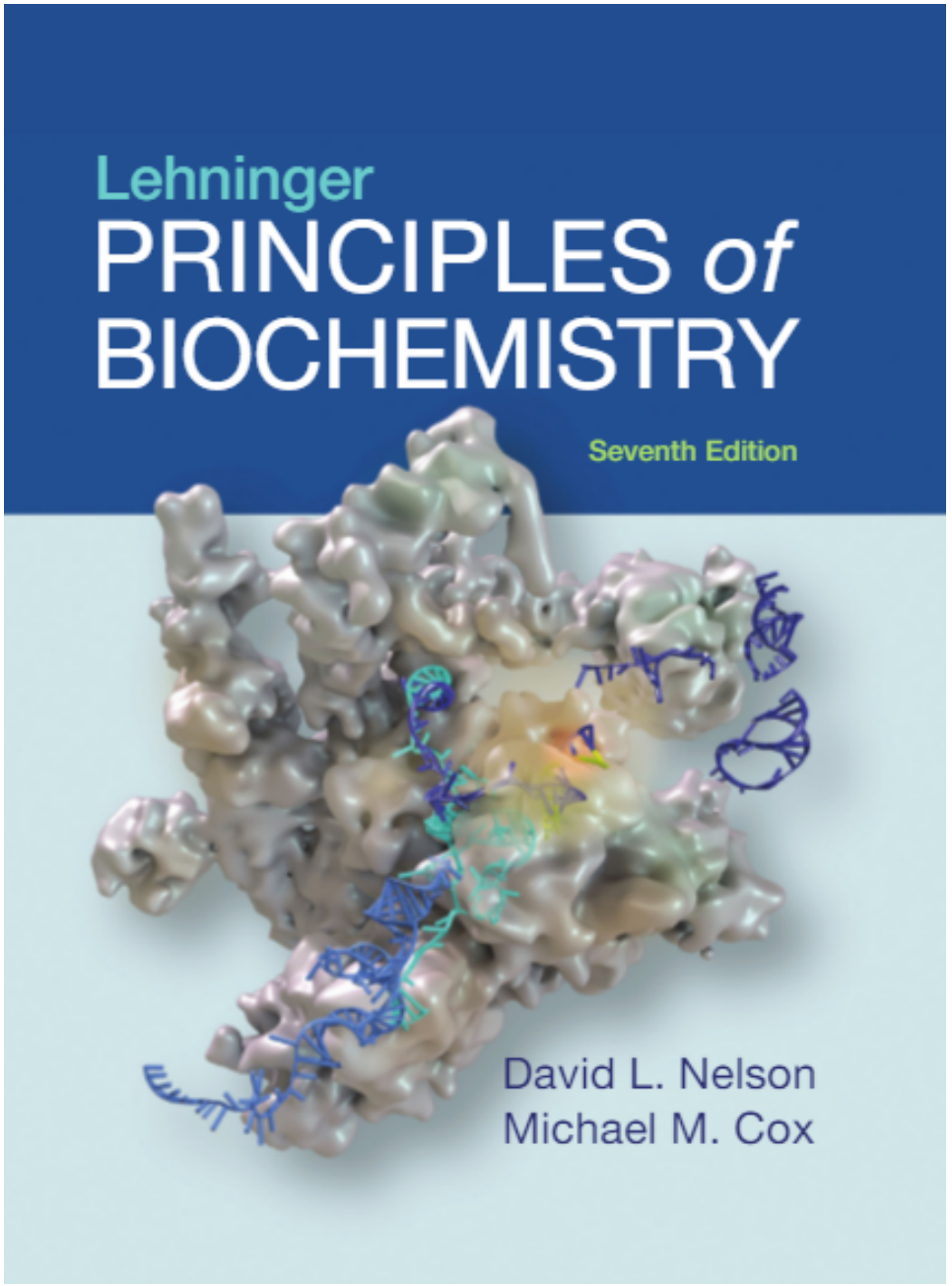
21| Lipid Biosynthesis



CHAPTER 21
Lipid Biosynthesis

Learning goals:

- Biosynthesis of fatty acids and eicosanoids
- Assembly of fatty acids and glycerol into triacylglycerols
- Biosynthesis of cholesterol
- Trafficking and metabolism of cholesterol
- Regulation and role of cholesterol in human disease

Lipids Fulfill a Variety of Biological Functions

- Energy storage
- Constituents of membranes
- Anchors for membrane proteins
- Cofactors for enzymes
- Signaling molecules
- Pigments
- Detergents
- Transporters
- Antioxidants

Catabolism and Anabolism of Fatty Acids Proceed via Different Pathways

- Catabolism of fatty acids **(excergonic and oxidative)**
  - *produces* acetyl-CoA
  - *produces* reducing power (NADH, $FADH_2$)
  - takes place in the *mitochondria*
- Anabolism of fatty acids **(endergonic and reductive)**
  - *requires* acetyl-CoA and malonyl-CoA
  - *requires* reducing power from NADPH
  - activation of fatty acids by 2 different –SH groups on protein
  - takes place in *cytosol* in animals, *chloroplast* in plants

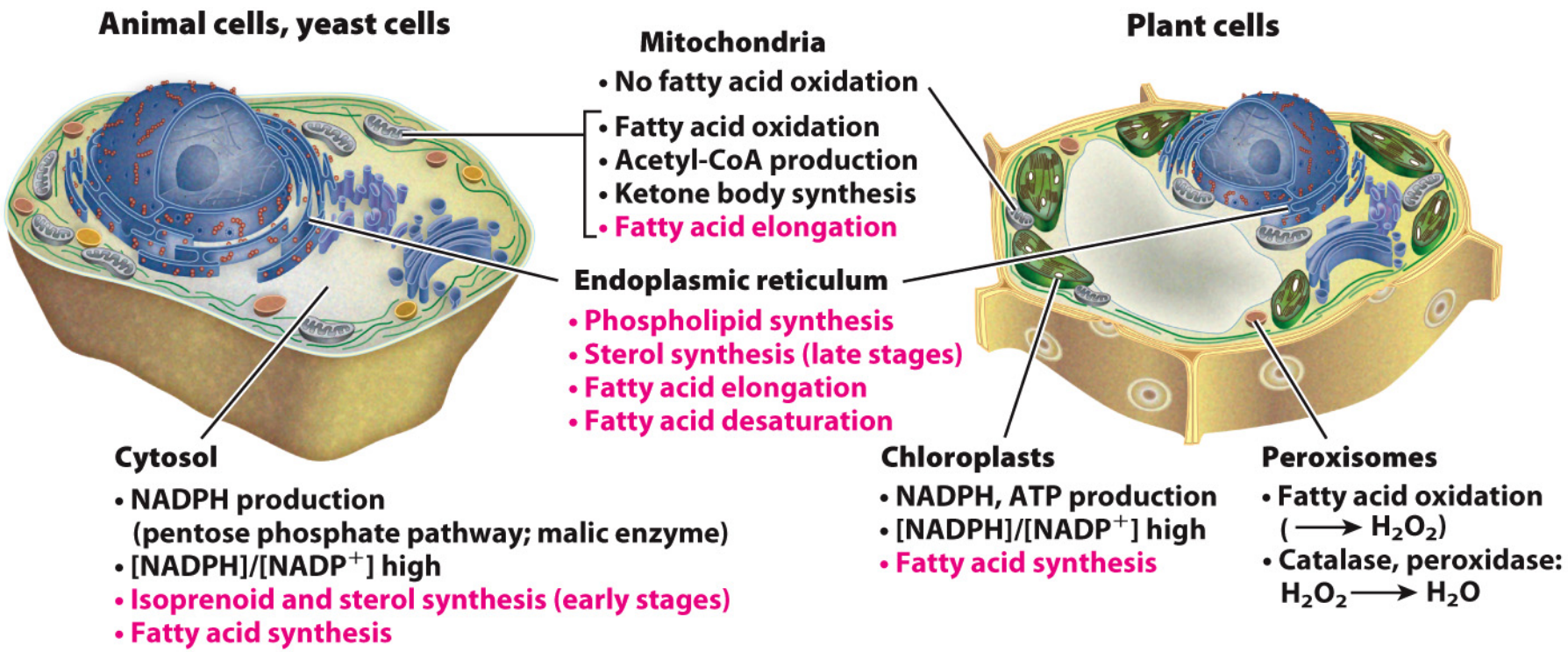


Figure 21-8
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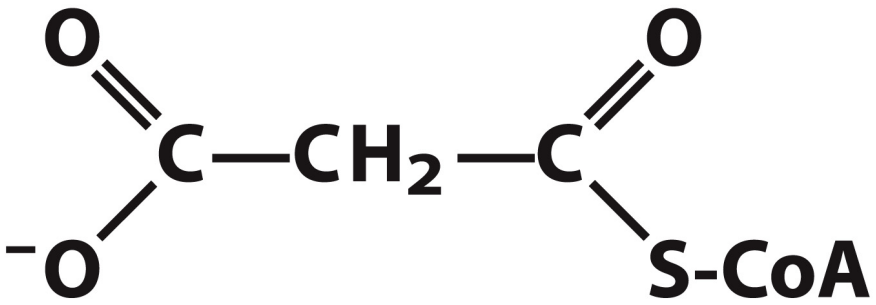
Overview of Fatty Acid Synthesis

- Fatty acids are built in several passes, processing one acetate unit at a time.
- The acetate is coming from activated malonate in the form of malonyl-CoA.
- Each pass involves reduction of a carbonyl carbon to a methylene carbon.



