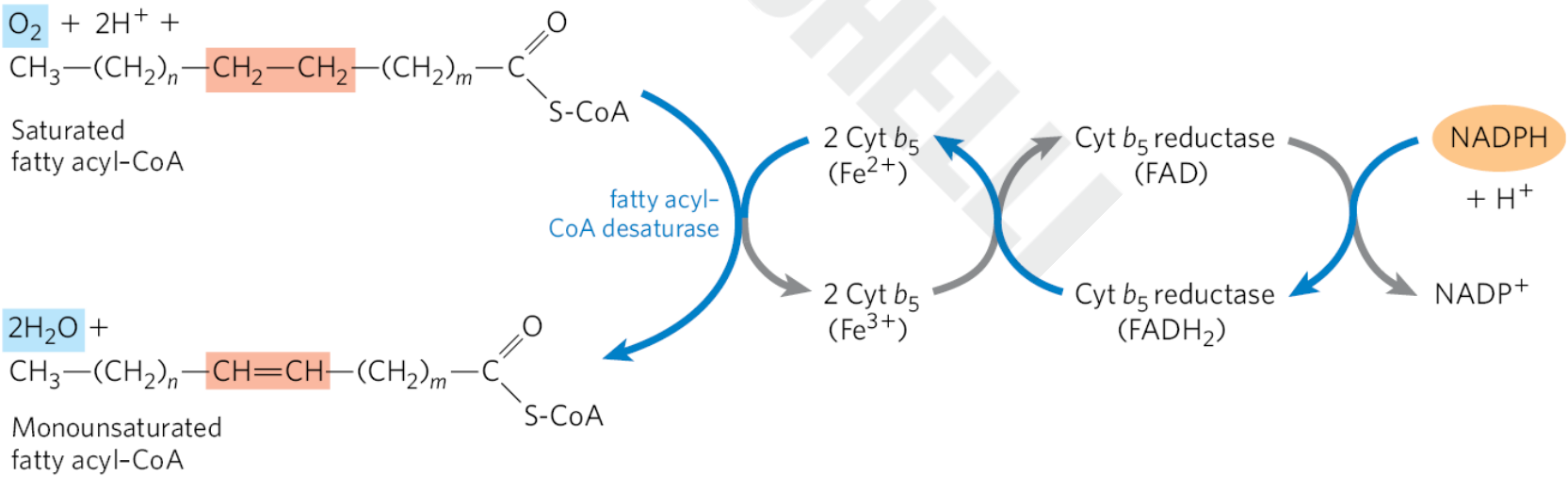
Desaturation of a Fatty Acid by Fatty Acyl-CoA Desaturase

- O_2 accepts four electrons from two substrates:
  - two electrons come from the saturated fatty acid.
  - two electrons come from ferrous state of cytochrome b_5



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Palmitate and Stearate Can Be Desaturated

- a Δ^9-desaturase reduces the bond between C-9 and C-10 to form:
  - palmitoleate (16:1; Δ^9) from palmitate (16:0)
  - oleate (18:1; Δ^9) from stearate (18:0)

Plants Can Desaturate Positions Beyond C-9

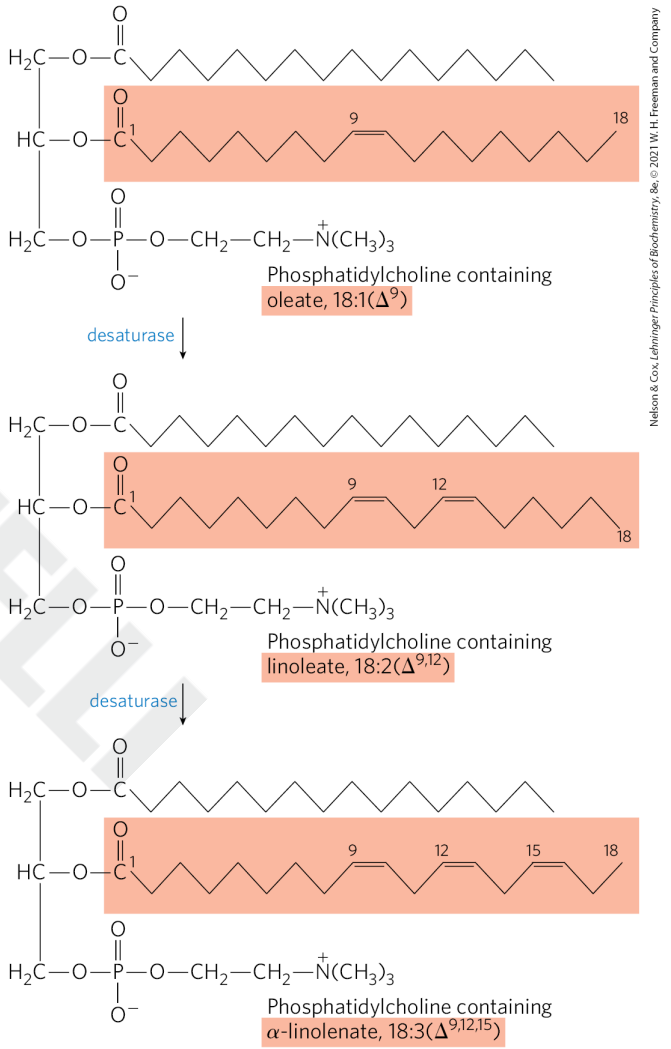
- humans cannot desaturate beyond Δ^9

- plants can, to produce:
  - linoleate 18:2($\Delta^{9,12}$)
  - α-linolenate 18:3 ($\Delta^{9,12,15}$)

Action of Plant Desaturases

- **stearoyl-ACP desaturase (SCD)** = uses reduced ferredoxin as the electron donor in the chloroplast stroma to produce oleate

- plant desaturases = oxidize phosphatidylcholine-bound fatty acids to polyunsaturated fatty acids



Linoleate and α-Linolenate Are Necessary Precursors

- **essential fatty acids** = must be obtained from dietary plant material
  - linoleate and α-linolenate for mammals

- linoleate may be converted to:
  - γ-linolenate
  - eicosatrienoate
  - **arachidonate (eicosatetraenoate)**

- α-linolenate may be converted to:
  - **eicosapentaenoic acid (EPA)**
  - **docosahexaenoic acid (DHA)**

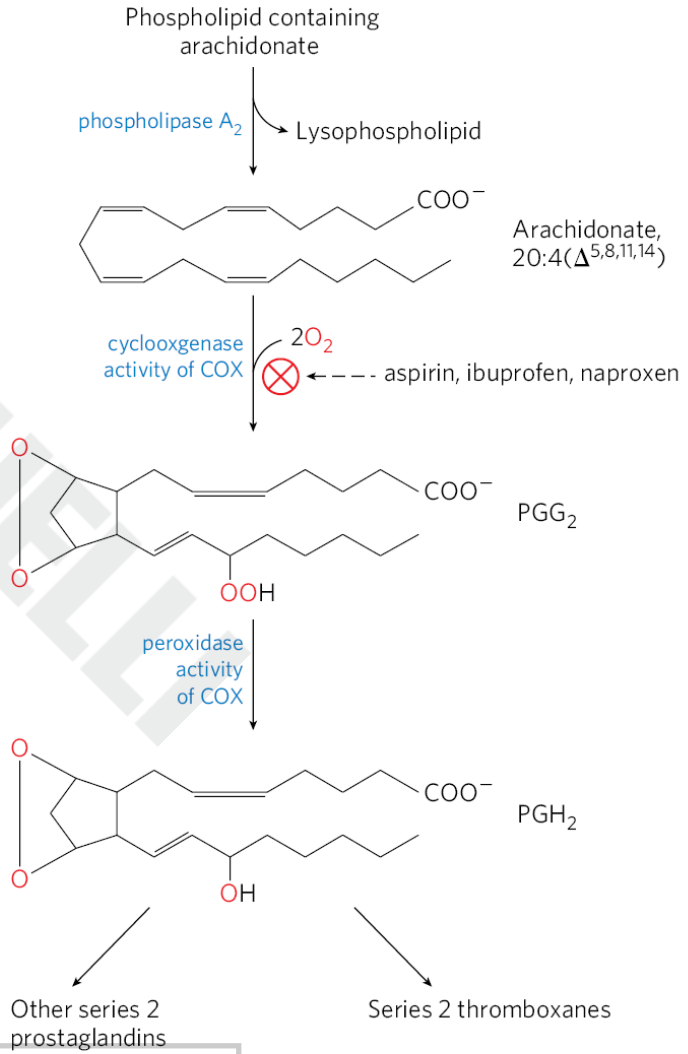
Eicosanoids Are Formed from 20- and 22-Carbon Polyunsaturated Fatty Acids

- eicosanoid hormones include prostaglandins, leukotrienes, and thromboxanes

- enzymes of the smooth ER convert arachidonate to **prostaglandins**
  - **cyclooxygenase (COX) = prostaglandin H_2 synthase** = catalyzes the formation of prostaglandin H_2 (PGH_2)

The Mechanism of Prostaglandin H_2 Synthase

- PGH_2 synthase has cyclooxygenase and peroxidase activity enzyme
  - cyclooxygenase activity adds 2 O_2 to form PGG_2
  - peroxidase activity converts peroxide to alcohol to form PGH_2



Prostaglandin H_2 Synthase Has Two Isoforms

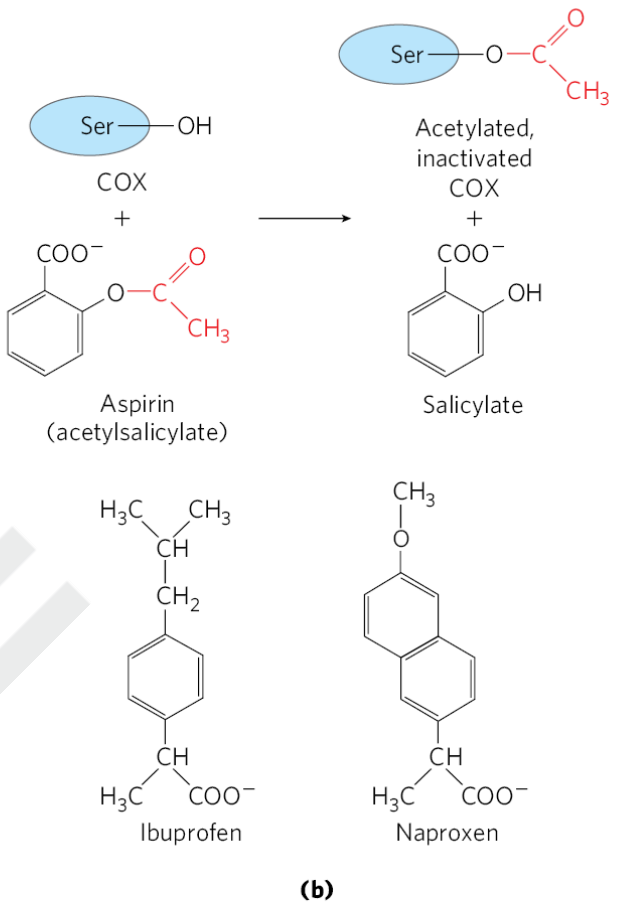
- COX-1 = catalyzes synthesis of prostaglandins that regulate gastric mucin secretion

- COX-2 = catalyzes synthesis of prostaglandins that mediate pain, inflammation, and fever

The Action of Aspirin and NSAIDs

- aspirin irreversibly inactivates the cyclooxygenase activity of both COX isozymes
  - acetylates a Ser residue and blocks the enzyme's active site
  - inhibits the synthesis of prostaglandins and thromboxanes

- NSAIDs also inhibit both COX isozymes



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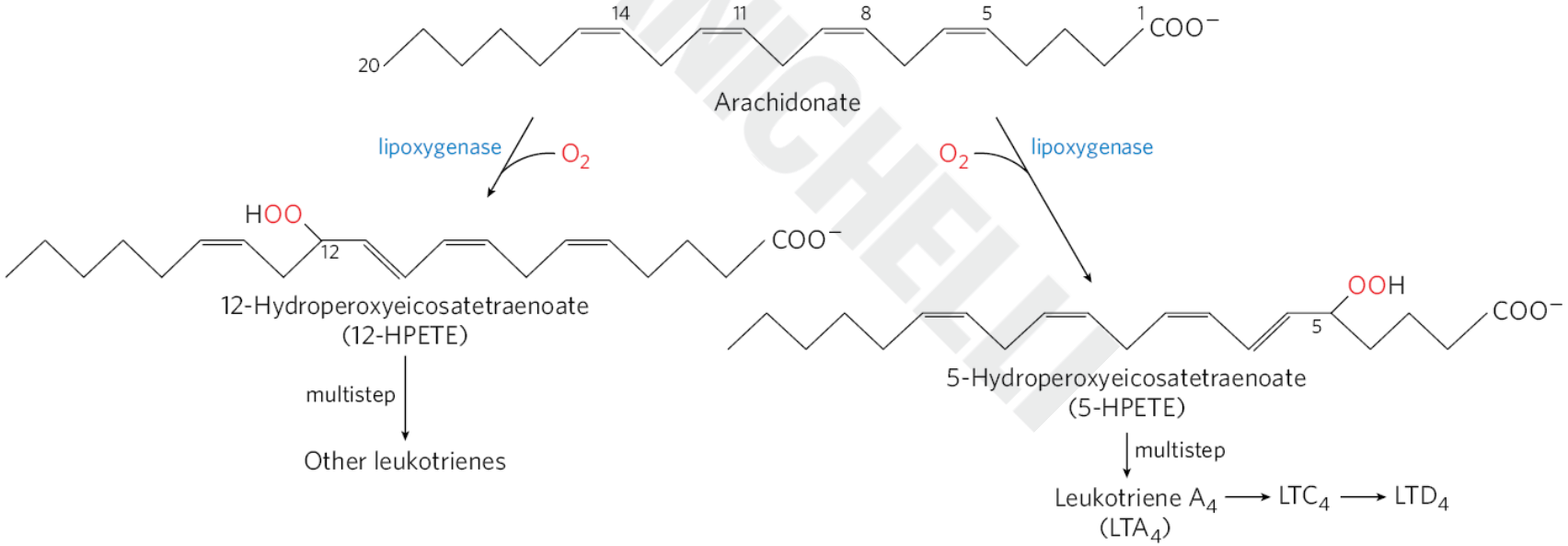
Thromboxane Synthase

- **thromboxane synthase =** converts PGH_2 to thromboxane A_2, from which other series 2 **thromboxanes** are derived
  - present in blood platelets (thrombocytes)

The Pathway from Arachidonate to Leukotrienes

- **leukotrienes** = linear eicosanoids



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Catabasis

- **catabasis** = resolution of inflammation
  - promoted by leukotrienes and prostaglandins

- **specialized pro-resolving mediators (SPMs)** = set of eicosanoids that promote catabasis
  - includes **lipoxins**

21.2 Biosynthesis of Triacylglycerols

P1 Principle 1 (3 of 3)

Lipids are the principal form of stored energy in most higher organisms, as well as the major constituents of membranes.