Malonyl-CoA

Fatty Acid Synthesis Occurs in Cell Compartments Where NADPH Levels Are High

- *Cytosol* for animals, yeast
- *Chloroplast* for plants

- Sources of NADPH:
  - in adipocytes: pentose phosphate pathway and malic enzyme
    - NADPH made as malate converts to pyruvate + CO_2.
  - in hepatocytes and mammary gland: pentose phosphate pathway
    - NADPH made as glucose-6-phosphate converts to ribulose 6-phosphate.
  - in plants: photosynthesis

Pathways for NADPH Production

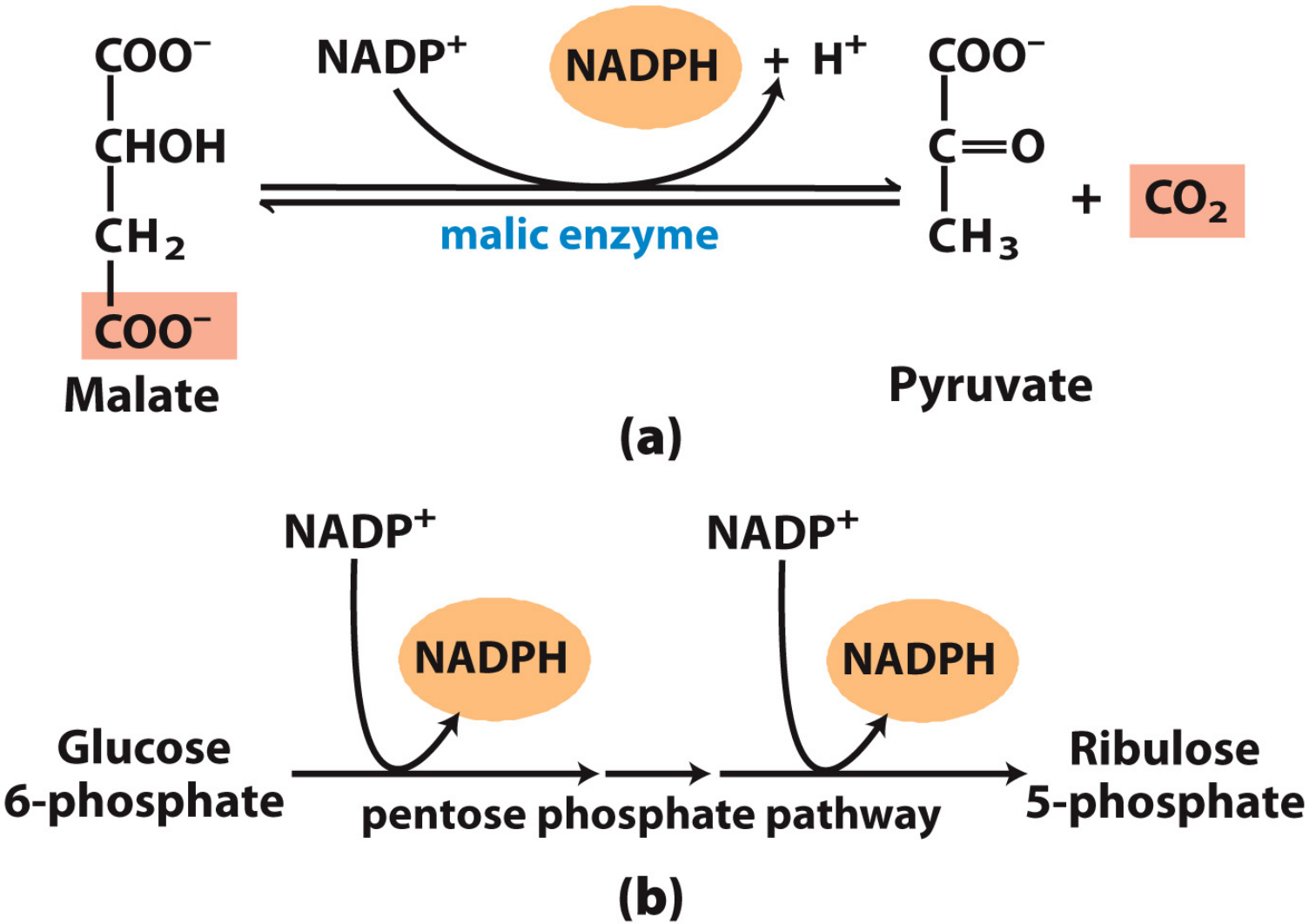


Figure 21-9
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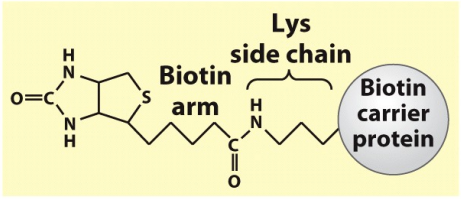
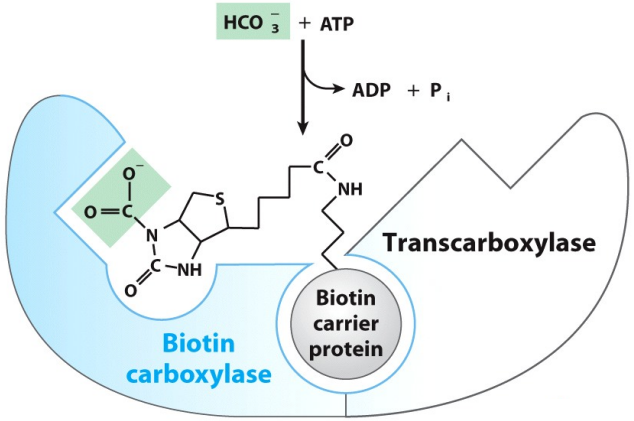
Malonyl-CoA Is Formed from Acetyl-CoA and Bicarbonate

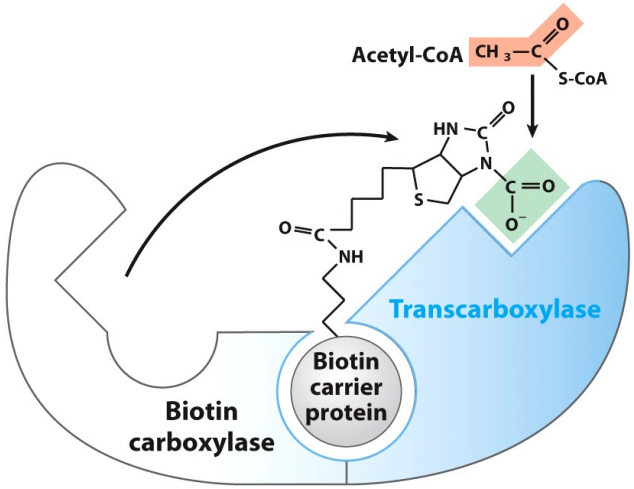
- Reaction carboxylates acetyl-CoA
- Catalyzed by *acetyl-CoA carboxylase (ACC)*
  - The enzyme has three subunits:
    - One unit has biotin covalently linked to Lys.
    - Biotin carries CO_2.
    - In animals, all three subunits are on one polypeptide chain.
  - HCO_3^- (bicarbonate) is the soluble source of CO_2.

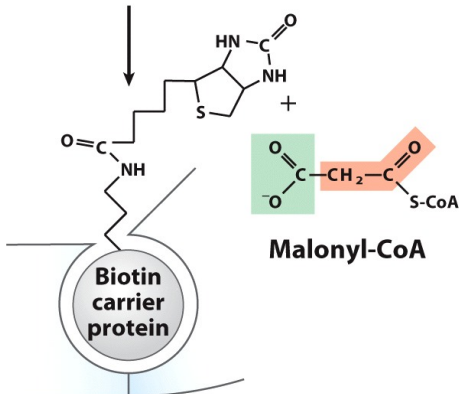
The Acetyl-CoA Carboxylase (ACC) Reaction

- Two-step rxn similar to carboxylations catalyzed by *pyruvate carboxylase* (gluconeogenesis) and *propionyl-CoA carboxylase* (odd f.a. metabolism)
- CO_2 binds to biotin
  - CO_2 is activated by attachment to N in ring of biotin
  - Reaction with ATP produces carbamoyl.









Synthesis of Fatty Acids Is Catalyzed by Fatty Acid Synthase (FAS)

- Catalyzes a *repeating four-step sequence* that elongates the fatty acyl chain by two carbons at each step
- See Fig. 21-2
  - uses NADPH as the electron donor
  - uses two enzyme-bound -SH groups as activating groups
- FAS I in vertebrates and fungi
- FAS II in plants and bacteria

FAS I vs. FAS II

FAS I

- Single polypeptide chain in vertebrates
- Leads to single product: palmitate 16:0
- C-15 and C-16 are from the acetyl-CoA used to prime the rxn

FAS II

- Made of separate, diffusible enzymes
- Makes many products (saturated, unsaturated, branched, many lengths, etc.)
- Mostly in plants and bacteria

Fatty Acid Synthase Type I Systems

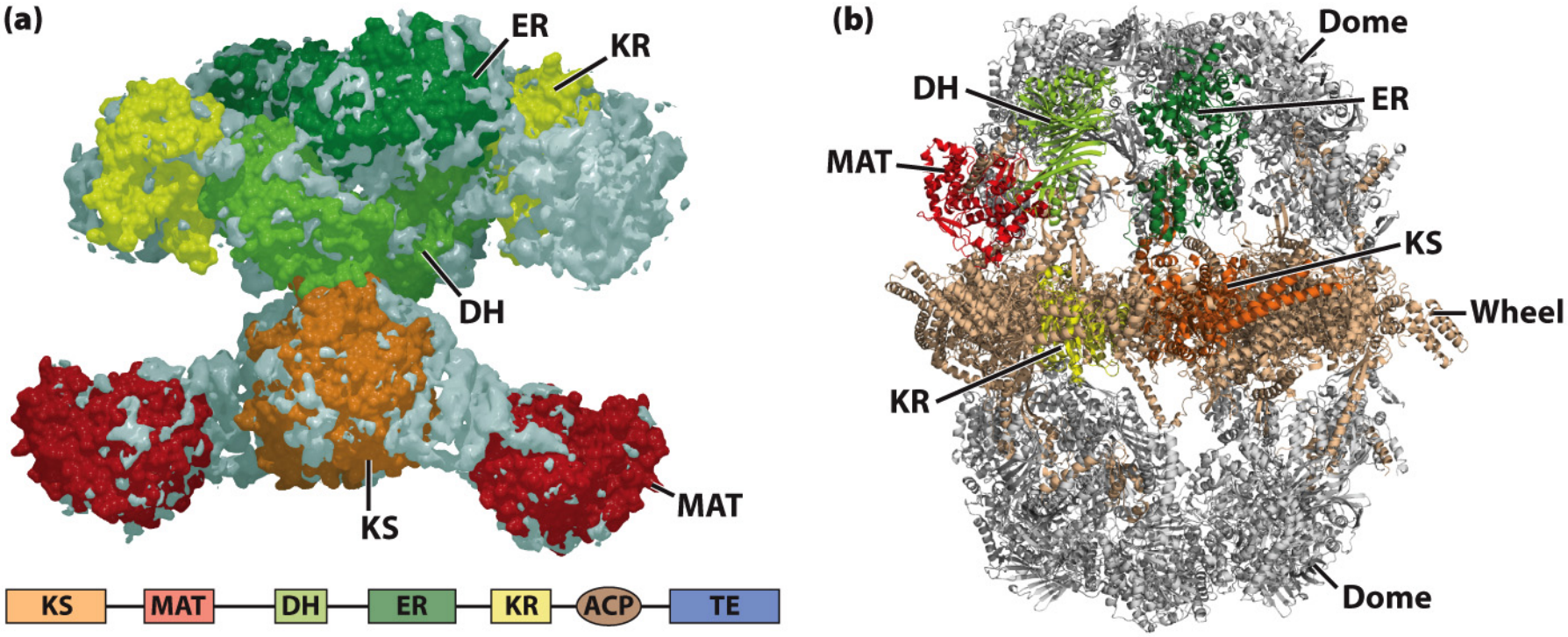


Figure 21-3
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Fatty Acid Synthesis

- *Overall goal:* attach two-C acetate unit from malonyl-CoA to a growing chain and then reduce it
- Reaction involves cycles of four enzyme-catalyzed steps
  - Condensation of the growing chain with activated acetate
  - Reduction of carbonyl to hydroxyl
  - Dehydration of alcohol to *trans*-alkene
  - Reduction of alkene to alkane
- The growing chain is initially attached to the enzyme via a thioester linkage
- During condensation, the growing chain is transferred to the acyl carrier protein (ACP)
- After the second reduction step, the elongated chain is transferred back to fatty acid synthase

The General Four-Step Fatty Acid Synthase I Reaction in Mammals

Prep: Malonyl CoA and acetyl CoA (or longer fatty acyl chain) are bound to FAS I and lose CoA.

- bind via thioester terminus or a Cys of the FAS
- activates the acyl group

Step 1: Condensation reaction attaches two C from acetyl group (or longer fatty acyl chain) to two C from malonyl group.

- release of CO_2 activates malonyl group for attachment
- the decarboxylation facilitates the rxn
- creates β-keto intermediate

Fatty Acid Synthesis in Detail: Condensation and Elongation

- Activated acetyl and malonyl groups form acetoacetyl-ACP and CO_2.
  - Claisen condensation reaction
- Catalyzed by β-ketoacyl-ACP synthase
- Coupling condensation to decarboxylation of malonyl-CoA makes the reaction energetically favorable.

Step 1 of FAS I: Elongation

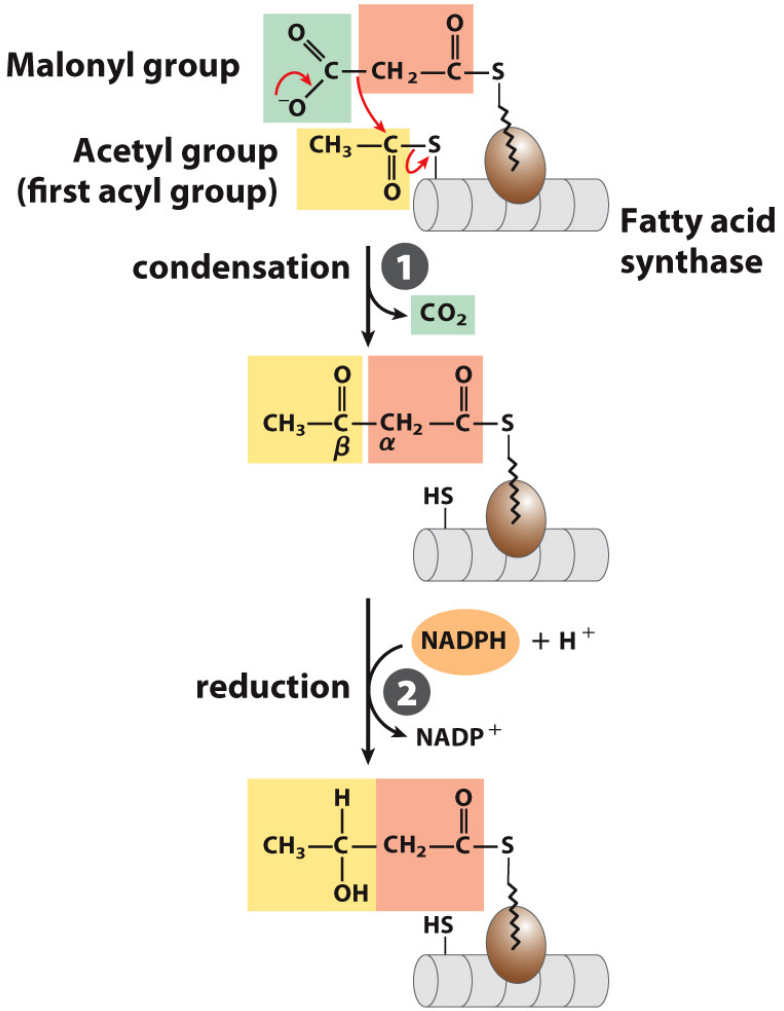

Figure 21-2 part 1
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Note that malonyl-CoA and acetyl-CoA have already been attached to complex via thioester linkages to enzyme and have shed their CoA attachments.

The General Four-Step Fatty Acid Synthase I Reaction in Mammals

Step 2: First reduction: NADPH reduces the β-keto intermediate to an alcohol.

- carbonyl at C-3 reduced to form d-β-hydroxybutyryl-ACP
- NADPH is e^- donor
- catalyzed by β-ketoacyl-ACP reductase (KR)

The General Four-Step Fatty Acid Synthase I Reaction in Mammals

Step 3: Dehydration: OH group from C-2 and H from neighboring CH_2 are eliminated, creating double bond (trans-alkene).

- OH and H removed from C-2 and C-3 of β-hydroxybutyryl-ACP to form *trans*-Δ^2-butenoyl-ACP
- catalyzed by β-hydroxyacyl-ACP dehydratase (DH)

The General Four-Step Fatty Acid Synthase I Reaction in Mammals

Step 4: Second reduction: NADPH reduces double bond to yield saturated alkane.

- NADPH is the electron donor to reduce double bond of *trans*-Δ^2-butenoyl-ACP to form butyryl-ACP.
- catalyzed by enoyl-ACP reductase (ER)