Fatty Acids Have Two Fates

- fatty acids synthesized or ingested have one of two fates:
  - incorporation into triacylglycerols for the storage of metabolic energy
  - incorporation into the phospholipid components of membranes

- both pathways begin with the formation of fatty acyl esters of glycerol

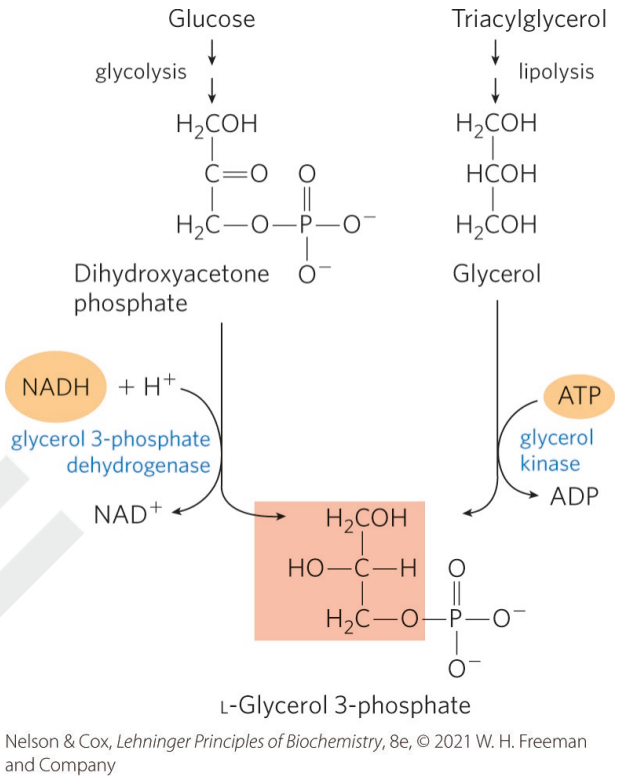
Triacylglycerols and Glycerophospholipids Are Synthesized from the Same Precursors

- triacylglycerols and glycerophospholipids share two precursors:
  - fatty acyl–CoA
  - L-glycerol 3-phosphate

Glycerol 3-Phosphate Is Formed from DHAP and Glycerol

- **glycerol 3-phosphate dehydrogenase** = catalyzes the formation of glycerol 3-phosphate from the glycolytic intermediate dihydroxyacetone phosphate (DHAP)
  - cytosolic NAD-linked enzyme

- **glycerol kinase** = catalyzes the formation of small amounts of glycerol 3-phosphate from glycerol
  - in liver and kidney



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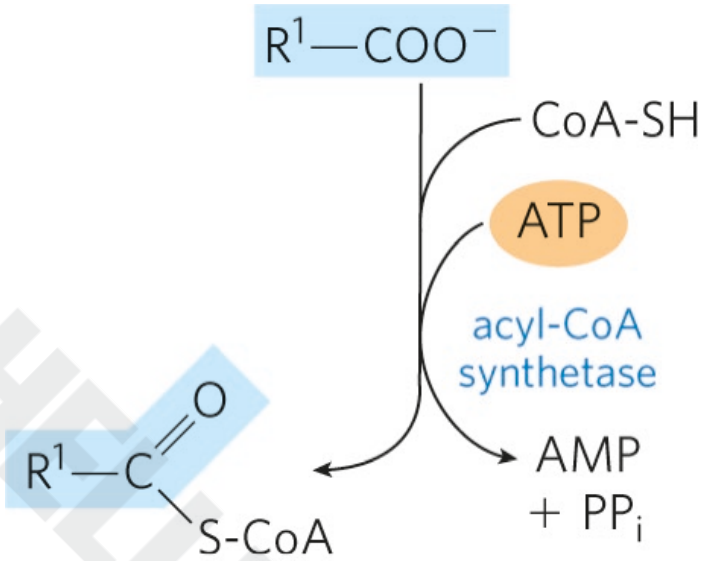
Fatty Acyl-CoAs Are Formed from Fatty Acids

- **acyl-CoA synthetases** = catalyzes the formation of fatty acyl-CoAs from fatty acids
  - the same enzymes responsible for the activation of fatty acids for β oxidation



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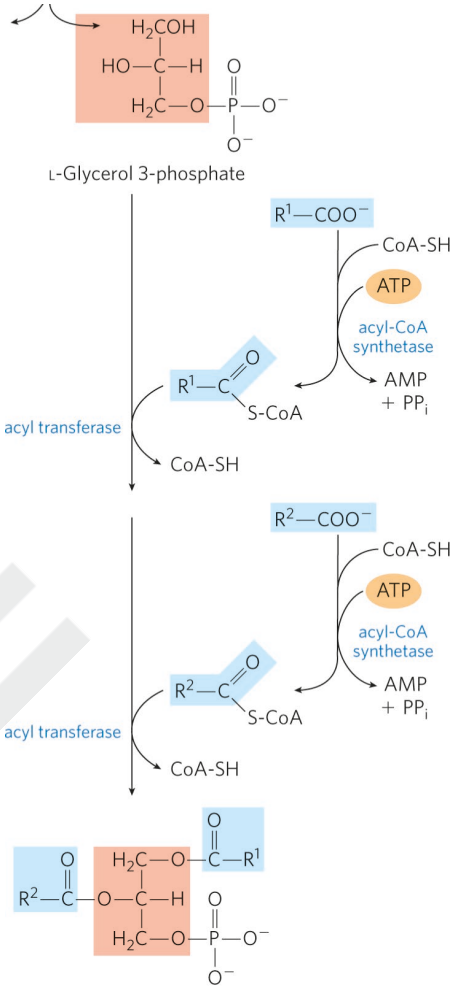
The First Stage in the Biosynthesis of Triacylglycerols

- **acyl transferase** = catalyzes the acylation of the two free hydroxyl groups of L-glycerol 3-phosphate by two molecules of fatty acyl–CoA to yield **diacylglycerol 3-phosphate** (**phosphatidic acid**)



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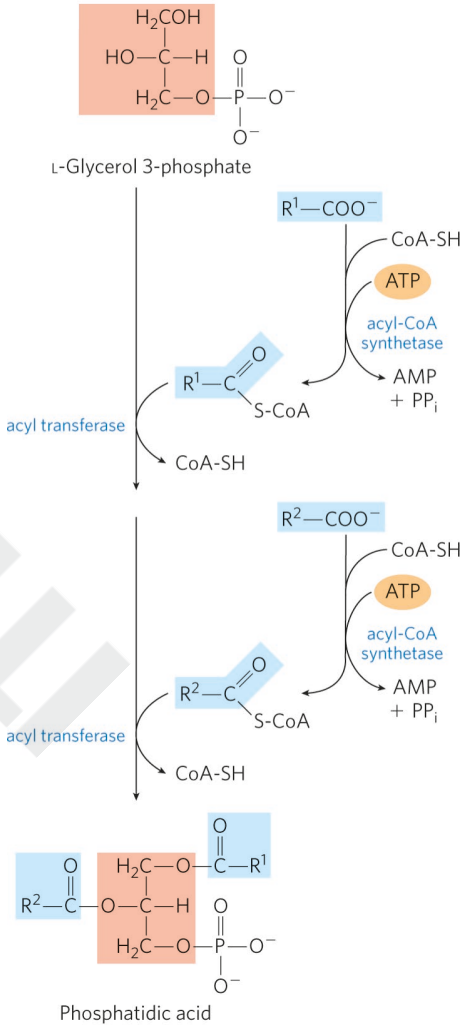
Formation of Triacylglycerols from Phosphatidic Acid

- **phosphatidic acid phosphatase** = hydrolyzes phosphatidic acid to form a 1,2-diacylglycerol

- diacylglycerols are converted to triacylglycerols by transesterification with a third fatty acyl–CoA



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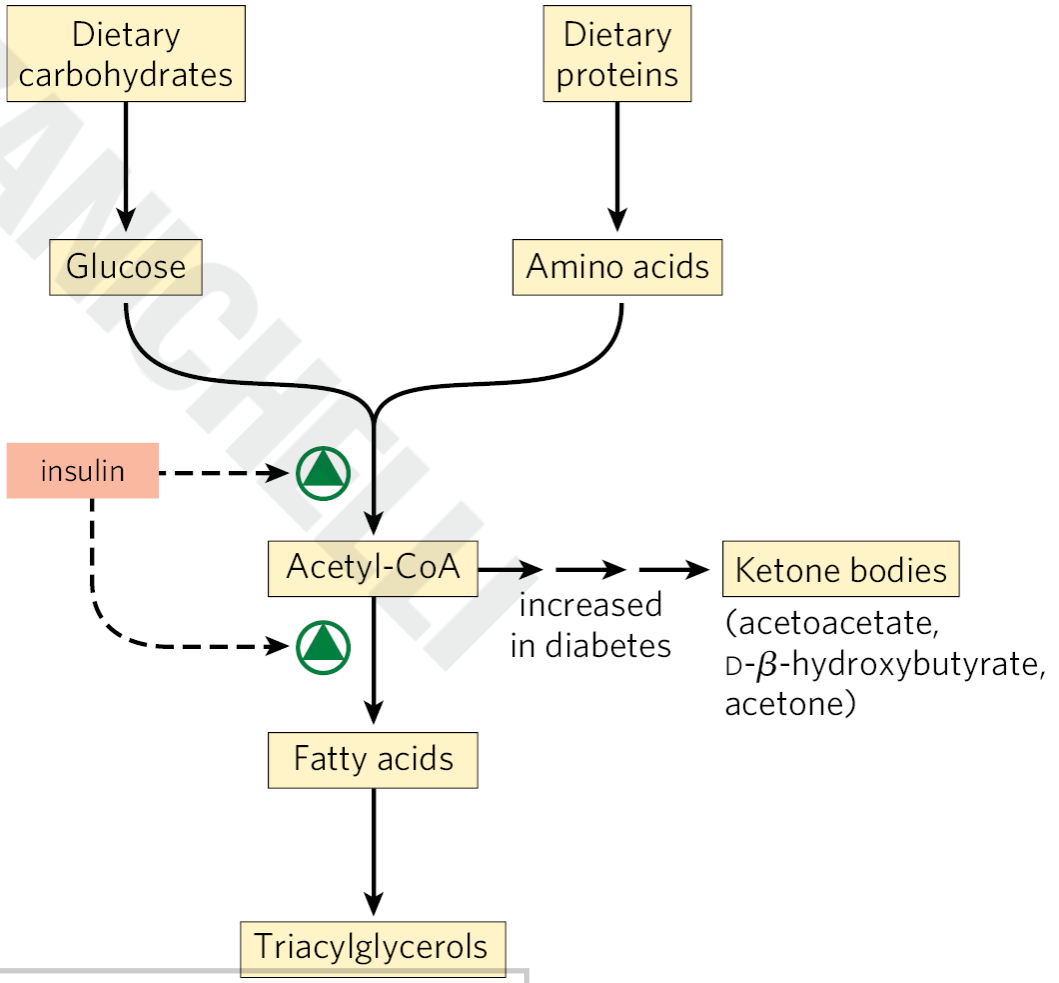
Triacylglycerol Biosynthesis in Animals Is Regulated by Hormones

- the synthesis and degradation of triacylglycerols are hormonally regulated
- people with severe diabetes mellitus fail to synthesize fatty acids



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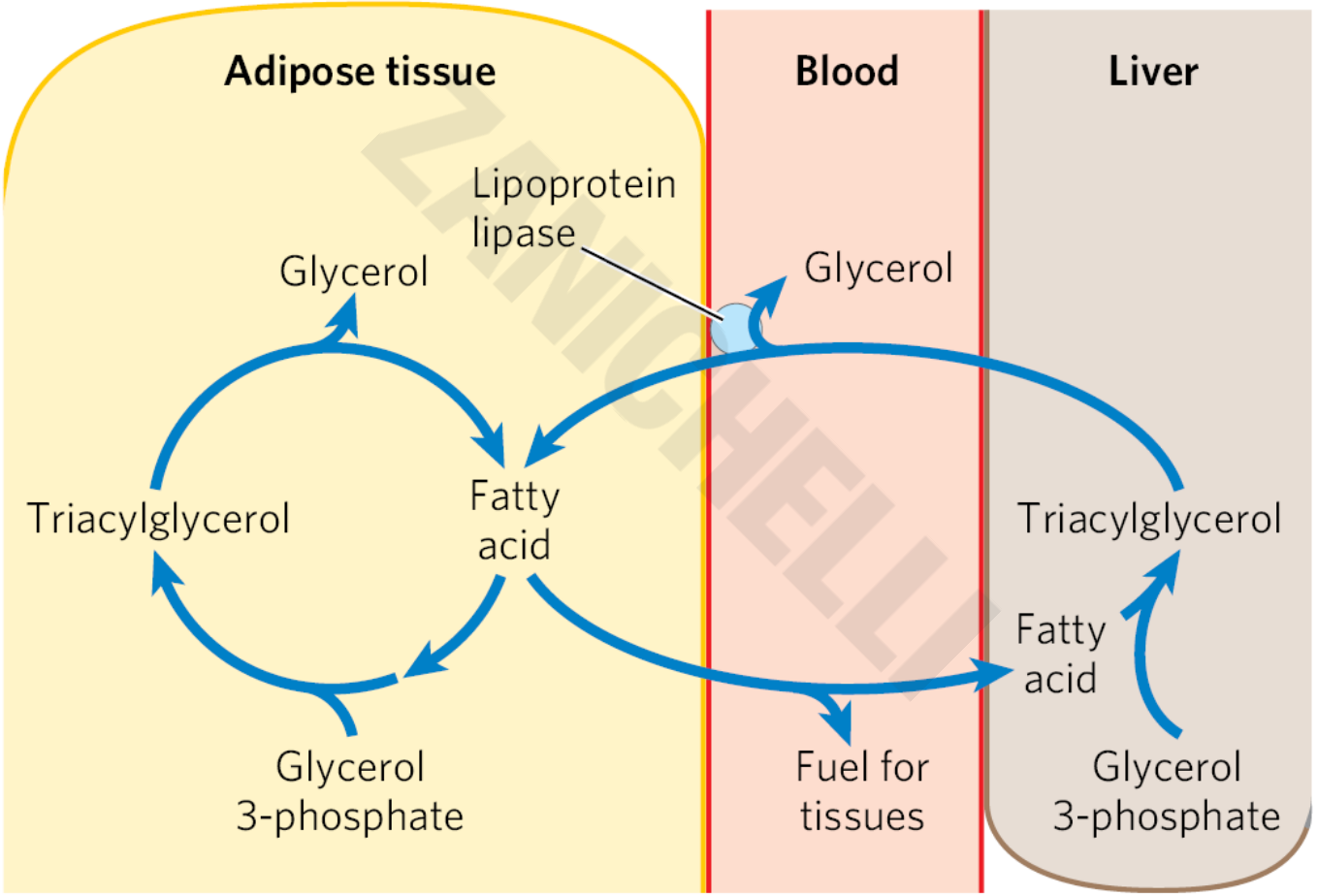
Triacylglycerol Breakdown and Resynthesis Create a Futile Cycle

- ~75% of all fatty acids released by TAG breakdown are reesterified to form TAGs, rather than used for fuel.
  - occurs even during starvation

- some fatty acid recycling takes place in adipose tissue before release into the bloodstream

- **triacylglycerol cycle** = a systemic cycle in which FFAs are transported to the liver, recycled to TAGs, exported into the blood, and taken up again by adipose tissue after release from TAG by lipoprotein lipase

The Triacylglycerol Cycle



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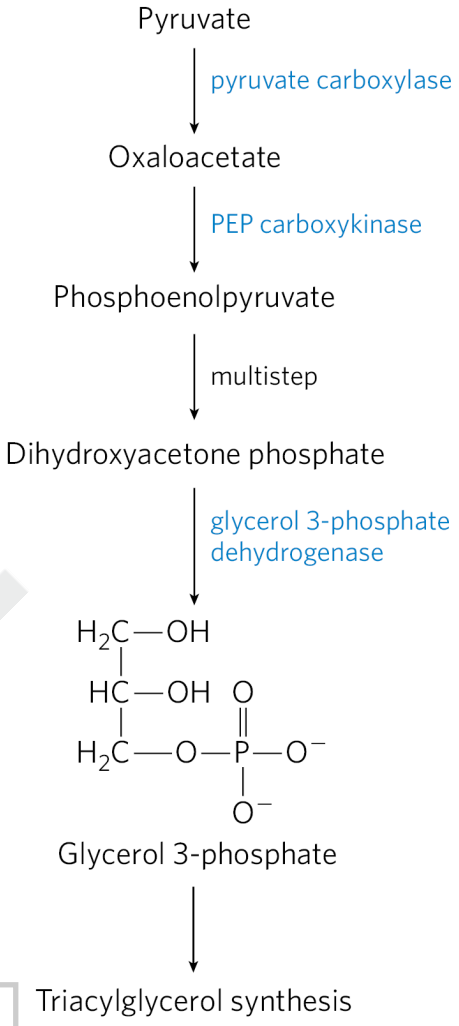
Adipose Tissue Generates Glycerol 3-Phosphate by Glyceroneogenesis

- **glyceroneogenesis** = a shortened version of gluconeogenesis, from pyruvate to DHAP, followed by conversion of the DHAP to glycerol 3-phosphate

- glycerol 3-phosphate is used in triacylglycerol synthesis



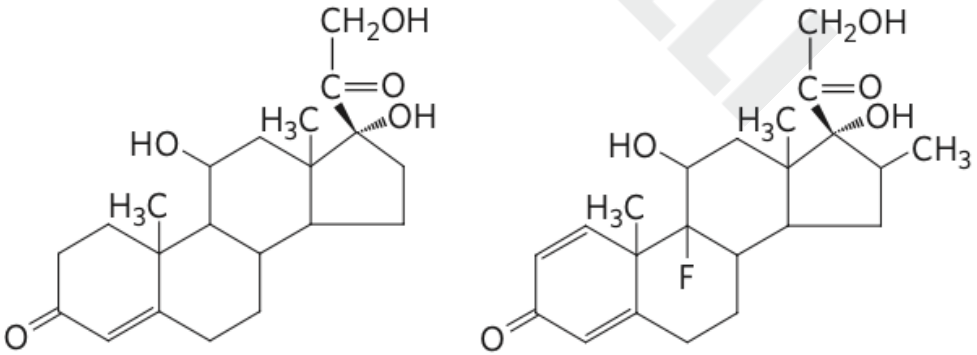
Roles of Glyceroneogenesis

- glyceroneogenesis functions to:
  - help control the rate of fatty acid release to the blood
  - control the rate at which free fatty acids are delivered to mitochondria for use in thermogenesis
  - support the synthesis of glycerol 3-phosphate in fasting humans

PEP Carboxykinase Controls Flux Through the Triacylglycerol Cycle

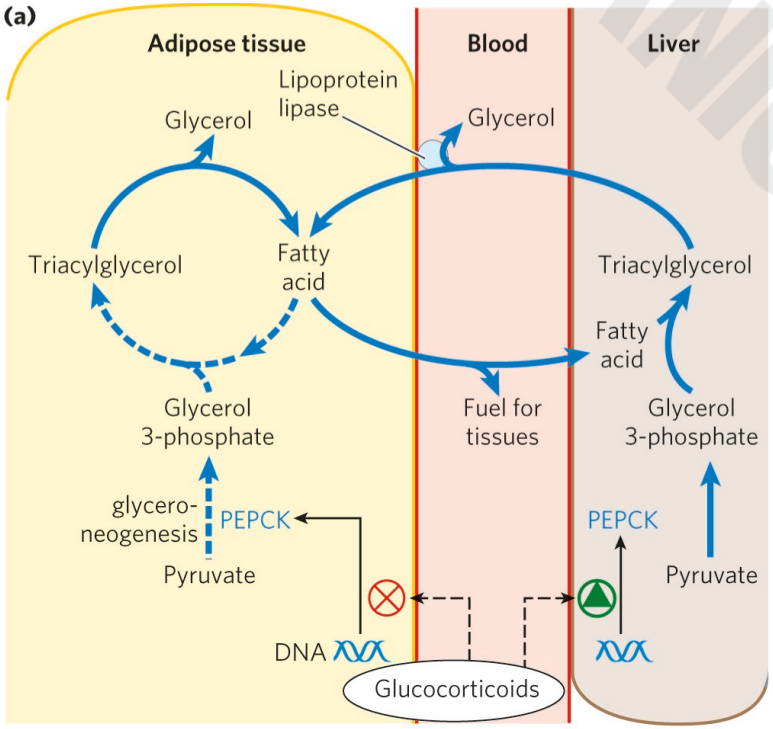
- PEP carboxykinase = limits the rate of both gluconeogenesis and glyceroneogenesis