Steps 2–4 of the FAS I rxn

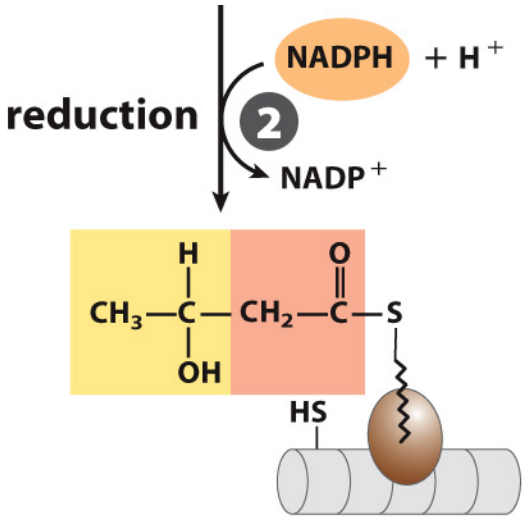

Figure 21-2 part 1
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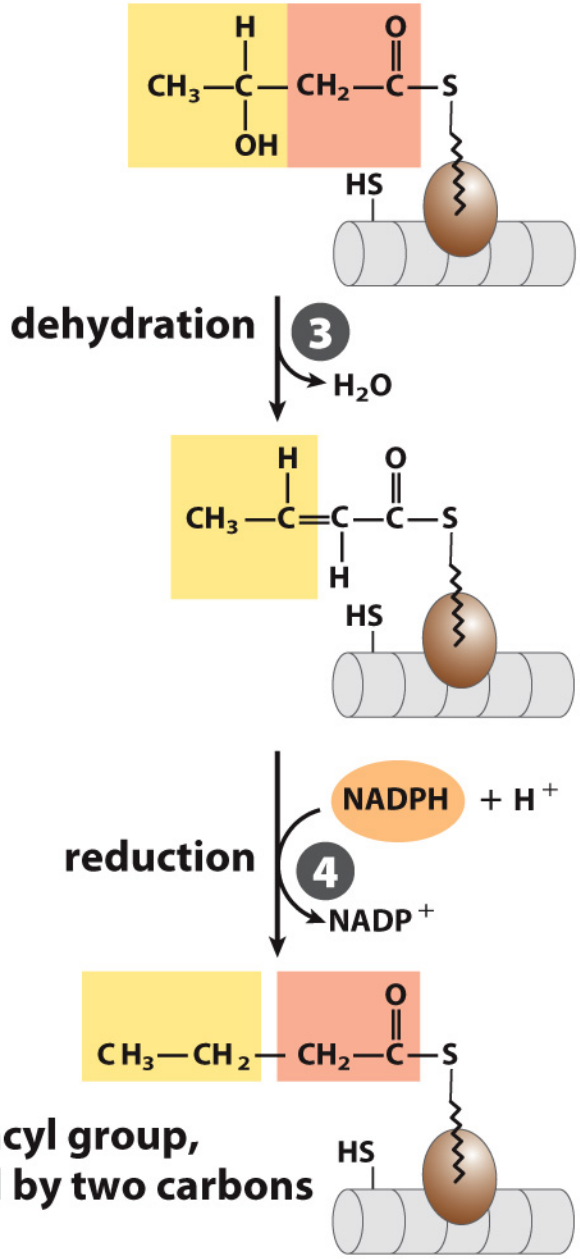

Figure 21-2 part 2
Lehninger Principles of Biochemistry, Seventh Edition

The Transferase and FAS rxns are repeated in new rounds

- Product of first round is butyryl-ACP
  - (bound to phosphopantetheine-SH group of ACP)
- Butyrul gp is transferred to the Cys of β-ketoacyl-ACP synthase
  - In the first round, acetyl-CoA was bound here
- New malonyl-CoA binds to ACP
- After new round of four steps, six-C product is made (bound to ACP)

Beginning of the Second Round of Fatty Acid Synthesis

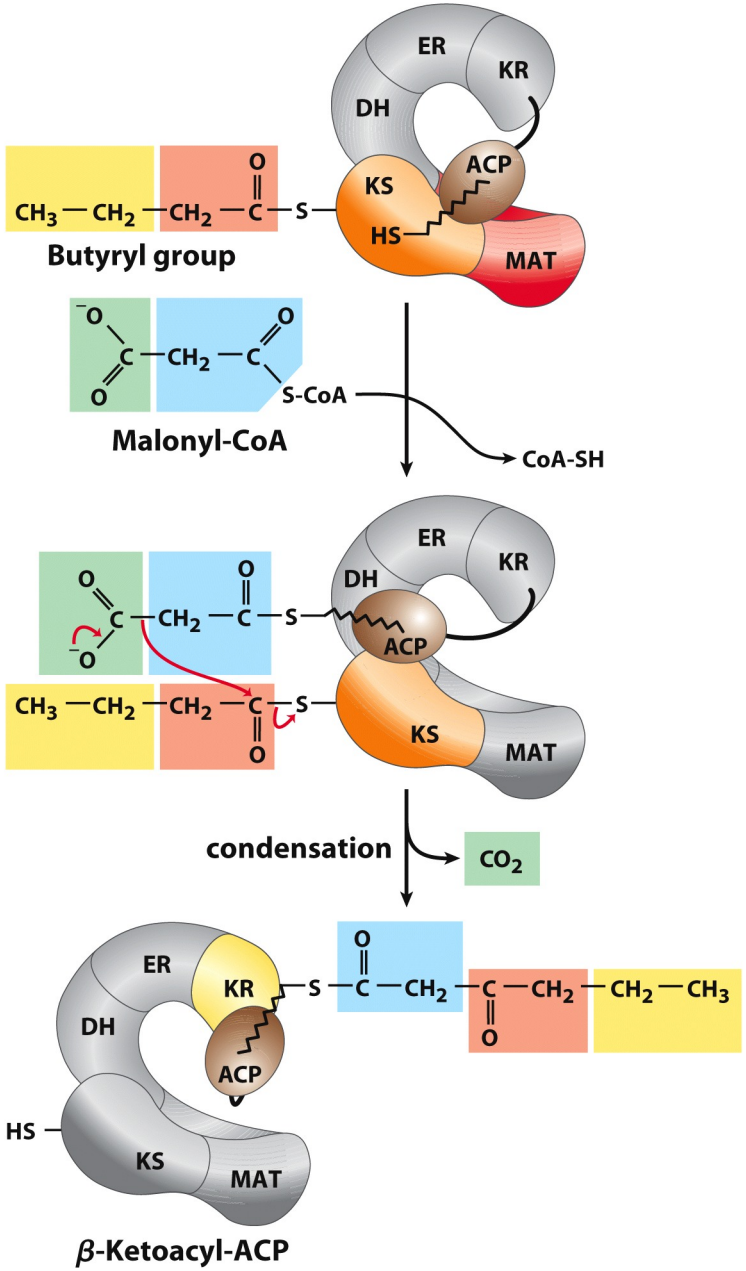

Figure 21-7
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Overall Palmitate (16C) Synthesis

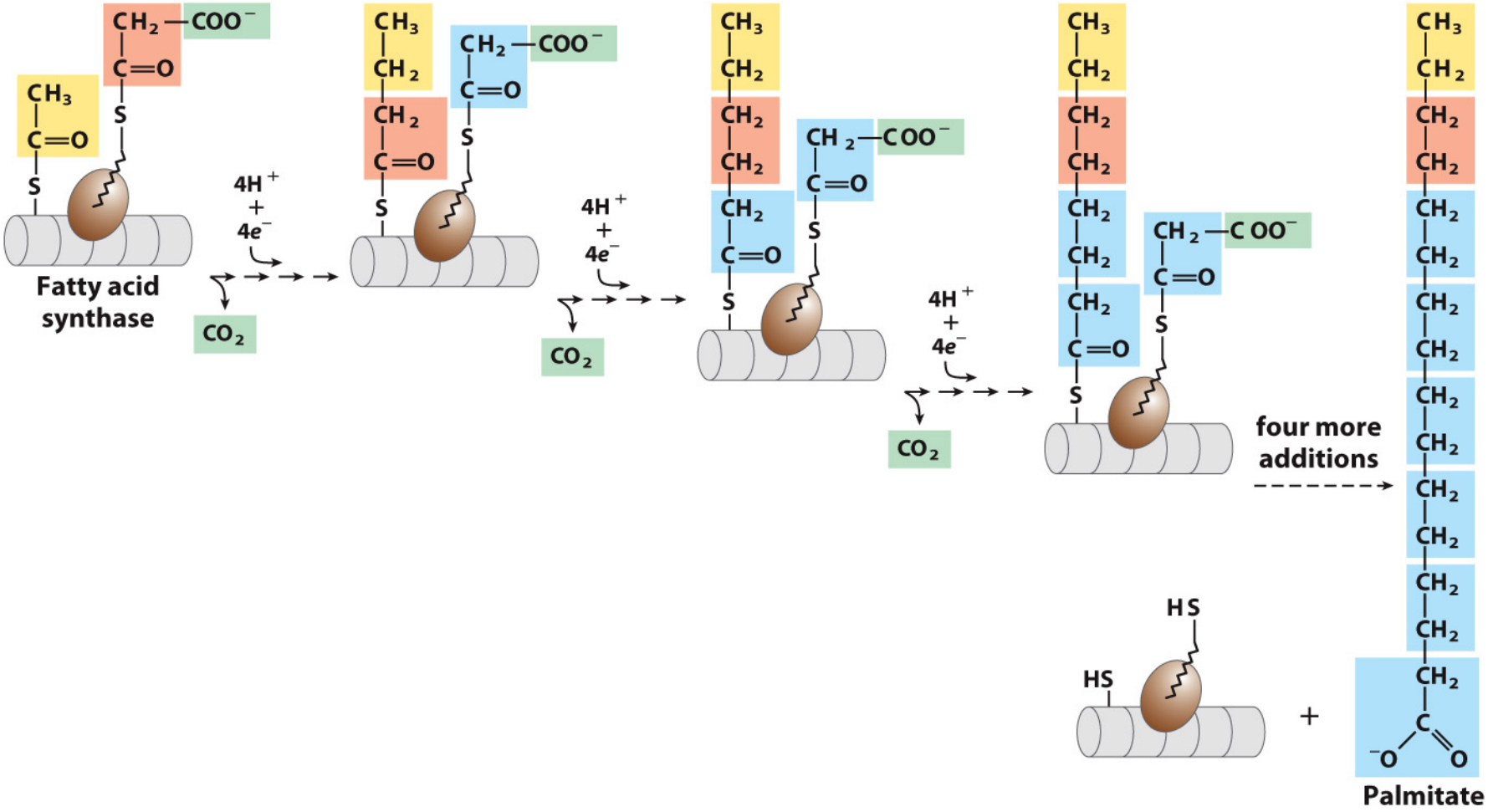

Figure 21-4
Lehninger Principles of Biochemistry, Seventh Edition

Acyl Carrier Protein (ACP) Serves as a Shuttle in Fatty Acid Synthesis

- Contains a covalently attached prosthetic group 4'-phosphopantetheine
  - flexible arm to tether acyl chain while carrying intermediates from one enzyme subunit to the next
- Delivers acetate (in the first step) or malonate (in all the next steps) to the fatty acid synthase
- Shuttles the growing chain from one active site to another during the four-step reaction