- glucocorticoid hormones (cortisol, dexamethasone) = regulate the levels of PEP carboxykinase reciprocally in the liver and adipose tissue



Regulation of Glyceroneogenesis

- glucocorticoids increase the expression of the gene encoding PEP carboxykinase in the liver to increase gluconeogenesis and glyceroneogenesis



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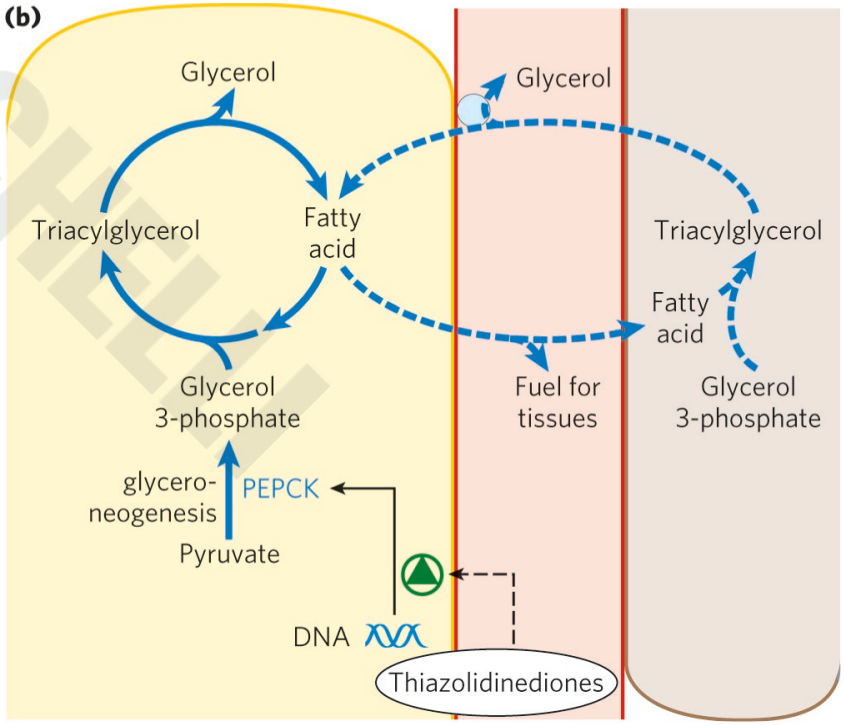

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Thiazolidinediones Treat Type 2 Diabetes by Increasing Glyceroneogenesis

- **thiazolidinediones** = class of drugs that reduces the levels of fatty acids circulating in the blood and increases sensitivity to insulin
  - promotes the increased expression of PEP carboxykinase in adipose tissue

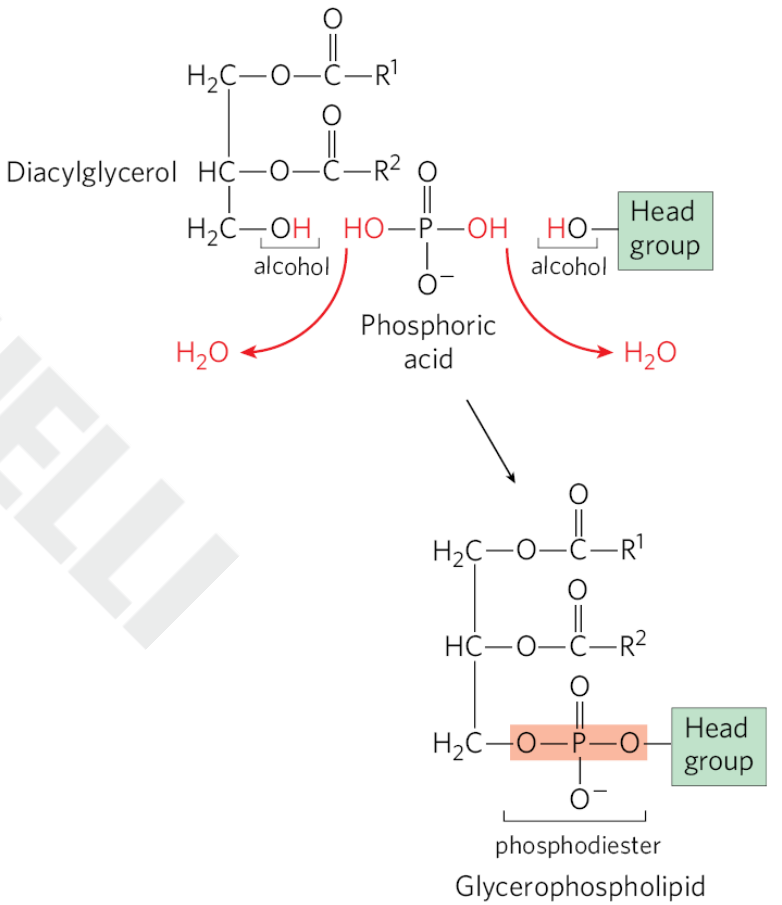
21.3 Biosynthesis of Membrane Phospholipids

Assembly of Phospholipids

- occurs primarily on the surfaces of the smooth ER and the inner mitochondrial membrane in eukaryotic cells

Cells Have Two Strategies for Attaching Phospholipid Head Groups

- begins with phosphatidic acid or diacylglcerols
- polar head group is attached through a phosphodiester bond
  - each of two alcohol hydroxyls forms an ester with phosphoric acid



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Attaching the Phospholipid Head Group Requires Activation by CDP

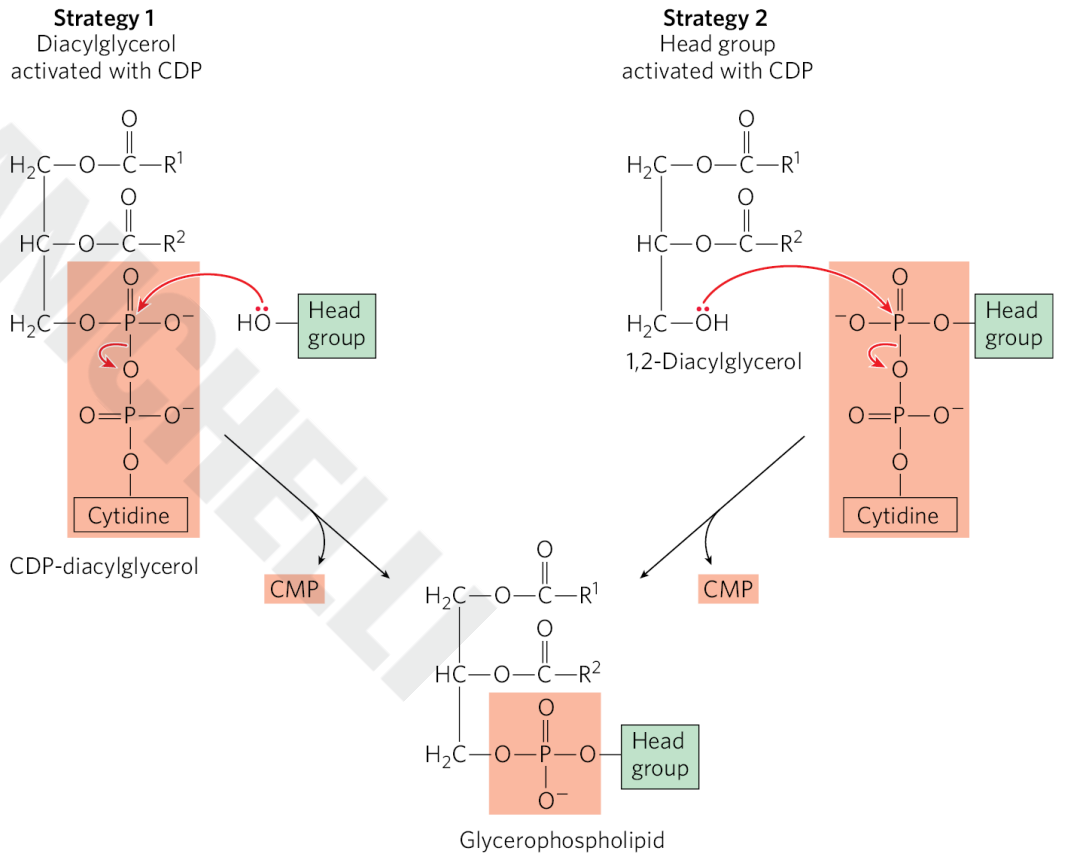
- one of the hydroxyls is first activated by attachment of a cytidine diphosphate (CDP) nucleotide

- CMP is then displaced in a nucleophilic attack by the other hydroxyl

Strategies for Forming the Phosphodiester Bond

- strategy 1 = CDP is attached to diacylglycerol, forming the activated phosphatidic acid **CDP-diacylglycerol**

- strategy 2 = CDP is attached to the hydroxyl of the head group

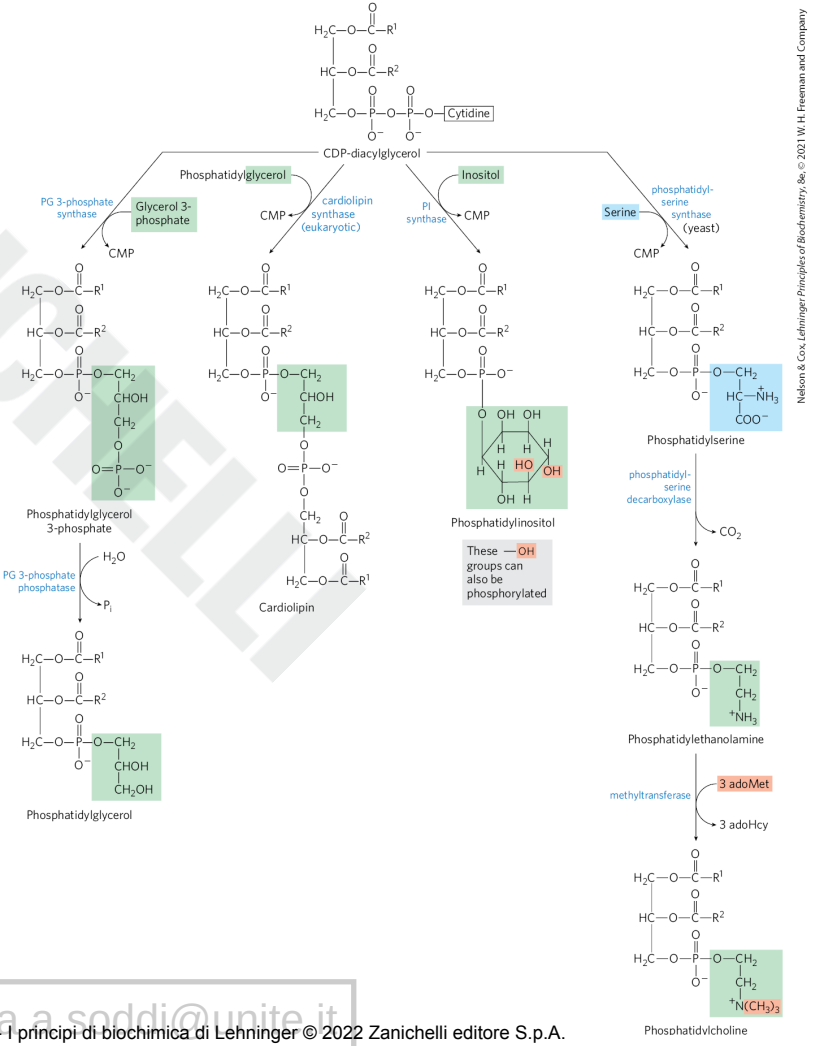


Pathways for Phospholipid Biosynthesis Are Interrelated

- many pathways begin with CDP-diacylglycerol, including synthesis of:
  - **phosphatidylglycerol**
  - **cardiolipin**
  - **phosphatidylinositol**
    - conversion to its phosphorylated derivatives requires specific **phosphatidylinositol kinases**
  - **phosphatidylserine → phosphatidylethanolamine → phosphatidylcholine**

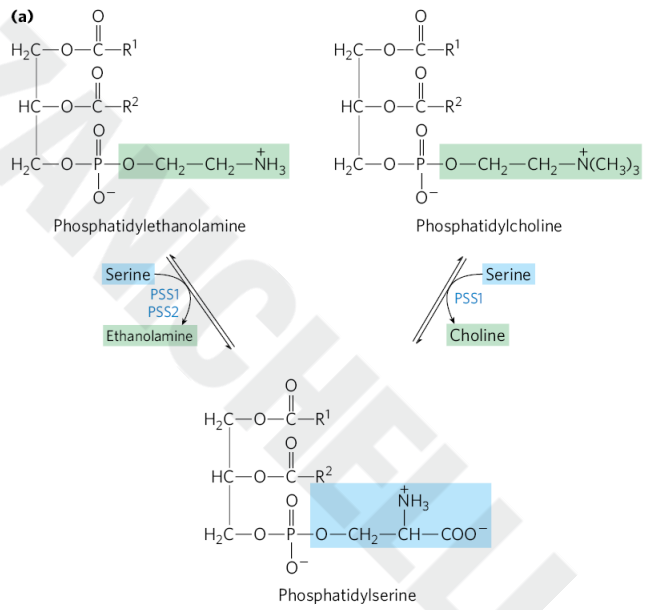
Synthesis of Glycerophospholipids from CDP-Diacylglycerol

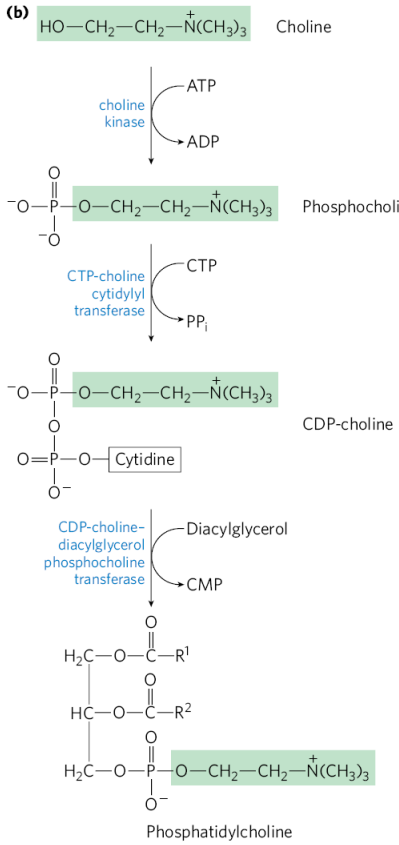
- phosphatidyl-ethanolamine and phosphatidylcholine are synthesized using strategy 1 in the mitochondria



Pathways For Phosphatidylserine and Phosphatidylcholine Synthesis in Mammals

- phosphatidyl-ethanolamine and phosphatidyl-choline are synthesized using strategy 2 in the ER and nucleus
- phosphatidyl-serine is derived from head-group exchange





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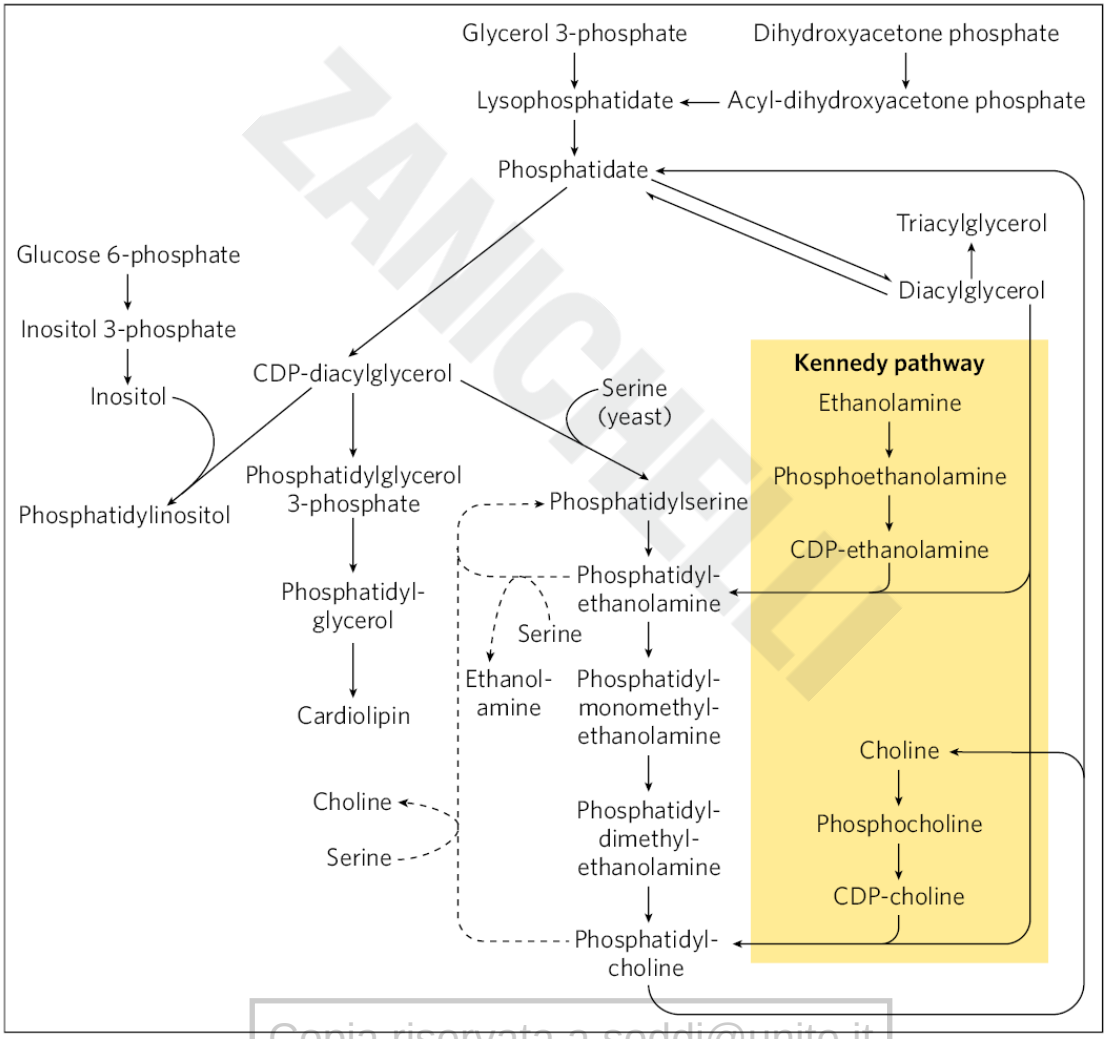
Phospholipid and Triacylglycerol Biosynthetic Pathways



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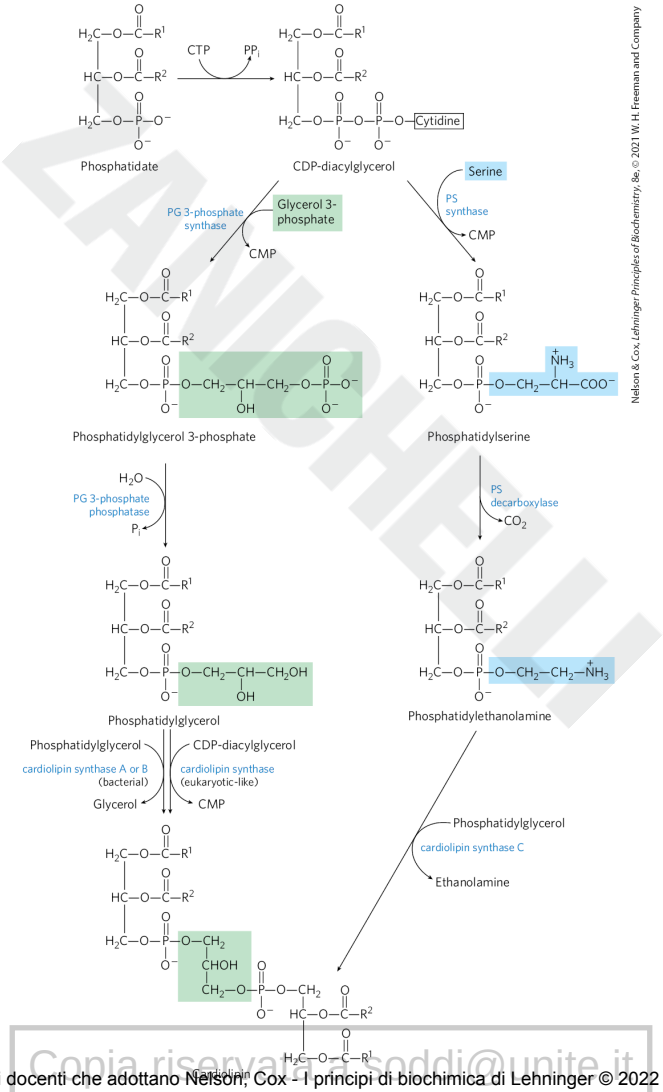
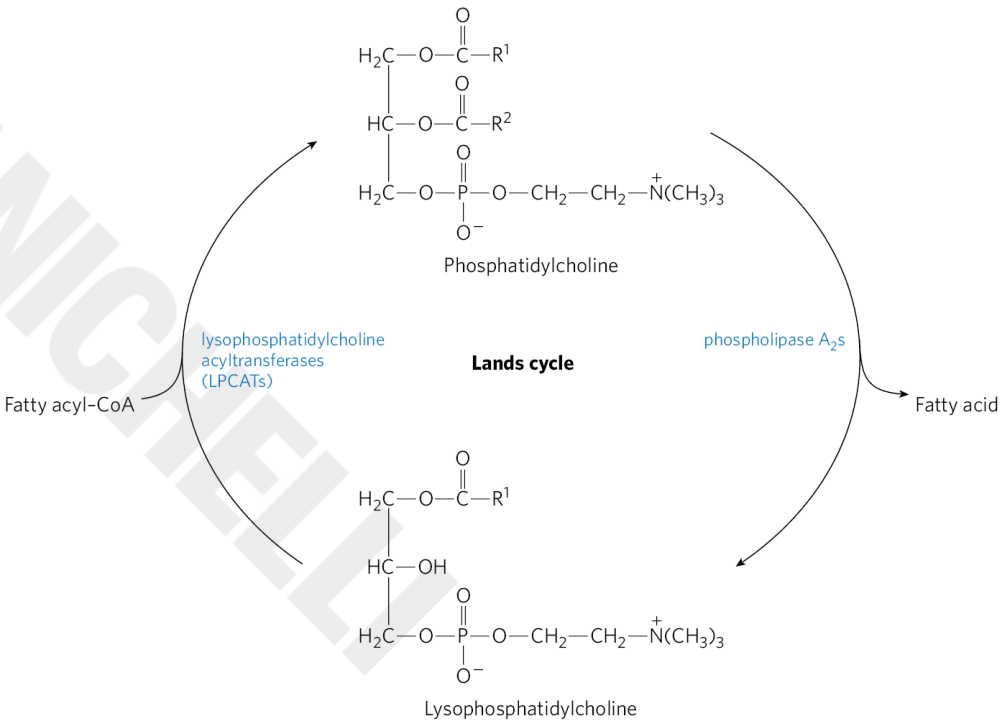
Origin of Polar Head Groups of Phospholipids in *E. coli*



Eukaryotic Membrane Phospholipids Are Subject to Remodeling

- in mammals, phospholipids are remodeled in membranes via the **Lands cycle**
  - facilitated by **lysophosphatidyl-choline acyltransferases (LPCATs)**



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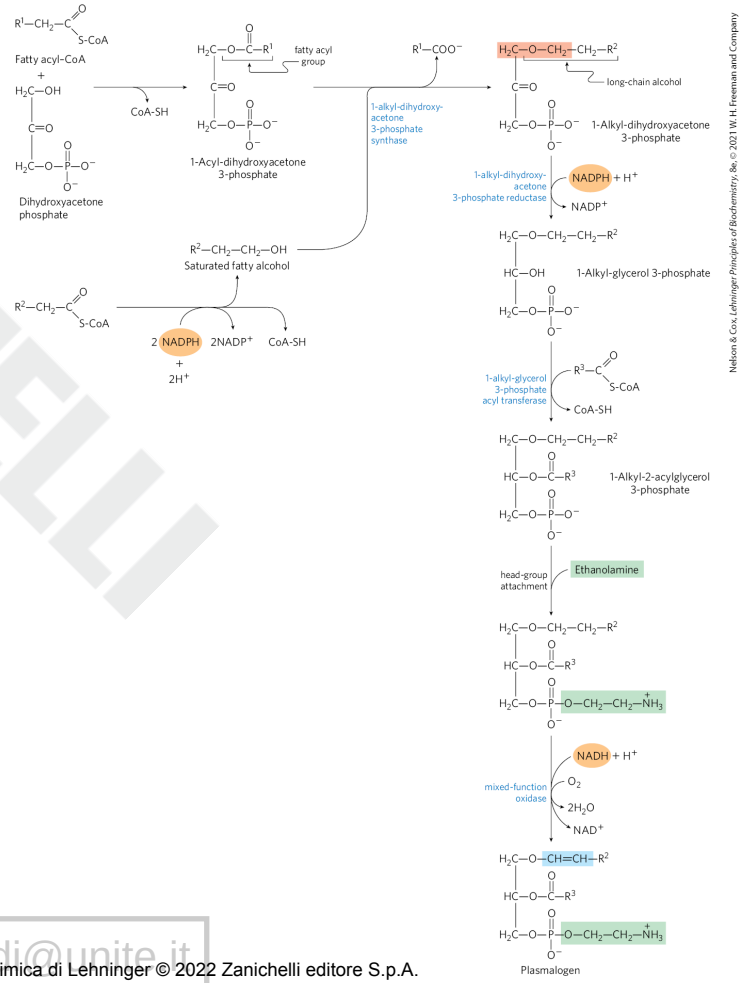
P5 Principle 5 (2 of 7)

Like other major classes of biological molecules, lipids have a plethora of cellular functions. Specialized lipids serve as pigments (retinal, carotene), cofactors (vitamin K), detergents (bile salts), transporters (dolichols), hormones (vitamin D derivatives, sex hormones), extracellular and intracellular messengers (eicosanoids, phosphatidylinositol derivatives), and anchors for membrane proteins (covalently attached fatty acids, prenyl groups, phosphatidylinositol). The ability to synthesize a variety of lipids is essential to all organisms.

Plasmalogen Synthesis Requires Formation of an Ether-Linked Fatty Alcohol

- biosynthesis of ether lipids (including **plasmalogens** and the **platelet-activating factor**) uses similar pathways

- the characteristic double bond in plasmalogens is introduced by a mixed-function oxidase



P5 Principle 5 (3 of 7)

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Sphingolipid and Glycerophospholipid Synthesis Share Precursors and Some Mechanisms

- four stages of sphingolipid biosynthesis:
  - synthesis of the 18-carbon amine **sphinganine** from palmitoyl-CoA and serine
  - attachment of a fatty acid in amide linkage to yield ***N*-acylsphinganine**
  - desaturation of the sphinganine moiety to form ***N*-acylsphingosine** (ceramide)
  - attachment of a head group to produce a sphingolipid such as a **cerebroside** or **sphingomyelin**

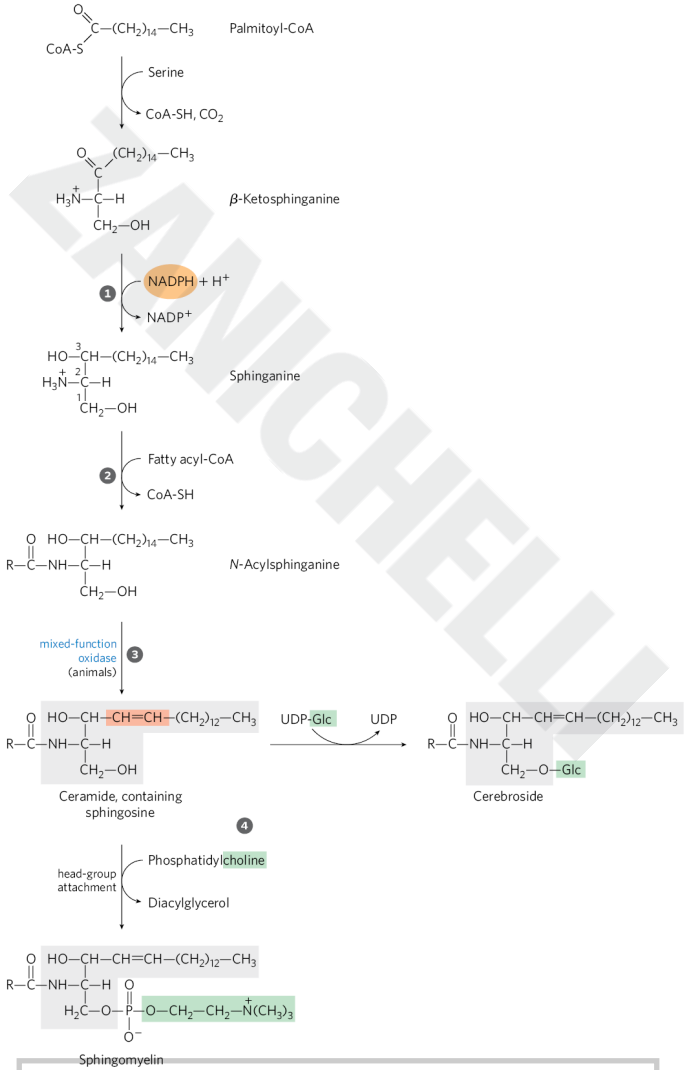
P5 Principle 5 (4 of 7)

Like other major classes of biological molecules, lipids have a plethora of cellular functions. Specialized lipids serve as pigments (retinal, carotene), cofactors (vitamin K), detergents (bile salts), transporters (dolichols), hormones (vitamin D derivatives, sex hormones), extracellular and intracellular messengers (eicosanoids, phosphatidylinositol derivatives), and anchors for membrane proteins (covalently attached fatty acids, prenyl groups, phosphatidylinositol). The ability to synthesize a variety of lipids is essential to all organisms.

Glycolipids

- glycolipids = cerebrosides and **gangliosides**
  - the head-group sugar is attached directly to the C-1 hydroxyl of sphingosine in glycosidic linkage
  - the sugar donor is a UDP-sugar

Biosynthesis of Sphingolipids



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Polar Lipids Are Targeted to Specific Cellular Membranes

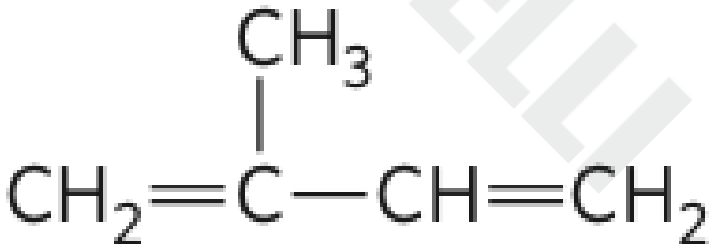
- membrane lipids are insoluble in water and cannot diffuse to their point of insertion

- membrane lipids travel to their intracellular destinations via:
  - transport vesicles
  - specific proteins

21.4 Cholesterol, Steroids, and Isoprenoids: Biosynthesis, Regulation, and Transport

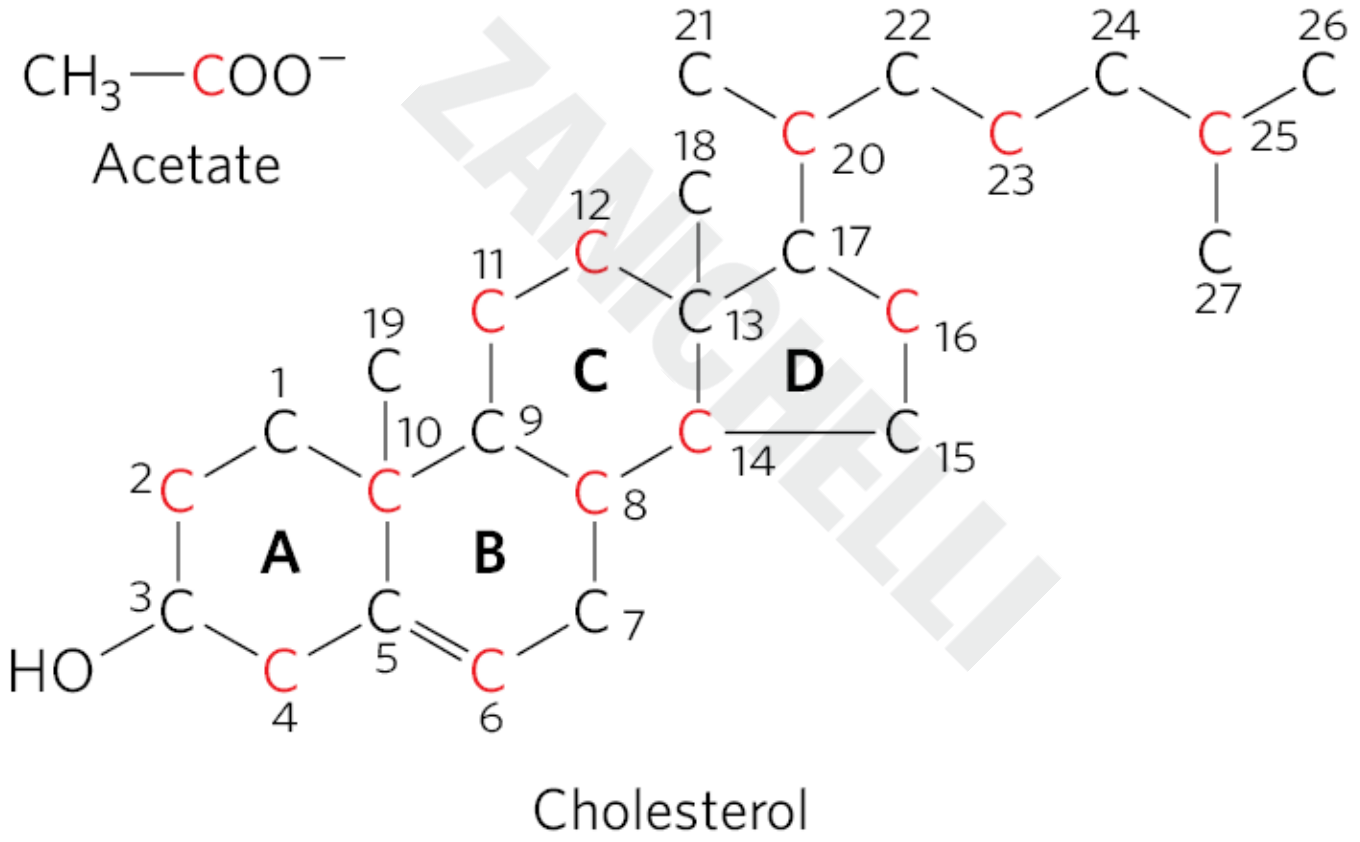
Synthesis of Cholesterol

- all of its carbon atoms are provided by acetate
- **isoprene** units are essential intermediates in the pathway