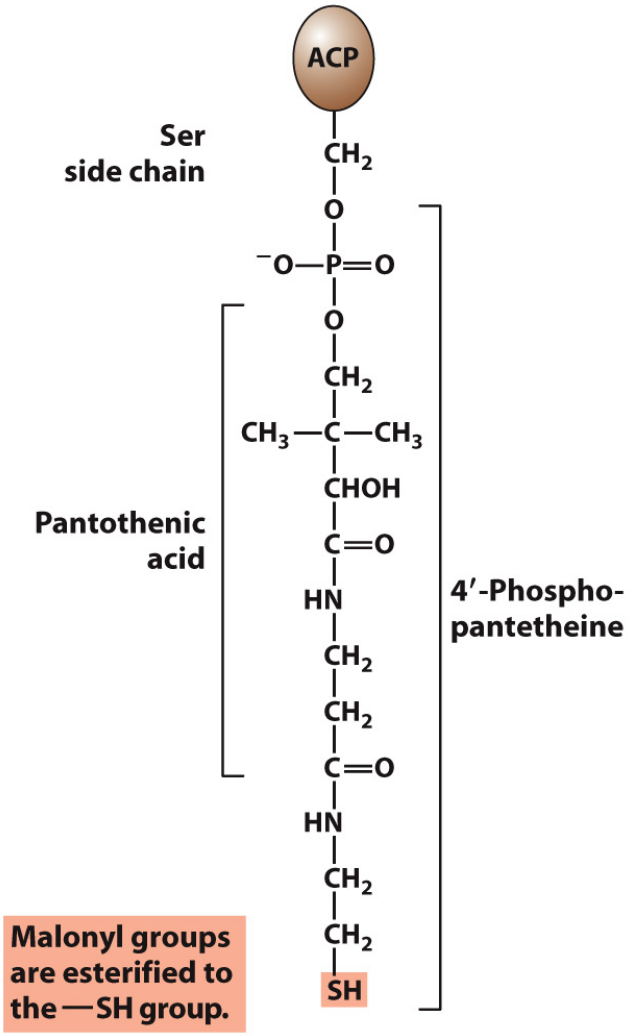

Figure 21-5
Lehninger Principles of Biochemistry, Seventh Edition

Stoichiometry of Synthesis of Palmitate (16:0)

1. 7 acetyl-CoAs are carboxylated to make 7 malonyl-CoAs… using ATP. (1 ATP/2C units)

7 acetyl-CoA + 7 CO_2 + 7 ATP → 7 malonyl-CoA + 7 ADP + 7 P_i

2. Seven cycles of condensation, reduction, dehydration, and reduction… using NADPH to reduce the β-keto group and trans-double bond

acetyl-CoA + 7 malonyl-CoA + 14 NADPH + 14 H^+ → palmitate (16-carbons) + 7 CO_2 + 8 CoA + 14 $NADP^+$ + 6 H_2O

Acetyl-CoA Is Transported into the Cytosol for Fatty Acid Synthesis

- In *nonphotosynthetic eukaryotes*…
- Acetyl-CoA is made in the *mitochondria*
- But fatty acids are made in the *cytosol*
- So acetyl-CoA is **transported into the cytosol** with a **cost of 2 ATPs**
- Therefore, *total cost of FA synthesis in eukaryotes is 3 ATPs per 2-C unit*

Shuttle for Transfer of Acetyl Groups from Mitochondria to Cytosol

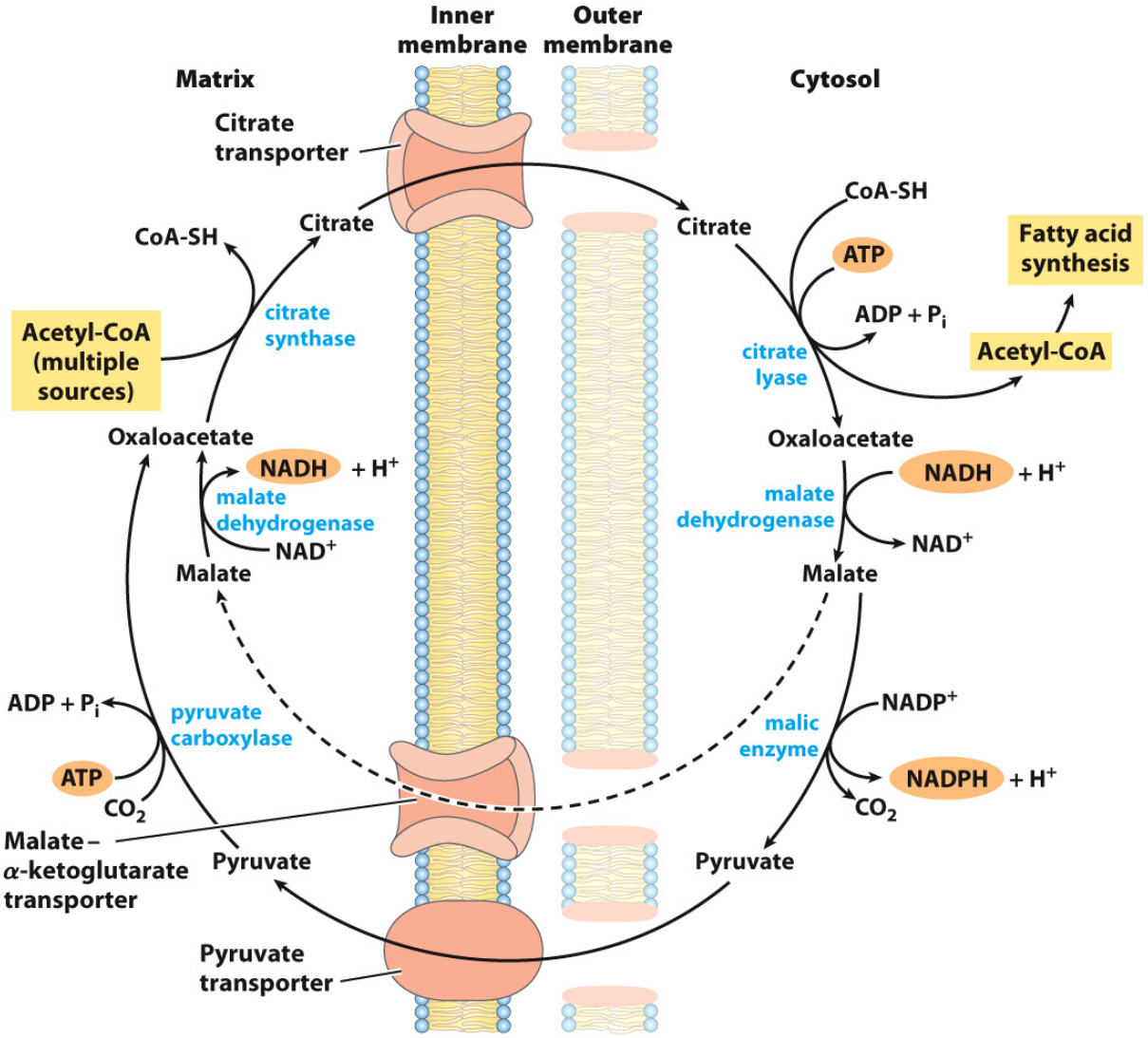

Figure 21-10
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Fatty Acid Synthesis Is Tightly Regulated via ACC

- Acetyl CoA carboxylase (ACC) catalyzes the rate-limiting step.
  - ACC is feedback-inhibited by palmitoyl-CoA.
  - ACC is *activated* by **citrate**.
    - Citrate is made from acetyl-CoA in mitochondria (acetyl-CoA^{mt}).
    - Citrate signals excess energy to be converted to fat.
  - When [acetyl-CoA]^{mt} ↑ is converted to citrate… citrate is exported to cytosol.