Isoprene

Origin of the Carbon Atoms of Cholesterol

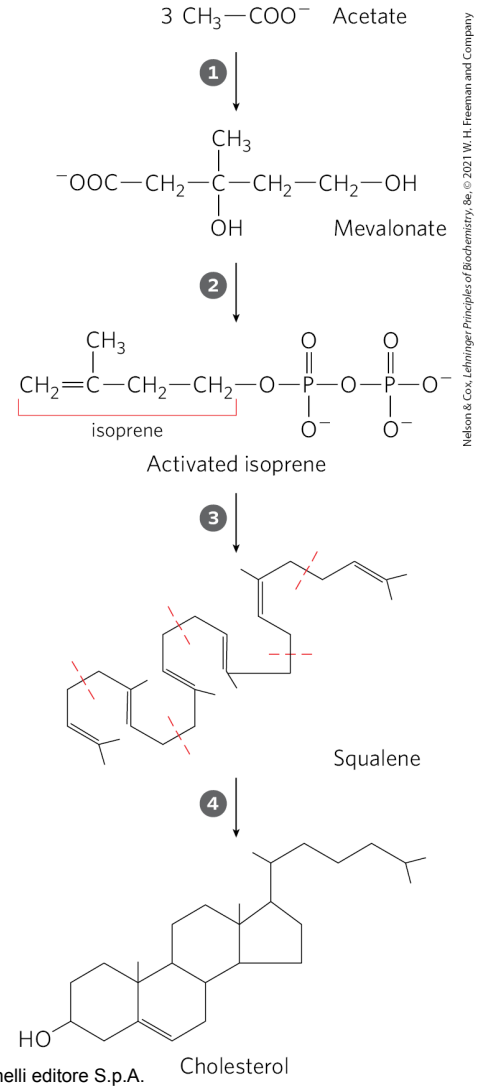


P5 Principle 5 (5 of 7)

Like other major classes of biological molecules, lipids have a plethora of cellular functions. Specialized lipids serve as pigments (retinal, carotene), cofactors (vitamin K), detergents (bile salts), transporters (dolichols), hormones (vitamin D derivatives, sex hormones), extracellular and intracellular messengers (eicosanoids, phosphatidylinositol derivatives), and anchors for membrane proteins (covalently attached fatty acids, prenyl groups, phosphatidylinositol). The ability to synthesize a variety of lipids is essential to all organisms.

Cholesterol Is Made from Acetyl-CoA in Four Stages

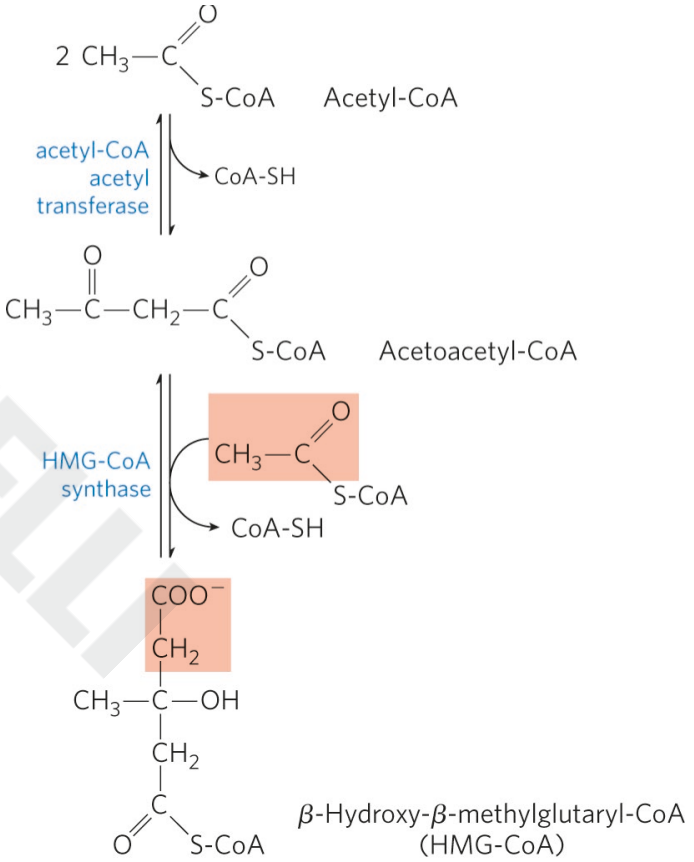
- four stages:
  - condensation of three acetate units to form mevalonate
  - conversion of mevalonate to activated isoprene units
  - polymerization of six isoprene units to form the 30-carbon linear squalene
  - cyclization of squalene to form the four rings of the steroid nucleus



Stage 1: Synthesis of Mevalonate from Acetate

- **acetyl-CoA acetyl transferase** = catalyzes the condensation of two acetyl-CoA molecules

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



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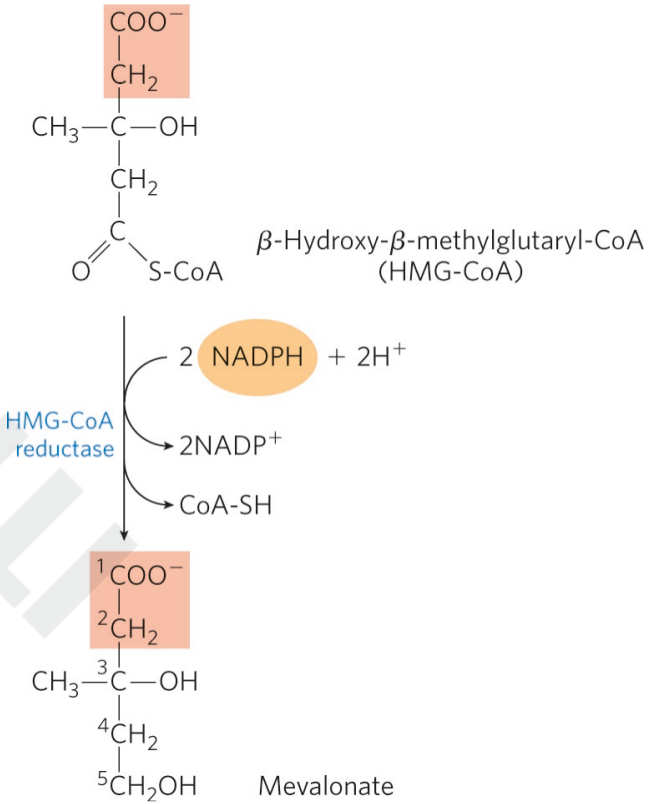
P3 Principle 3 (5 of 5)

Like other anabolic pathways, the reaction sequences in lipid biosynthesis are endergonic and reductive. They use ATP as a source of metabolic energy and a reduced electron carrier (usually NADPH) as a reductant.

Stage 1: Synthesis of Mevalonate from Acetate, Continued

- **HMG-CoA reductase** = an integral membrane protein of the smooth ER that catalyzes the reduction of HMG-CoA to **mevalonate**
  - the major point of regulation on the pathway to cholesterol
  - catalyzes the committed step
  - requires 2 molecules of NADPH



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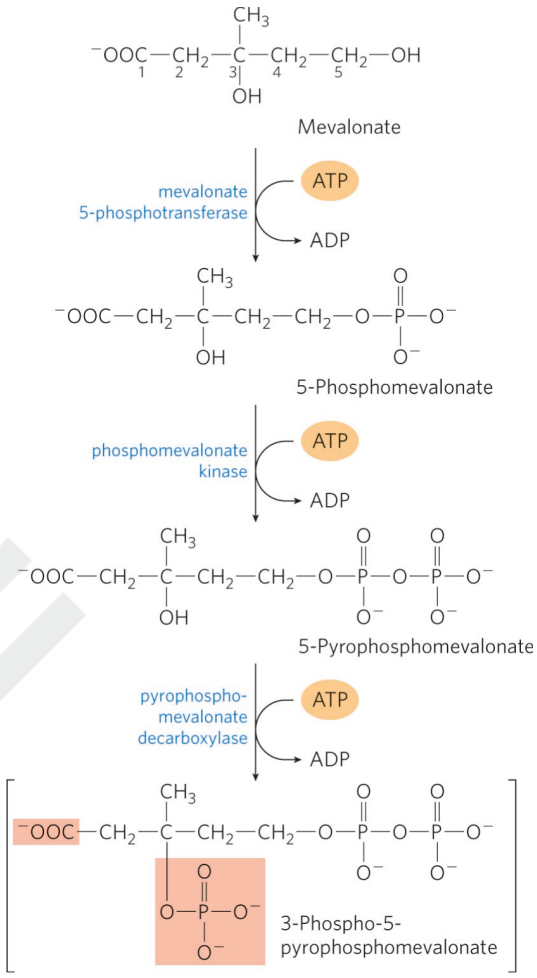
Stage 2: Conversion of Mevalonate to Two Activated Isoprenes

- three phosphate groups are transferred from three ATP molecules to mevalonate to form 3-phospho-5-pyrophosphomevalonate



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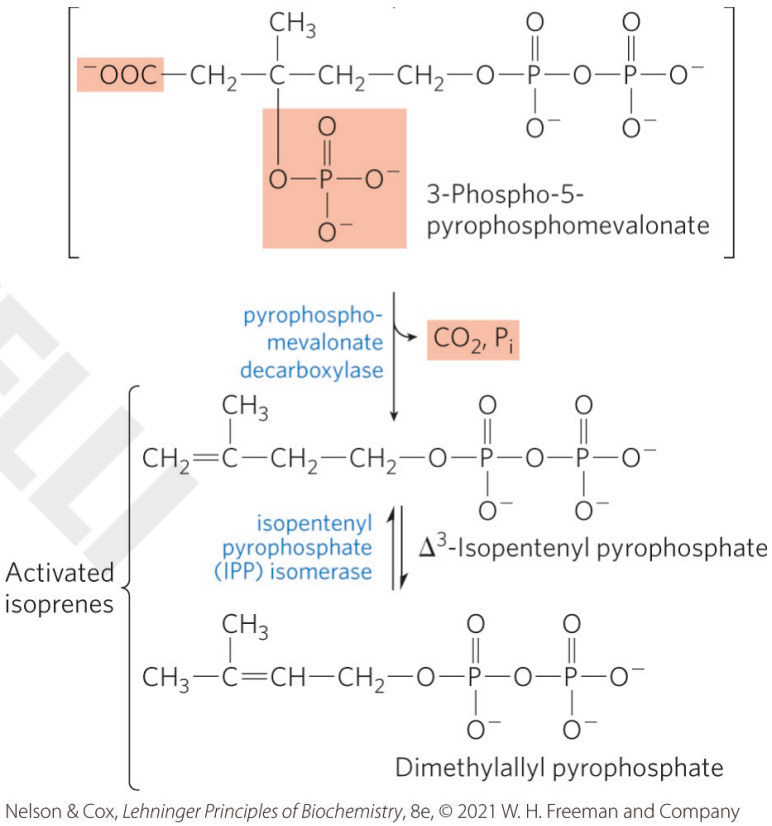
Stage 2: Conversion of Mevalonate to Two Activated Isoprenes, Continued

- CO_2 and P_i leave to produce a double bond in **Δ^3-isopentenyl pyrophosphate**
  - the first activated isoprene
- isomerization of Δ^3-isopentenyl pyrophosphate yields **dimethylallyl pyrophosphate**
  - the second activated isoprene



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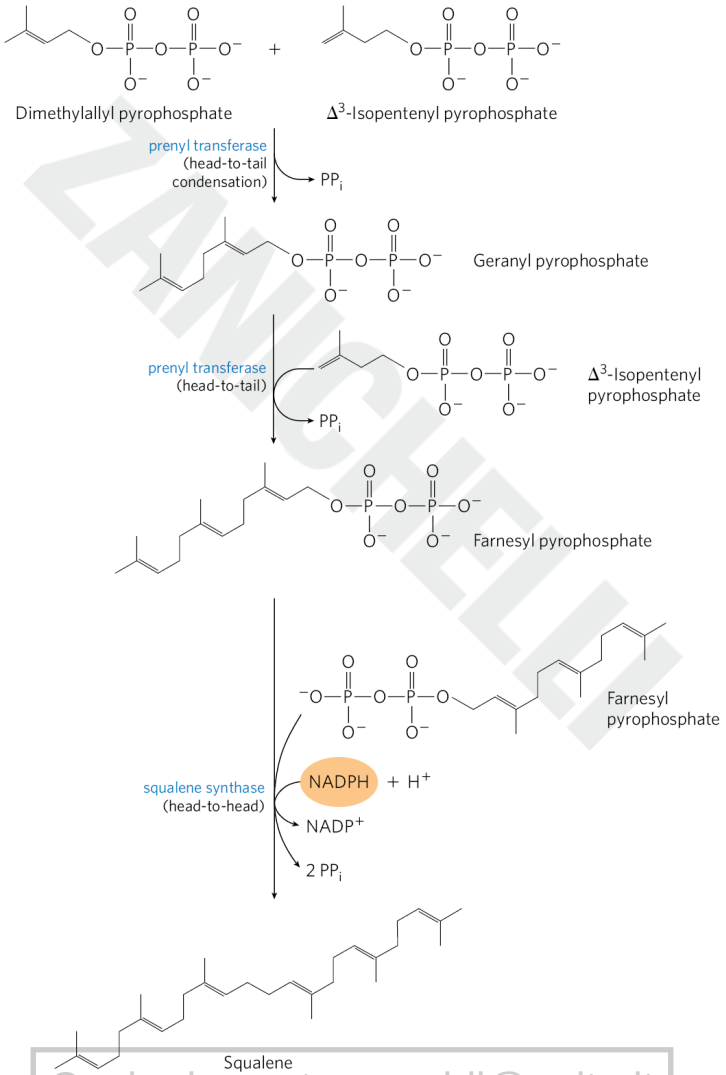
Stage 3: Condensation of Six Activated Isoprene Units to Form Squalene

- the two activated isoprenes undergo head-to-tail condensation to form **geranyl pyrophosphate**
- geranyl pyrophosphate undergoes head-to-tail condensation with isopentenyl pyrophosphate to form **farnesyl pyrophosphate**
- two molecules of farnesyl pyrophosphate join head-to-head to form **squalene**

Formation of Squalene



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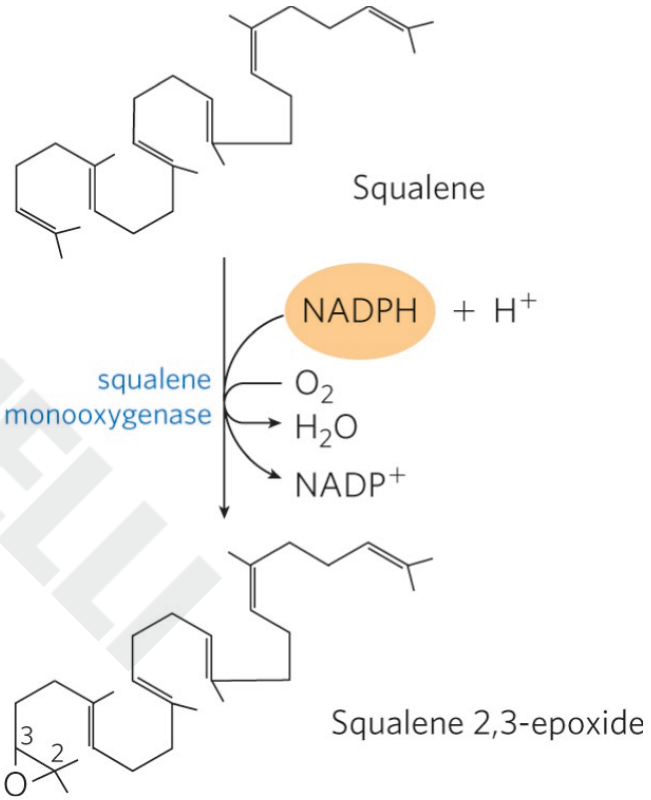
Stage 4: Conversion of Squalene to the Four-Ring Steroid Nucleus (1 of 2)

- **squalene monooxygenase =** adds one oxygen atom from O_2 to the end of the squalene chain to form **squalene 2,3-epoxide**
  - mixed-function oxidase
  - requires NADPH



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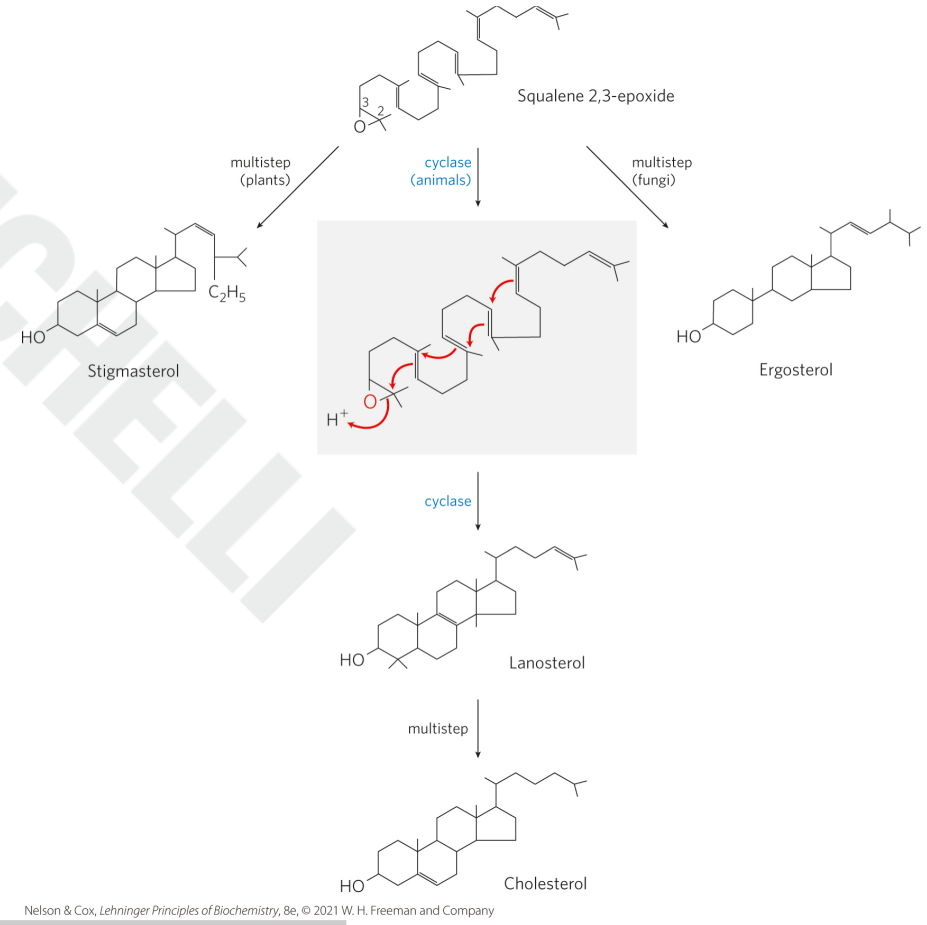
Stage 4: Conversion of Squalene to the Four-Ring Steroid Nucleus (2 of 2)

- cyclization of squalene 2,3-epoxide forms **lanosterol**
- a series of ~20 reactions converts lanosterol to cholesterol
- in plants, the epoxide cyclizes to other sterols, such as ergosterol



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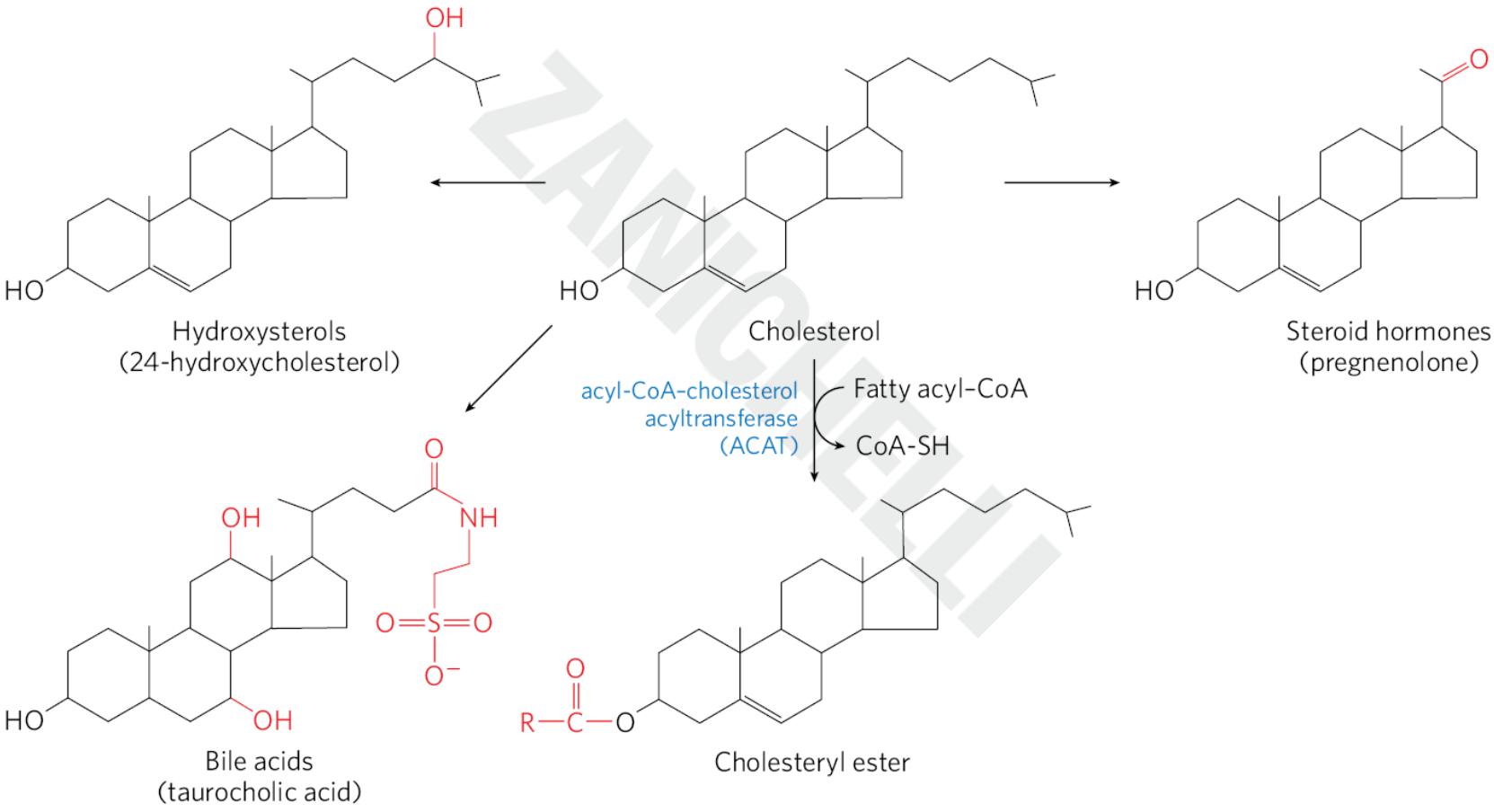
Cholesterol Has Several Fates

- cholesterol is synthesized primarily in the liver
- most of it is exported as:
  - bile acids
  - biliary cholesterol
  - **cholesteryl esters**
    - formed in the liver by **acyl-CoA–cholesterol acyltransferase (ACAT)**

Metabolic Fates of Cholesterol



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Export of Cholesterol as Bile Acids

- **bile acids =** the principal components of bile, a fluid stored in the gallbladder
  - excreted into the small intestine to aid in the digestion
  - relatively hydrophilic cholesterol derivatives that serve as emulsifiers

Export of Cholesterol as Biliary Cholesterol

- biliary cholesterol = cholesterol contained in bile
  - bile removes excess cholesterol from the intestine and facilitates excretion
  - dietary fiber binds to bile and interferes with bile reabsorption in the intestines

Export of Cholesterol as Cholesteryl Esters

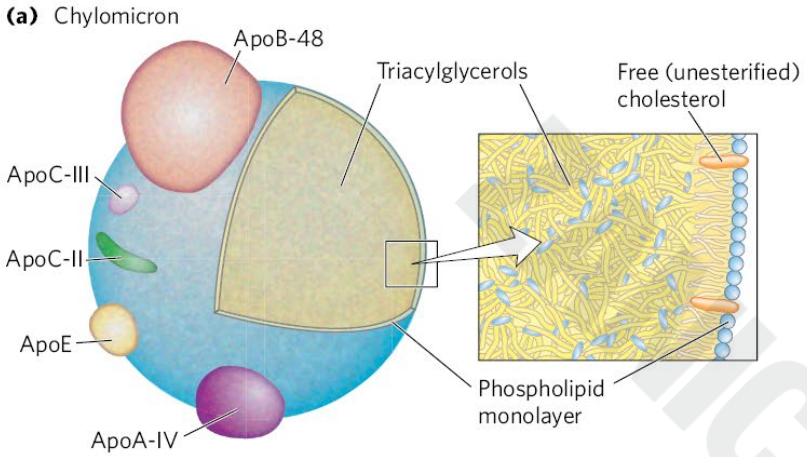
- **cholesteryl esters** = cholesterol molecule with a fatty acid from coenzyme A attached to its hydroxyl group
  - formed in the liver by **acyl-CoA–cholesterol acyltransferase (ACAT)**
  - cannot function appropriately in membranes due to high hydrophobicity
  - transported to other tissues or stored in the liver in lipid droplets

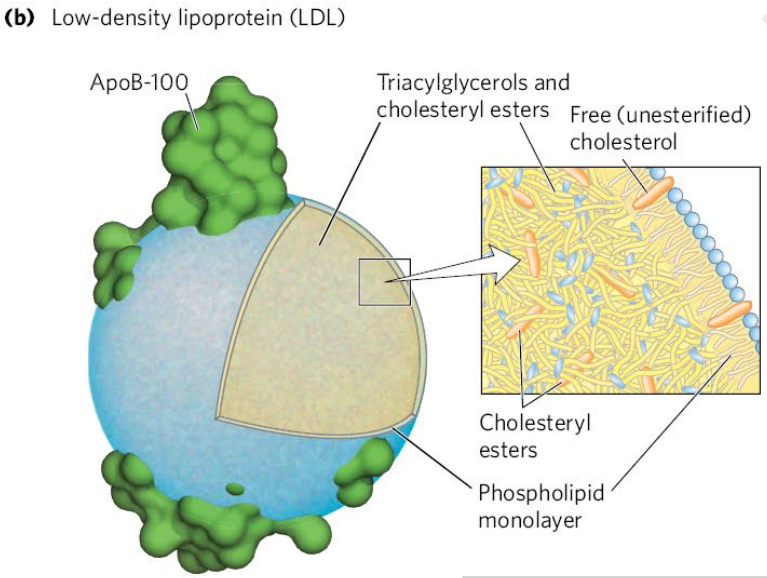
Cholesterol and Other Lipids Are Carried on Plasma Lipoproteins

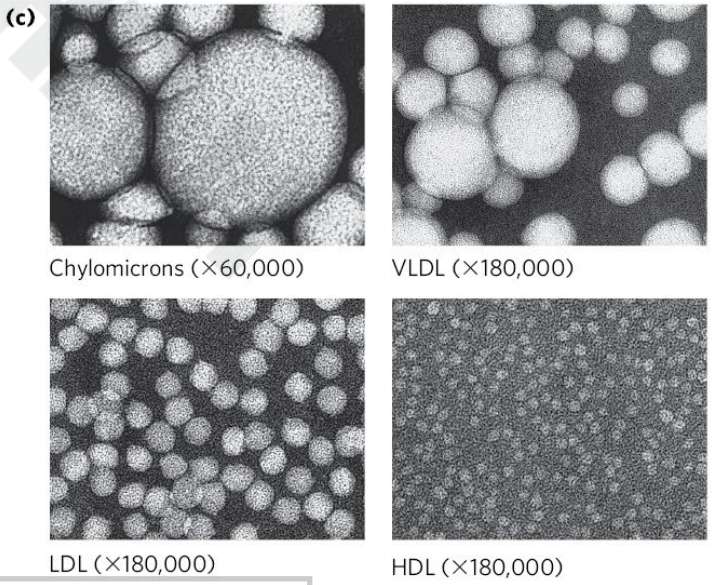
- **apolipoproteins** = specific carrier proteins

- **plasma lipoproteins** = macromolecular complexes of apolipoproteins and various combinations of phospholipids, cholesterol, cholesteryl esters, and triacylglycerols
  - carry cholesterol and cholesteryl ester in the blood

Lipoproteins







Four Major Classes of Human Plasma Lipoproteins

- different combinations of lipids and proteins produce particles of different densities
  - can be separated by ultracentrifugation

Table 21-1 Major Classes of Human Plasma Lipoproteins: Some Properties

Lipoprotein	Density (g/mL)	Protein	Phospholipids	Composition (wt %): Free cholesterol	Composition (wt %): Cholesteryl esters	Triacylglycerols
Chylomicrons	<1.006	2	9	1	3	85
VLDL	0.95–1.006	10	18	7	12	50
LDL	1.006–1.063	23	20	8	37	10
HDL	1.063–1.210	55	24	2	15	4

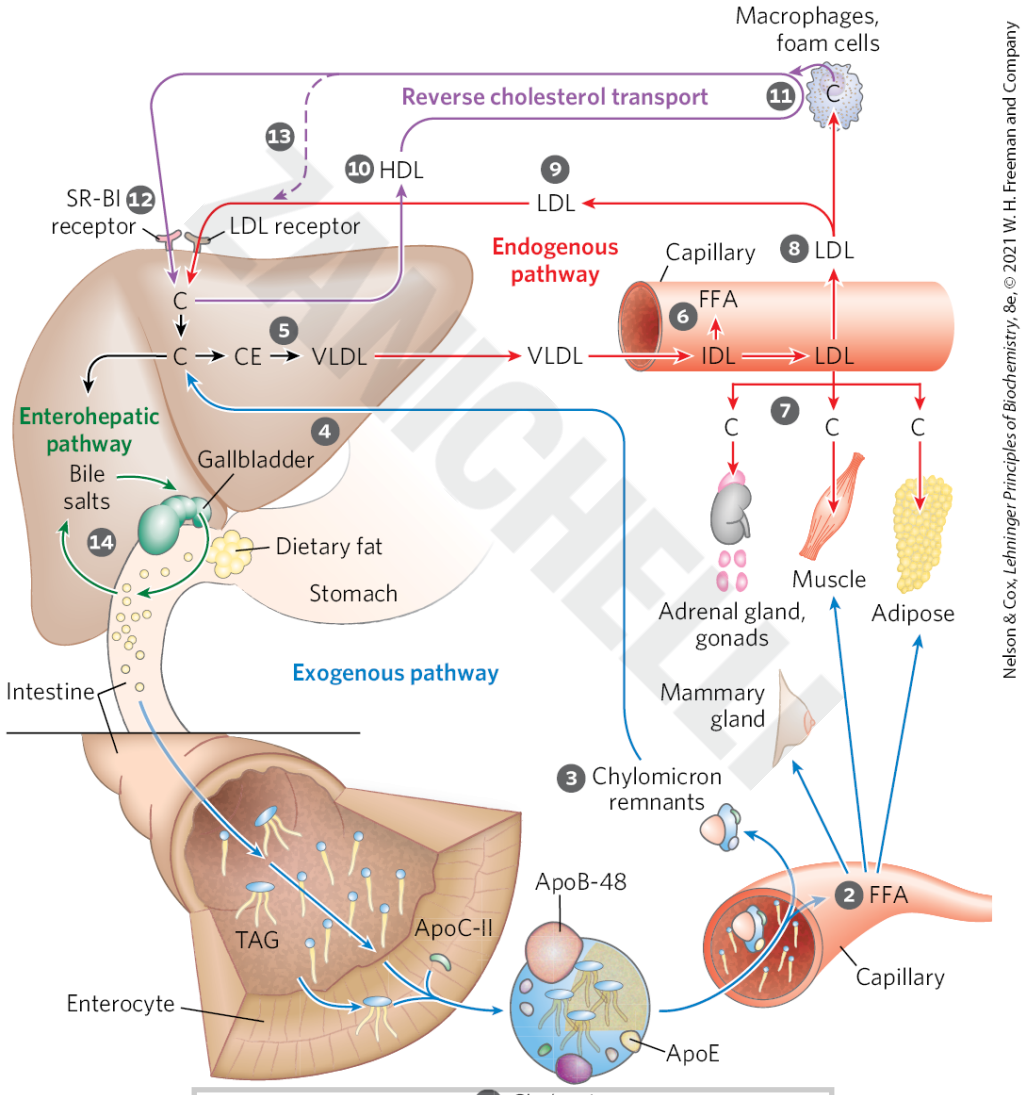
Apolipoproteins of the Human Plasma Lipoproteins

- "apo" designates the protein in its lipid-free form

Table 21-2 Apolipoproteins of the Human Plasma Lipoproteins

Apolipoprotein	Polypeptide molecular weight	Lipoprotein association	Function (if known)
ApoA-I	28,100	HDL	Activates LCAT; interacts with ABC transporter
ApoA-II	17,400	HDL	Inhibits LCAT
ApoA-IV	44,500	Chylomicrons, HDL	Activates LCAT; cholesterol transport/clearance
ApoB-48	242,000	Chylomicrons	Cholesterol transport/clearance
ApoB-100	512,000	VLDL, LDL	Binds to LDL receptor
ApoC-I	7,000	VLDL, HDL	
ApoC-II	9,000	Chylomicrons, VLDL, HDL	Activates lipoprotein lipase
ApoC-III	9,000	Chylomicrons, VLDL, HDL	Inhibits lipoprotein lipase
ApoD	32,500	HDL	
ApoE	34,200	Chylomicrons, VLDL, HDL	Triggers clearance of VLDL and chylomicron remnants
ApoH	50,000	Possibly VLDL, binds phospholipids such as cardiolipin	Roles in coagulation, lipid metabolism, apoptosis, inflammation

Lipoproteins and Lipid Transport



Chylomicrons

- **chylomicrons** = the largest and least dense of the lipoproteins
  - contain a high proportion of triacylglycerols

The Exogenous Pathway

- **exogenous pathway** = the pathway from dietary cholesterol to the liver
  - chylomicrons are synthesized from dietary fats in the ER of enterocytes and enter the bloodstream
  - apoC-II activates lipoprotein lipase in tissues to release FFAs
  - chylomicron remnants move through the bloodstream to the liver
  - receptors in the liver bind to the apoE in the remnants and mediate uptake of these remnants by endocytosis

Very-Low-Density Lipoprotein (VLDL)