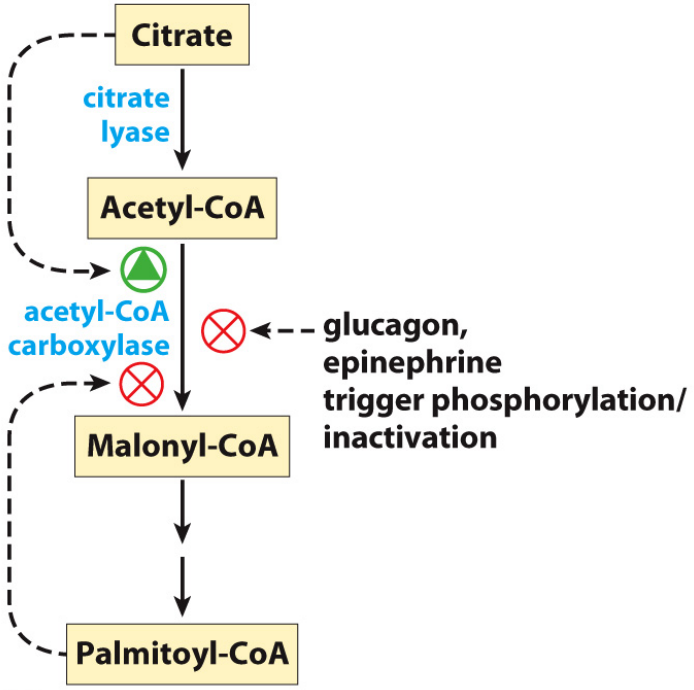
Importance of Citrate to Regulation of Fatty Acid Synthesis

- In animals, citrate stimulates fatty acid synthesis!
  - Precursor for acetyl-CoA
    - Sent to cytosol and cleaved to become AcCoA when AcCoA and ATP ↑ (energy excess)
  - Allosteric activator of ACC
  - Inhibitor of PFK-1
    - Reduces glycolysis

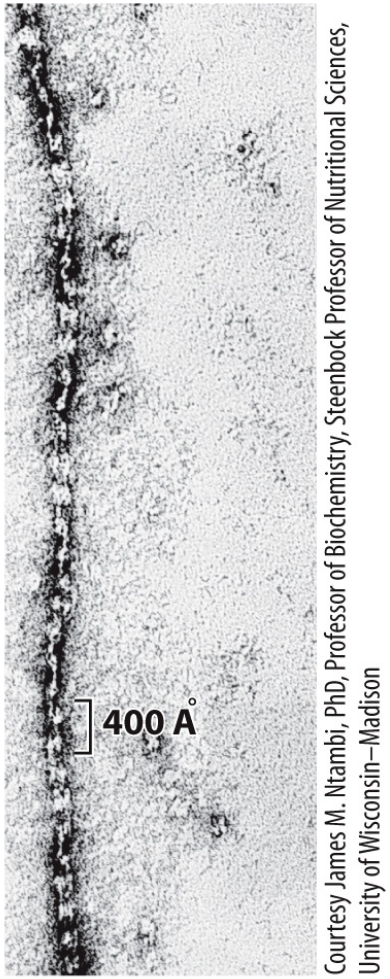
ACC is also regulated by covalent modification

- Inhibited when energy is needed
- Glucagon and epinephrine:
  - reduce sensitivity of citrate activation
  - lead to phosphorylation and inactivation of ACC via AMPK and PKA
    - ACC is active as dephosphorylated form (polymeric)
    - When phosphorylated, ACC is inactivated
    - Dephosphorylation reverses the inactivation
- Insulin activates PP2A and reactivates ACC

Regulation of Fatty Acid Synthesis in Vertebrates



(a)



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

(b)

Figure 21-11
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Filaments of acetyl-CoA carboxylase from chicken hepatocytes (the active, dephosphorylated form) as seen with the electron microscope

Additional Modes of Regulation in Fatty Acid Synthesis

- Changes in gene expression
  - *Example:* Fatty acids (and eicosanoids) bind to transcription factors called **Peroxisome Proliferator-Activated Receptors** (PPARs) → inducing expression of some genes
- Reciprocal regulation
  - Malonyl-CoA inhibits fatty acid import into mito
    - One of many ways to ensure that fat synthesis and oxidation don't occur simultaneously

Clinical significance

- 2 mammalian isoforms ACC1 and ACC2
- Mice without ACC2 (null mice) consume more food but show continuous fatty acid oxidation, reduced body fat mass, and reduced body weight
- These mice are protected from diabetes
- ACC1 null mice are embryonically lethal
- Research of new drugs specific to ACC2 but not to ACC1 as weight loss drugs

Palmitate Can Be Lengthened to Longer-Chain Fatty Acids

- Elongation systems in the endoplasmic reticulum and mitochondria create longer fatty acids.
- As in palmitate synthesis, each step adds units of 2 C.
- Stearate (18:0) is the most common product.

Palmitate and Stearate Can Be Desaturated

- Palmitate(16:0) → palmitoleate(16:1; Δ^9)
- Stearate (18:0) → oleate (18;1; Δ^9)
  - catalyzed by fatty acyl-CoA desaturase in animals
    - also known as the fatty acid desaturases
    - requires NADPH; enzyme uses cytochrome b_5 and cytochrome b_5 reductase

Note that this is a Δ^9-desaturase!

It reduces the bond between C-9 and C-10.

Desaturation of a Fatty Acid by Fatty Acyl-CoA Desaturase

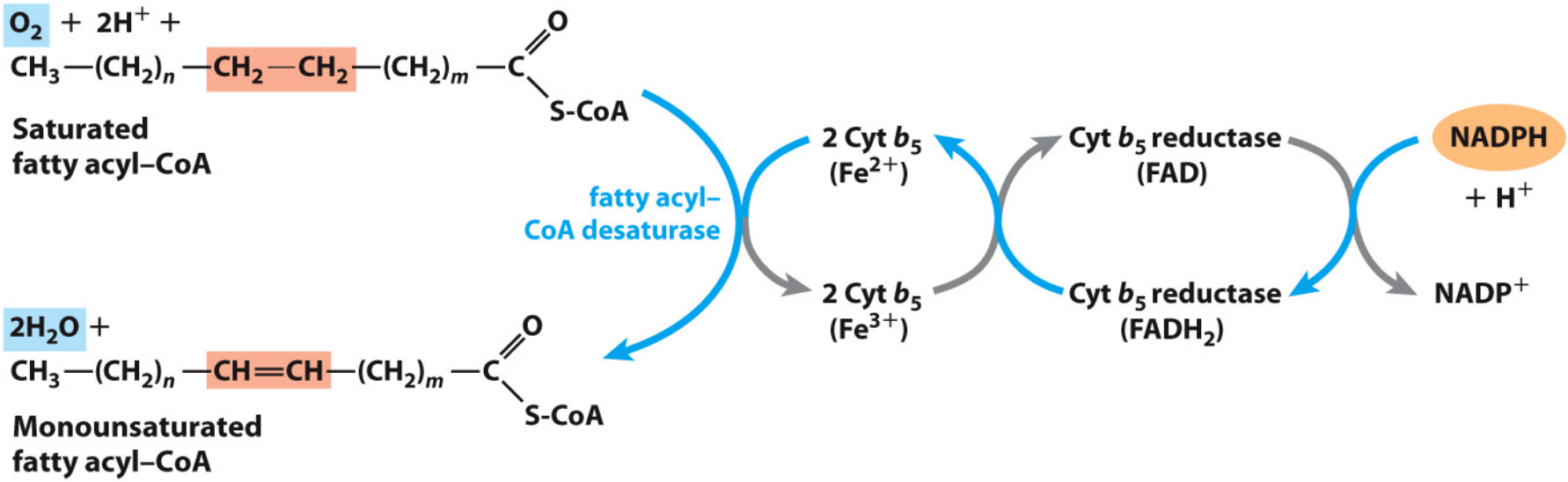

Figure 21-13
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- O_2 accepts four electrons from two substrates.
- Two electrons come from saturated fatty acid.
- Two electrons come from ferrous state of cytochrome b_5.

Plants can desaturate positions beyond C-9

- Humans have Δ^4, Δ^5, Δ^6, and Δ^9 desaturases but *cannot* desaturate beyond Δ^9
- Plants *can* produce:
  - linoleate 18:2($\Delta^{9,12}$)
  - α-linolenate 18:3 ($\Delta^{9,12,15}$)
- These fatty acids are "**essential**" to humans
  - Polyunsaturated fatty acids (PUFAs) help control membrane fluidity
  - PUFAs are precursors to eicosanoids
- Implications of stearoyl-ACP desaturase (SCD) on obesity
  - SCD1-mutant mice are resistant to diet-induced obesity!

Eicosanoids are potent short-range hormones made from arachidonate

- Eicosanoids are paracrine signaling molecules
- They include *prostaglandins*, *leukotrienes*, *thromboxanes*
- Created from arachidonic acid, 20:4 ($\Delta^{5,8,11,14}$)
- Arachidonate is incorporated into the phospholipids of membranes
- In response to stimuli (hormone, etc.), **phospholipase A_2** is activated and attacks the C-2 fatty acid, releasing arachidonate

Conversion of Arachidonate to Prostaglandins and Other Eicosanoids

COX (PGH_2 synthase) is a cyclooxygenase/peroxidase enzyme that functions in the smooth ER.

- **Step 1:** PGH_2's cyclooxygenase activity adds 2 O_2 to form PGG_2.
- **Step 2:** PGH_2's peroxidase activity converts peroxide to alcohol, creates PGH_2.