- **very-low-density lipoprotein (VLDL)** = lipoproteins that carry cholesteryl esters or triacylglycerols from the liver to muscle and adipose tissue
  - apoC-II activates lipoprotein lipase to release FFAs from triacylglycerols

Low-Density Lipoprotein (LDL) and LDL Receptors

- **low-density lipoprotein (LDL)** = formed by triacylglycerol loss in VLDL
  - rich in cholesterol and cholesteryl esters
  - carries cholesterol to extrahepatic tissues and macrophages

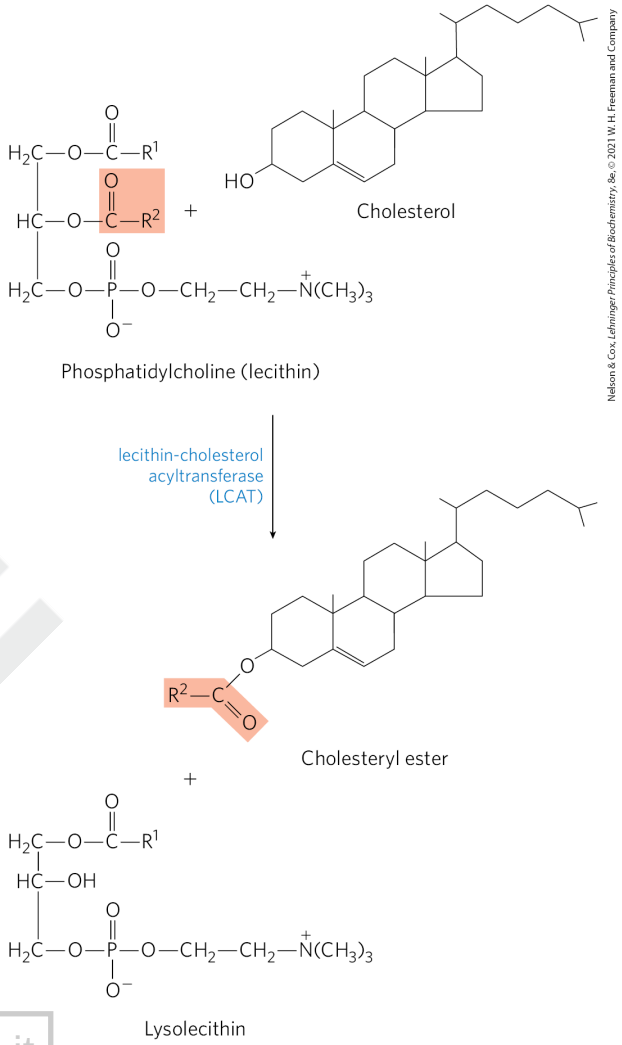
- **LDL receptors** = receptors in the hepatocyte plasma membrane that take up LDL not taken up by peripheral tissues and cells

The Endogenous Pathway (1 of 2)

- **endogenous pathway** = the pathway from VLDL formation in the liver to LDL return to the liver

HDL Carries Out Reverse Cholesterol Transport

- **high-density lipoprotein (HDL)** = lipoproteins that originate in the liver and small intestine as small, protein-rich particles
  - contain **lecithin-cholesterol acyltransferase (LCAT)** to catalyze the formation of cholesteryl esters
  - mediates cholesterol scavenging and transport back to the liver



The Endogenous Pathway (2 of 2)

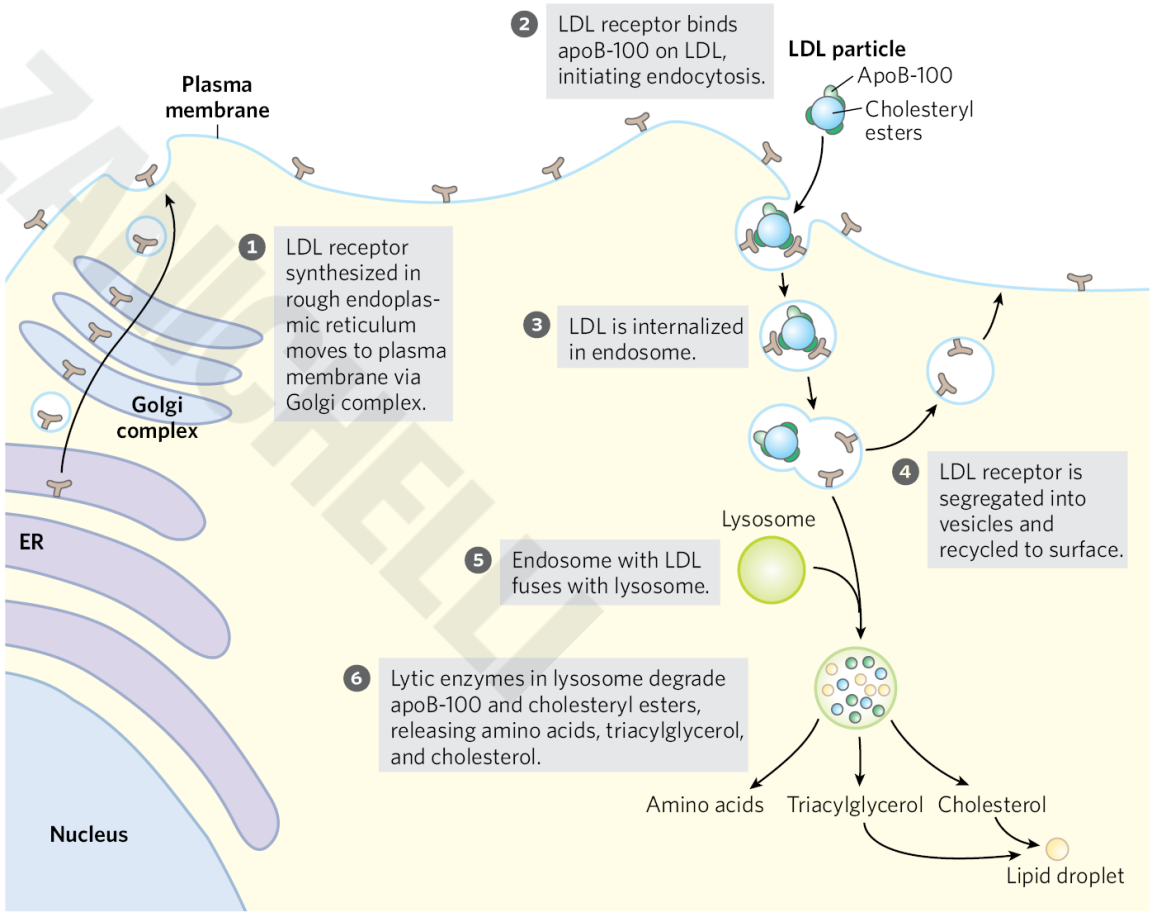
- **reverse cholesterol transport** = the HDL circuit where HDL picks up cholesterol from cholesterol-rich extrahepatic cells and returns it to the liver for unloading
  - much of this cholesterol is converted to bile salts and stored in the gallbladder

Enterohepatic Circulation

- **enterohepatic circulation** = cycle where bile salts are reabsorbed by the liver and recirculate through the gallbladder

Cholesterol Esters Enter Cells by Receptor-Mediated Endocytosis

- **receptor-mediated endocytosis** = apoB-100 of LDL is recognized by receptors in the plasma membrane



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Familial Hypercholesterolemia (FH) and Niemann-Pick Type-C (NPC)

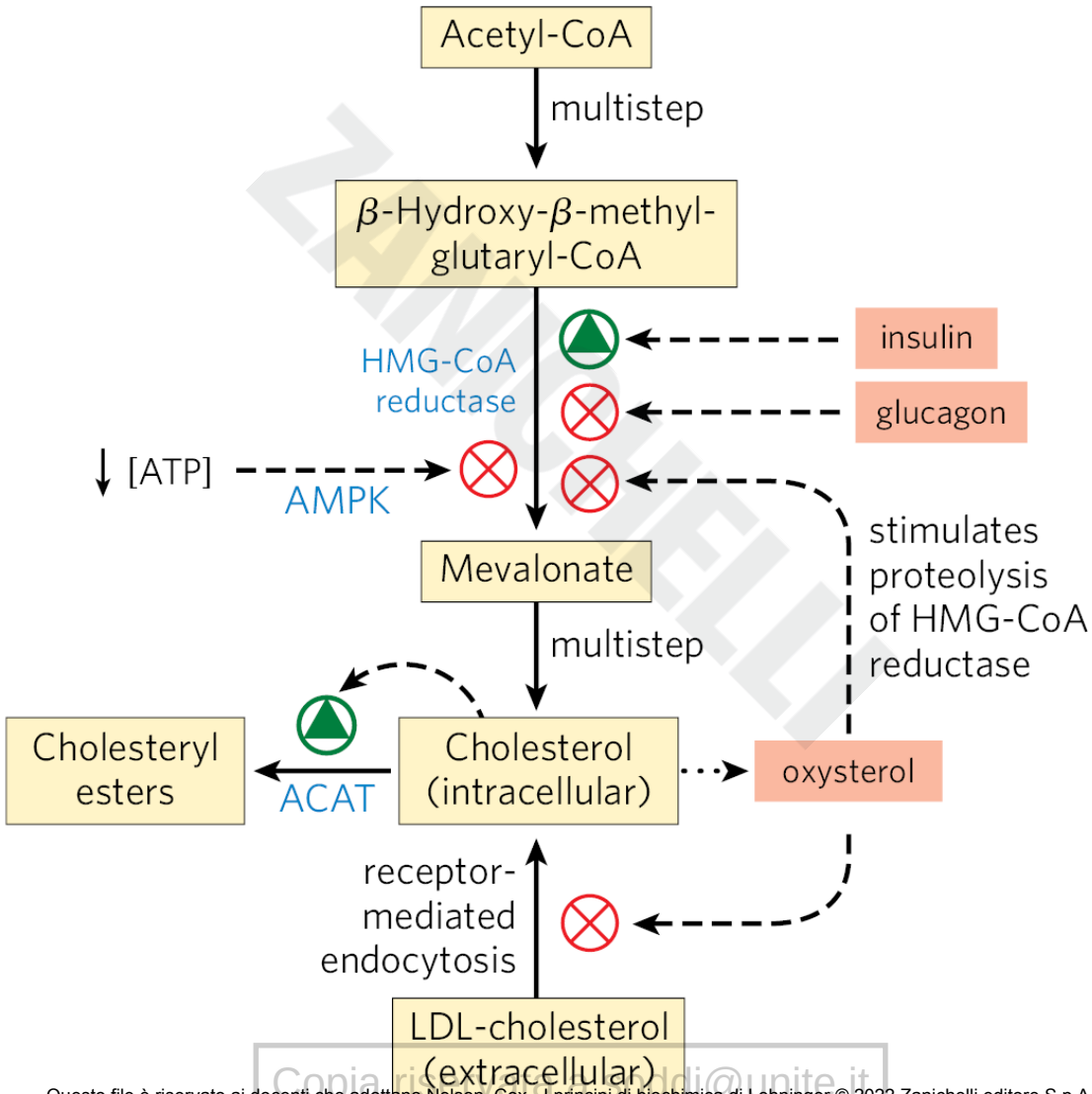
- **familial hypercholesterolemia (FH) =** genetic disease resulting when individuals have mutations in the LDL receptor that prevent the normal uptake of LDL by liver and peripheral tissues

- **Niemann-Pick type-C (NPC)** = inherited defect in lipid storage
  - cholesterol is not transported out of the lysosomes and accumulates in the lysosomes

Cholesterol Synthesis and Transport Are Regulated at Several Levels

- five modes of regulation:
  - covalent modification of HMG-CoA reductase
  - transcriptional regulation of HMG-CoA gene
  - proteolytic degradation of HMG-CoA reductase
  - activation of ACAT, which increases esterification for storage
  - transcriptional regulation of the LDL receptor

Regulation of Cholesterol Metabolism



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HMG-CoA Reductase is Most Active When Dephosphorylated

- covalent modification provides short-term regulation of HMG-CoA reductase
  - AMPK phosphorylates HMG-CoA to decrease its activity in response to rising AMP levels

- insulin promotes dephosphorylation (activation)

- glucagon and epinephrine promote phosphorylation (inactivation)

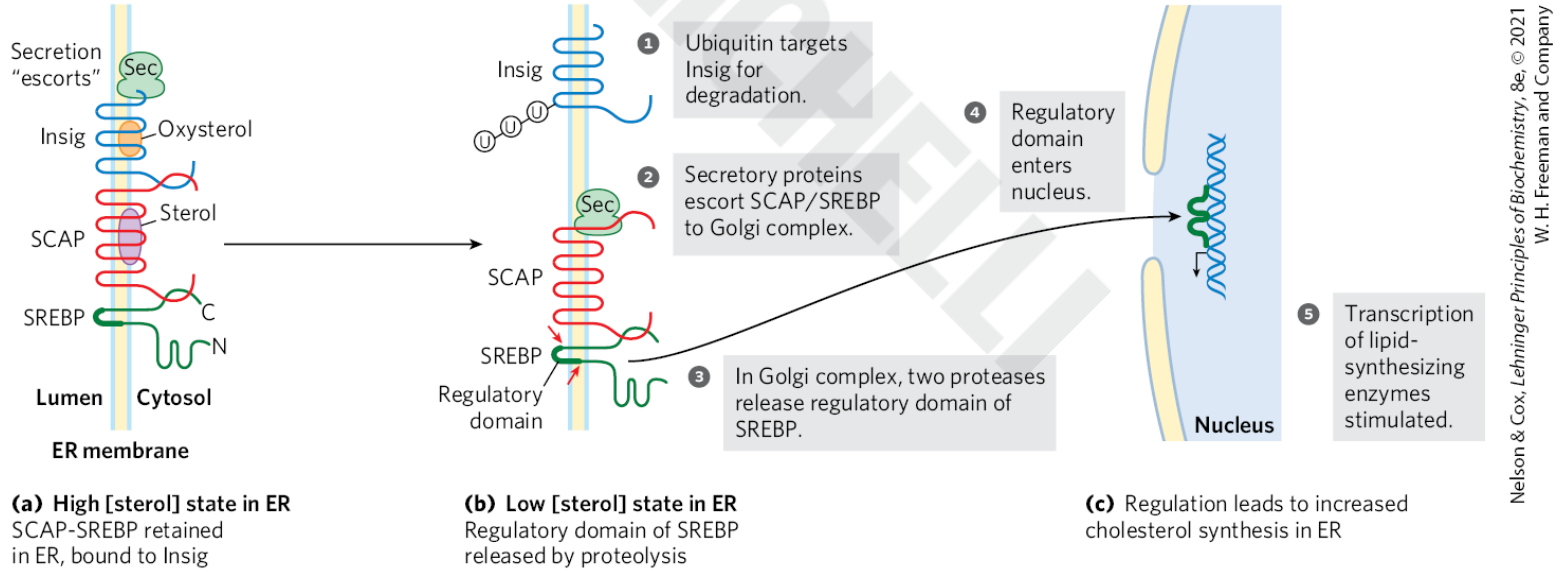
SREBP, SCAP, and Insig

- **sterol regulatory element-binding proteins (SREBPs)** = transcriptionally regulate the HMG-CoA gene and other genes encoding enzymes that mediate the uptake and synthesis of cholesterol and unsaturated fatty acids

- **SREBP cleavage-activating protein (SCAP)** and **Insig (*ins*ulin-*i*nduced *g*ene protein)** = membrane proteins that act as sterol sensors

Regulation of Cholesterol Synthesis by SREBP

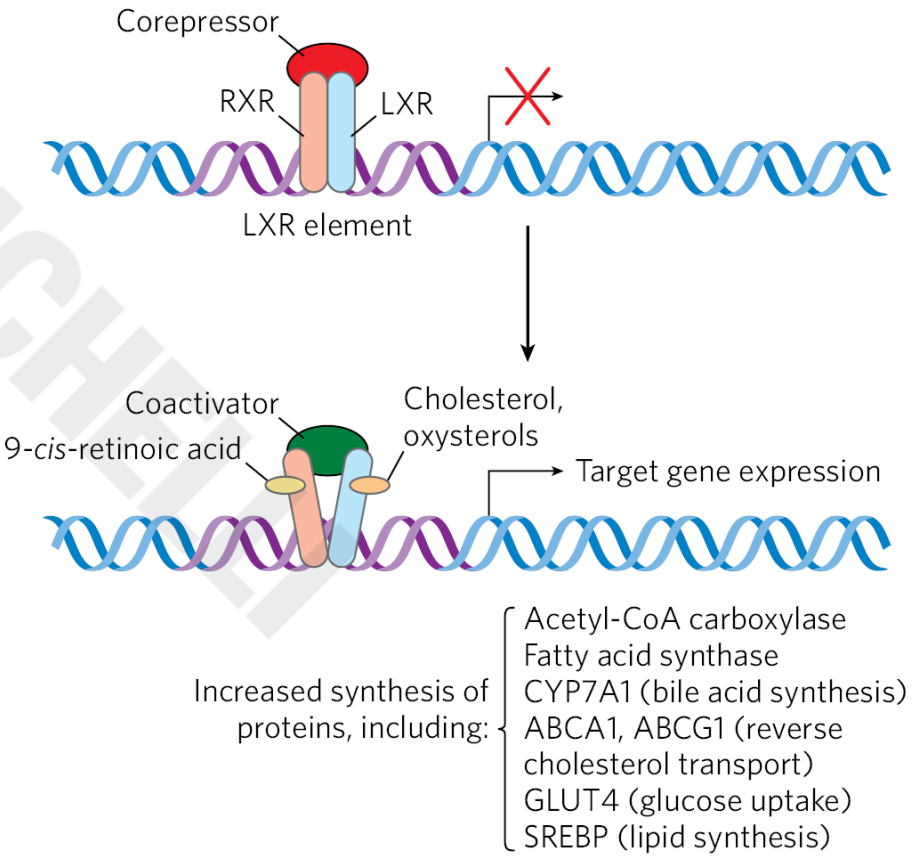
- the complex of Insig, SCAP, and SREBP senses cholesterol levels and triggers increased synthesis or degradation of HMG-CoA reductase



Regulation by LXR-Mediated Transcription

- **liver X receptor (LXR)** = nuclear transcription factor that forms a heterodimer with **retinoid X receptors (RXR)** when cholesterol levels are high

- the LXR- RXR dimer activates transcription from a set of genes



The Genes Activated by LXR-RXR Are Largely for Cholesterol Transport

- acetyl-CoA carboxylase
  - first enzyme in fatty acid synthesis
- apoproteins (C-I, C-II, D, and E)
  - for cholesterol transport
- GLUT4
- ABC transporters
  - for reverse cholesterol transport

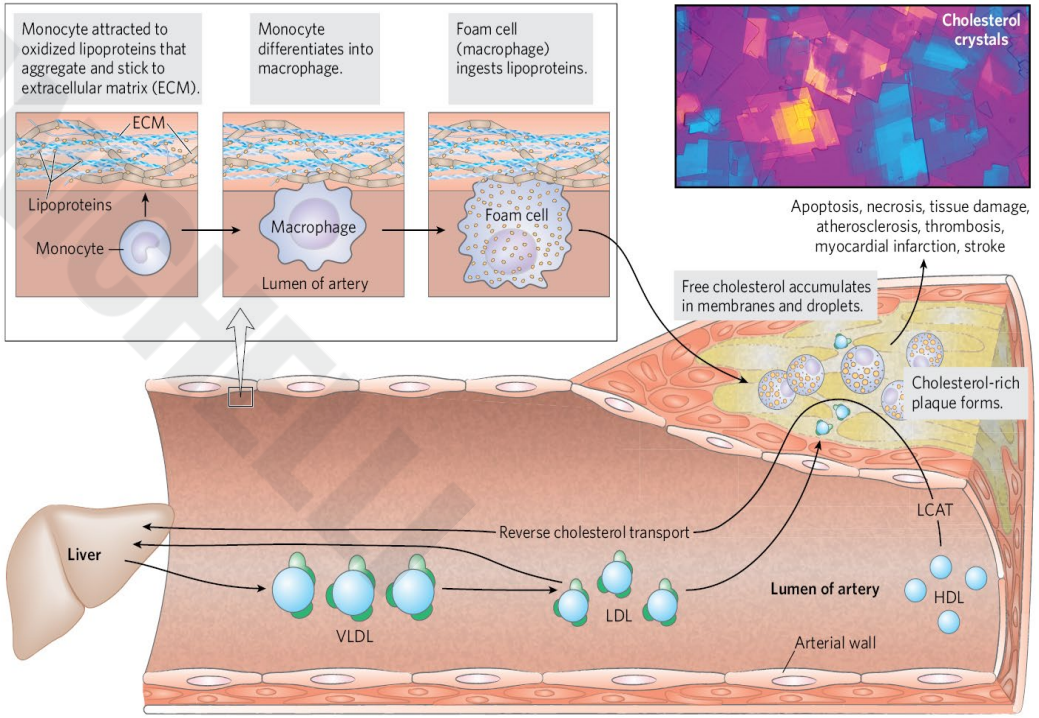
Regulation of LXRs By The Activity of Farnesoid X Receptor (FXR)

- **farnesoid X receptor (FXR)** = forms a heterodimer with RXR
  - represses many of the genes activated by LXR

Dysregulation of Cholesterol Metabolism Can Lead to Cardiovascular Disease

- **atherosclerosis** = the obstruction of blood vessels from the pathological accumulation of cholesterol (plaques)

- **foam cells** = form from macrophages



Cardiovascular Disease (CVD) is Multifactorial

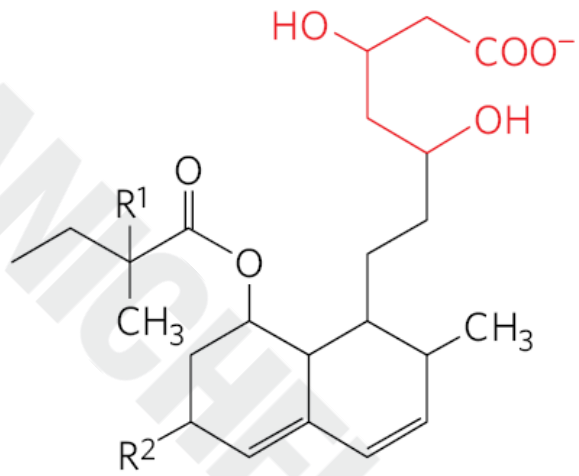
- very high LDL-cholesterol levels tend to correlate with atherosclerosis
- low HDL-cholesterol levels are negatively associated with heart disease

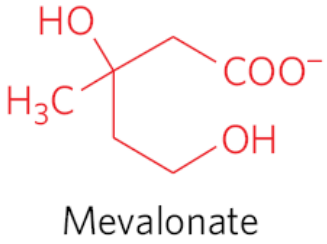
Familial Hypercholesterolemia

- familial hypercholesterolemia = characterized by extremely high blood levels of cholesterol
  - due to a defective LDL receptor
  - cholesterol accumulates in foam cells and contributes to the formation of atherosclerotic plaques

Statins

- **statins** = drug class used to treat patients with elevated serum cholesterol
  - resemble mevalonate
  - are competitive inhibitors of HMG-CoA reductase



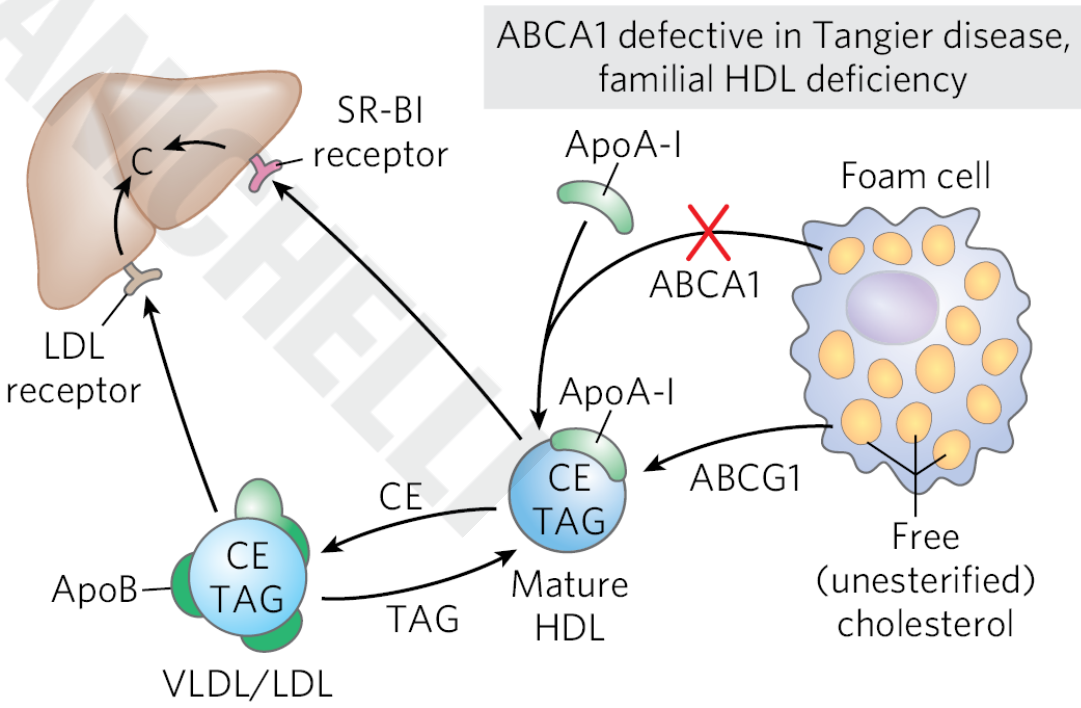


Mevalonate

$R^1 = H$	$R^2 = H$	Compactin
$R^1 = CH_3$	$R^2 = CH_3$	Simvastatin (Zocor)
$R^1 = H$	$R^2 = OH$	Pravastatin (Pravachol)
$R^1 = H$	$R^2 = CH_3$	Lovastatin (Mevacor)

Reverse Cholesterol Transport by HDL Counters Plaque Formation and Atherosclerosis

- reverse cholesterol transport = process by which HDL removes cholesterol from peripheral tissues and carries it to the liver
  - protects against atherosclerosis



Familial HDL Deficiency and Tangier Disease

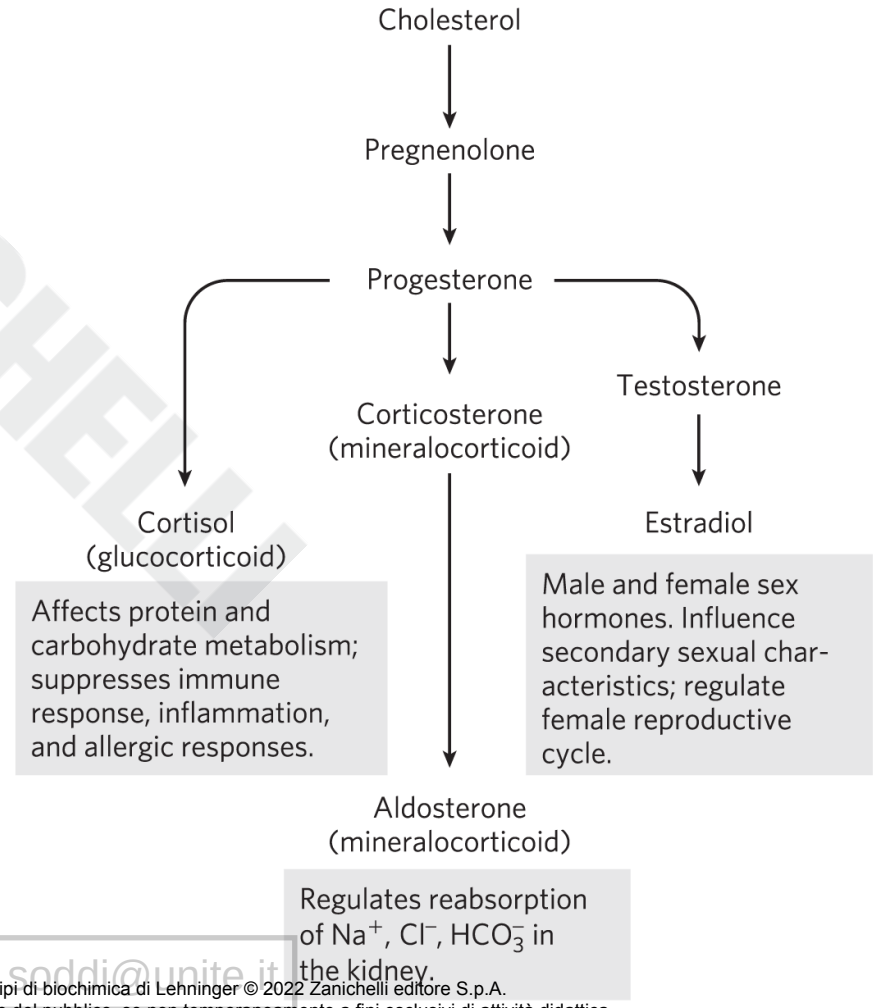
- **familial HDL deficiency =** HDL levels are very low
- **Tangier disease** = HDL levels are almost undetectable
- both are the result of mutations in the ABCA1 protein
  - apoA-I in cholesterol-depleted HDL cannot take up cholesterol from cells that lack ABCA1 protein

P5 Principle 5 (6 of 7)

Like other major classes of biological molecules, lipids have a plethora of cellular functions. Specialized lipids serve as pigments (retinal, carotene), cofactors (vitamin K), detergents (bile salts), transporters (dolichols), hormones (vitamin D derivatives, sex hormones), extracellular and intracellular messengers (eicosanoids, phosphatidylinositol derivatives), and anchors for membrane proteins (covalently attached fatty acids, prenyl groups, phosphatidylinositol). The ability to synthesize a variety of lipids is essential to all organisms.

Steroid Hormones Are Formed by Side-Chain Cleavage and Oxidation of Cholesterol

- steroid hormones are derived from cholesterol
  - **mineralocorticoids**
  - **glucocorticoids**
  - sex hormones **(progesterone, androgens, estrogens)**



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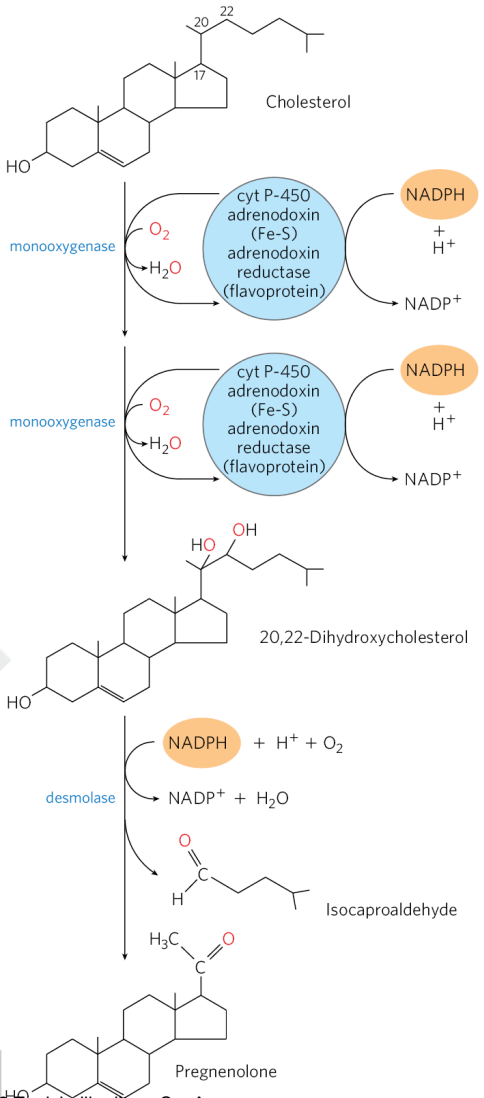
Side-Chain Cleavage in the Synthesis of Steroid Hormones

- takes place in the mitochondria of steroidogenic tissues
- catalyzed by mixed-function oxygenases that use NADPH, O_2, and mitochondrial cytochrome P-450

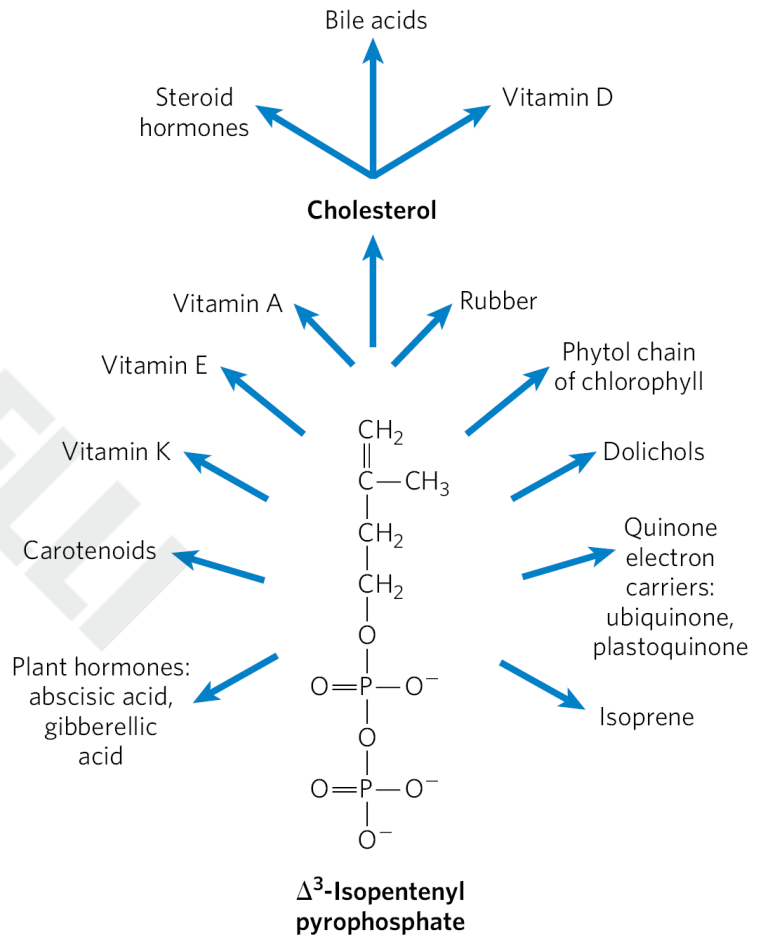


P5 Principle 5 (7 of 7)

Like other major classes of biological molecules, lipids have a plethora of cellular functions. Specialized lipids serve as pigments (retinal, carotene), cofactors (vitamin K), detergents (bile salts), transporters (dolichols), hormones (vitamin D derivatives, sex hormones), extracellular and intracellular messengers (eicosanoids, phosphatidylinositol derivatives), and anchors for membrane proteins (covalently attached fatty acids, prenyl groups, phosphatidylinositol). The ability to synthesize a variety of lipids is essential to all organisms.

Intermediates in Cholesterol Biosynthesis Have Many Alternative Fates

- isopentenyl pyrophosphate is the activated precursor of numerous biomolecules



Protein Prenylation

- prenylation = the covalent attachment of an isoprenoid
  - targets certain proteins for association with cellular membranes