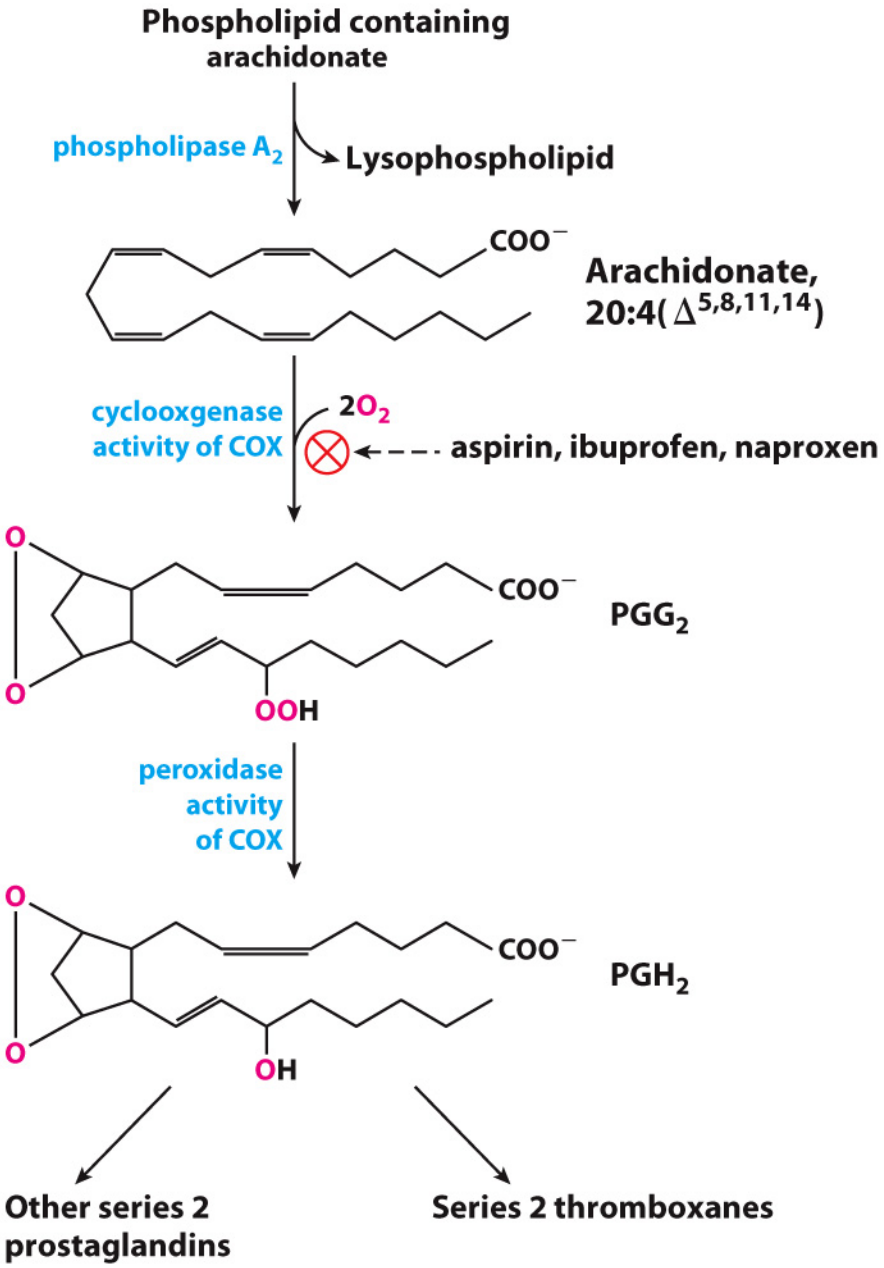

Figure 21-15a
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Thromboxanes

- Thromboxane synthase present in thrombocytes converts PGH_2 to thromboxane A_2
- Induces the constriction of blood vessels and blood clotting
- Low doses of aspirin reduce the risk of heart attacks and strokes by reducing thromboxane production

PGH_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.*
  - NSAIDs (aspirin, ibuprofen, acetaminophen) inhibit COX-2.

NSAIDs Inhibit Cyclooxygenase (COX) Activity

- Aspirin (acetylsalicylate) is an irreversible inhibitor.
  - acetylates a Ser in active site
  - blocks active site **in both COX isozymes**
- Ibuprofen and naproxen are competitive inhibitors.
  - resemble substrate; also block active site **in both isozymes**
  - *Undesired side effects such as stomach irritation, why?*

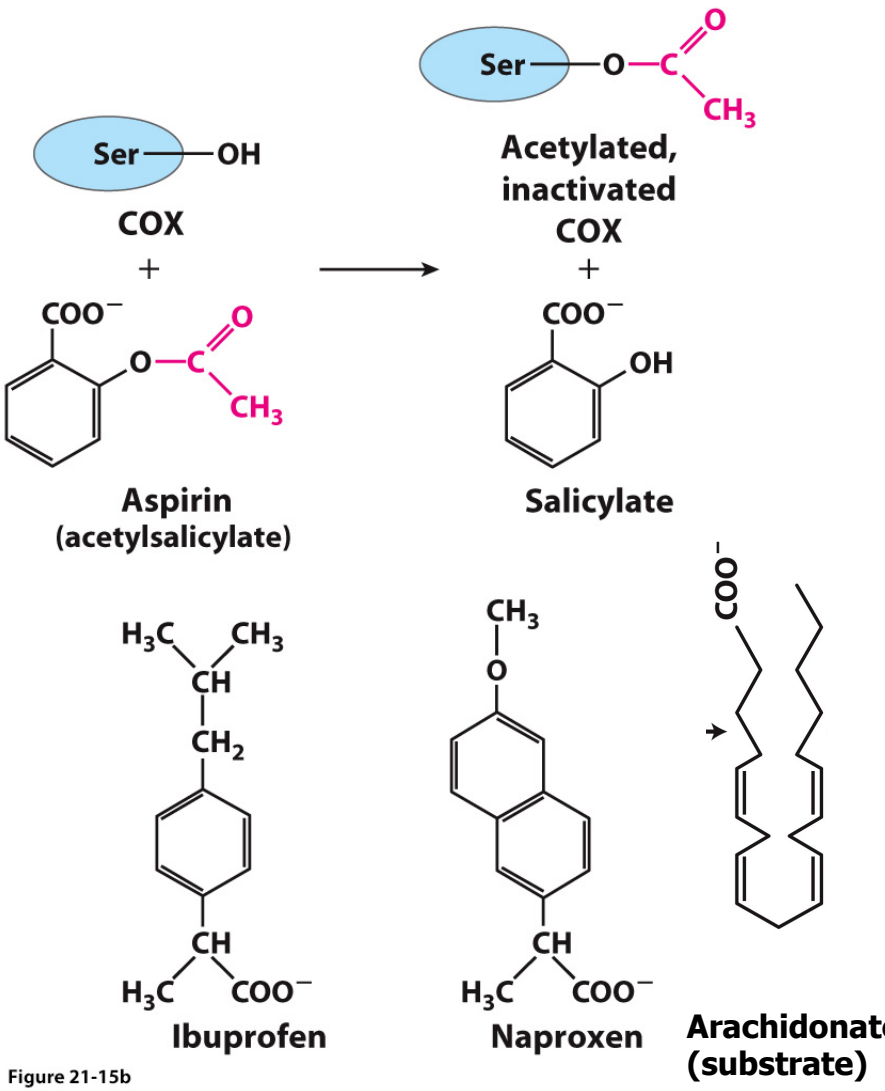

Figure 21-15b
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Synthesis of Leukotrienes Also Begins with Arachidonate

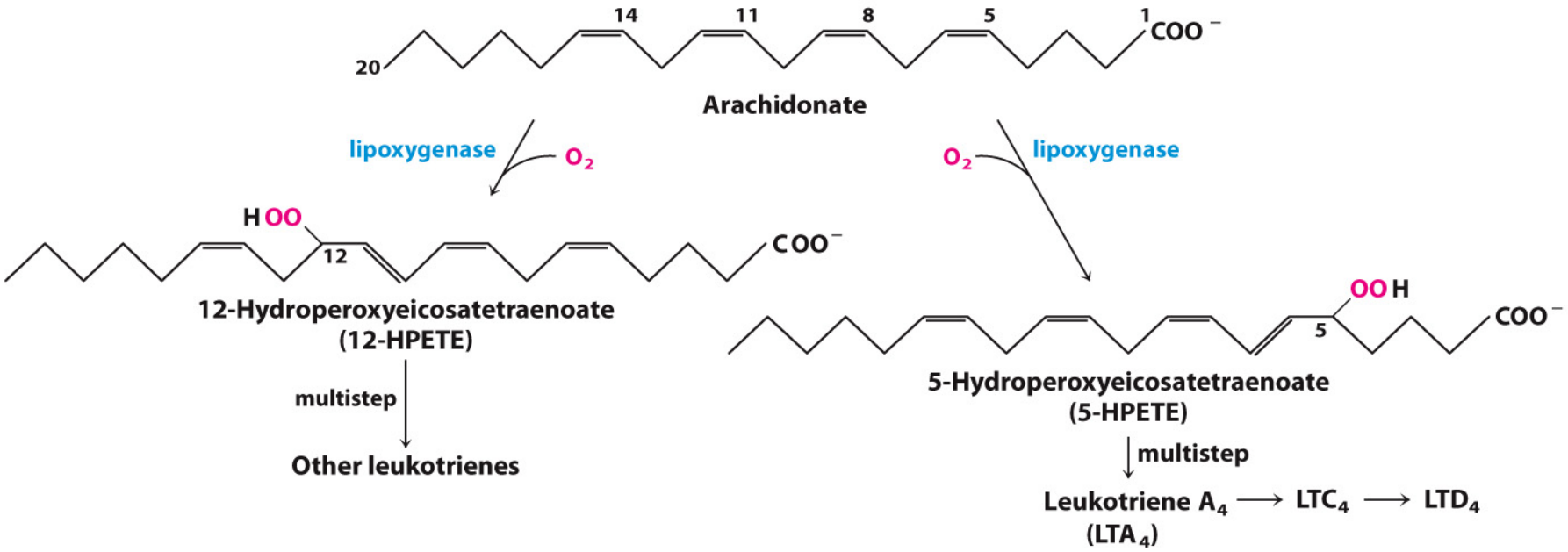

Figure 21-16
Lehninger Principles of Biochemistry, Seventh Edition

- O_2 added to arachidonate via lipoxygenases (mixed-function oxidases)
- Creates species that differ in the position of the OOH group

Fat (Triacylglycerol) and Phospholipids in Animals, Plants, and Bacteria

- Animals and plants store fat for fuel.
  - plants: in seeds, nuts
  - typical 70-kg human has ~15 kg fat
    - enough to last 12 weeks
    - compare with 12 hours worth of glycogen in liver and muscle
- Animals and plants and bacteria make phospholipids for cell membranes.
- Both molecules contain glycerol backbone and 2 (e.g., phospholipids) or 3 (e.g., triacylglycerides) fatty acids.

Synthesis of Backbone of TAGs and Phospholipids

- Most glycerol 3-phosphate comes from siphoning off **dihydroxyacetone phosphate** (DHAP) from glycolysis.
  - via glycerol 3-phosphate dehydrogenase
- Some glycerol 3-phosphate is made from glycerol.
  - via glycerol kinase
  - minor pathway in liver and kidney

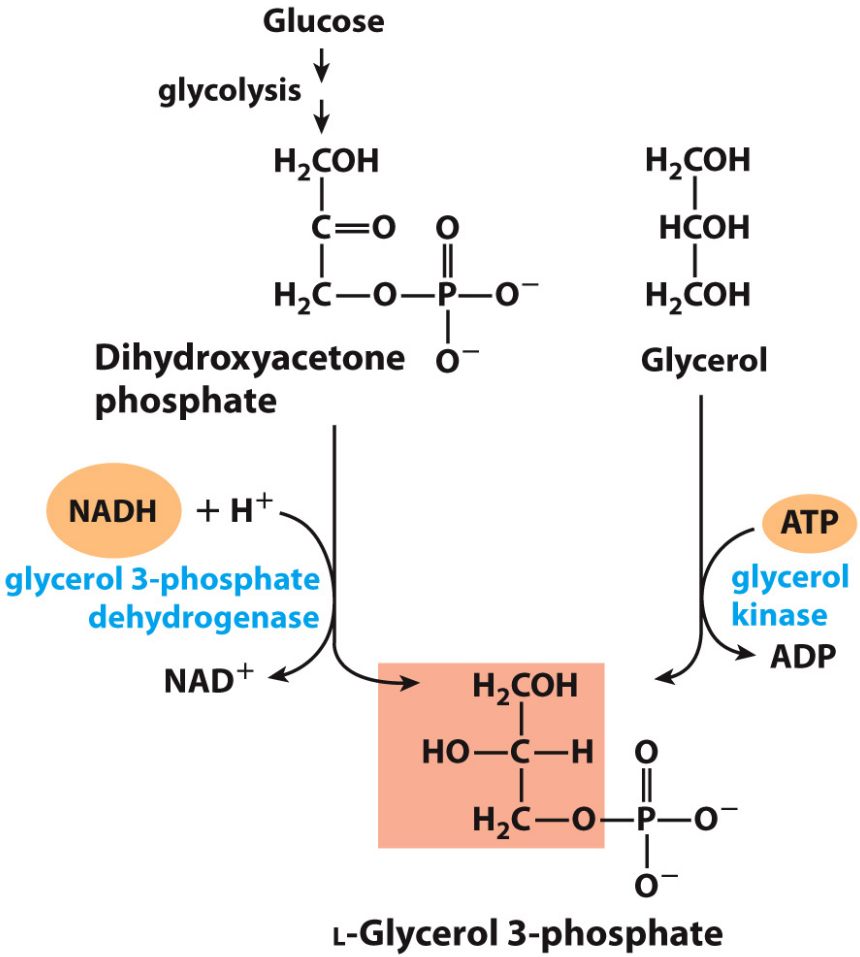

Figure 21-17 part 1
Lehninger Principles of Biochemistry, Seventh Edition

Synthesis of Phosphophatidic Acid Occurs Before TAGs

- Phosphatidic acid is the precursor to TAGs and phospholipids.
  - fatty acids attached by acyl transferases
  - releases CoA
- Advantage of making phosphatidic acid:
  - It can then be made into triacylglycerol OR phospholipid.

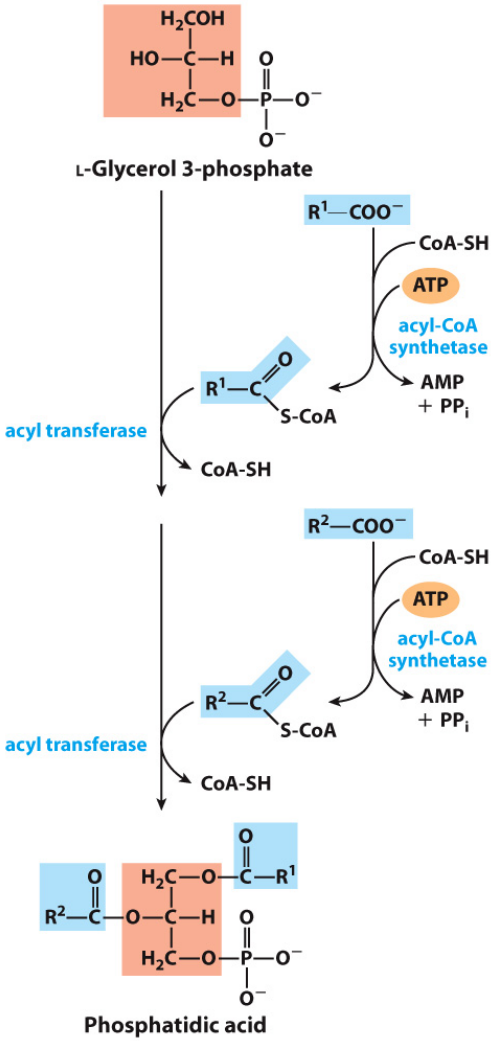

Figure 21-17 part 2
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Phosphatidic Acid Can Be Modified to Form Phosphlipids or TAGs

- Phosphatidic acid phosphatase (lipin) removes the 3-phosphate from the phosphatidic acid.
  - yields 1,2-diacylglycerol
- The third carbon is then acylated with a third fatty acid.
  - yields triacylglycerol

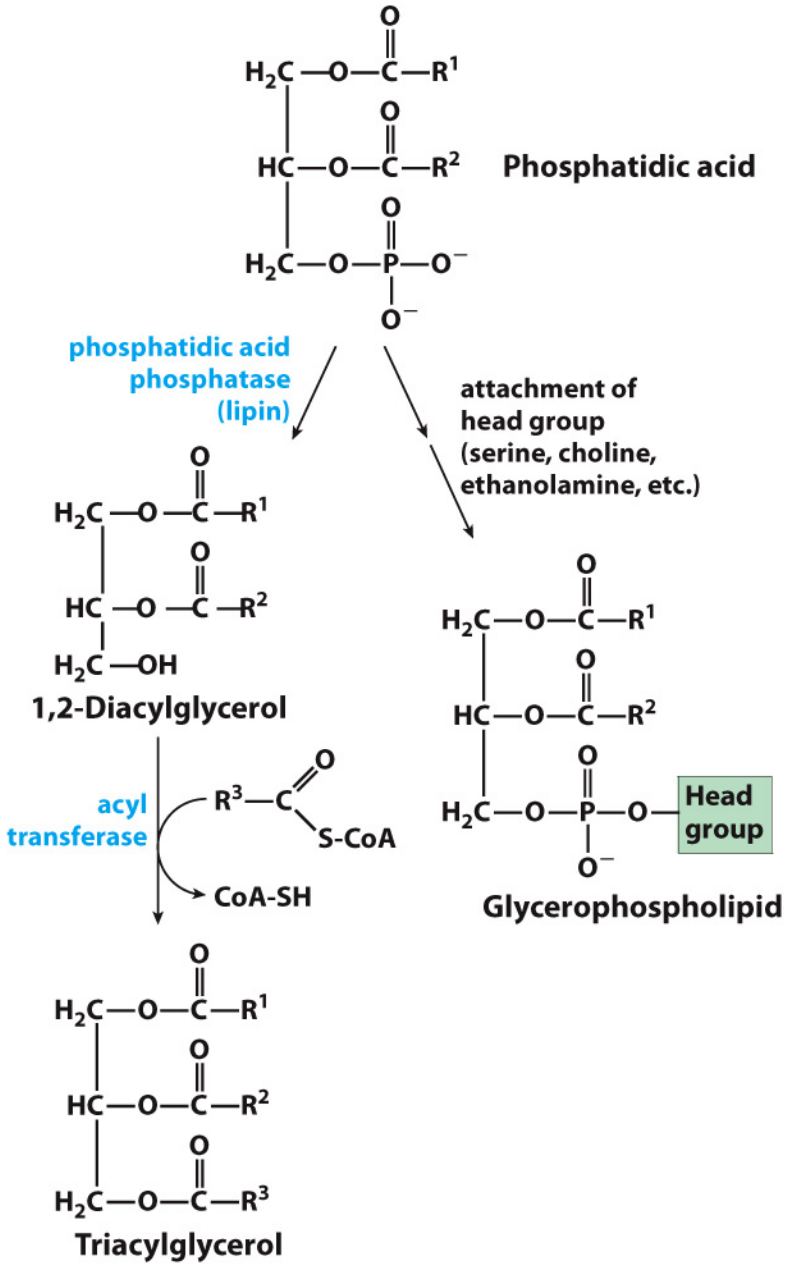

Figure 21-18
Lehninger Principles of Biochemistry, Seventh Edition

Regulation of Triacylglycerol Synthesis by Insulin

- Insulin results in stimulation of triacylglycerol synthesis.
- Lack of insulin results in:
  - increased lipolysis
  - increased fatty acid oxidation
    - sometimes to ketones if citric acid cycle intermediates (oxaloacetate) that react with acetyl CoA are depleted
  - failure to synthesize fatty acids

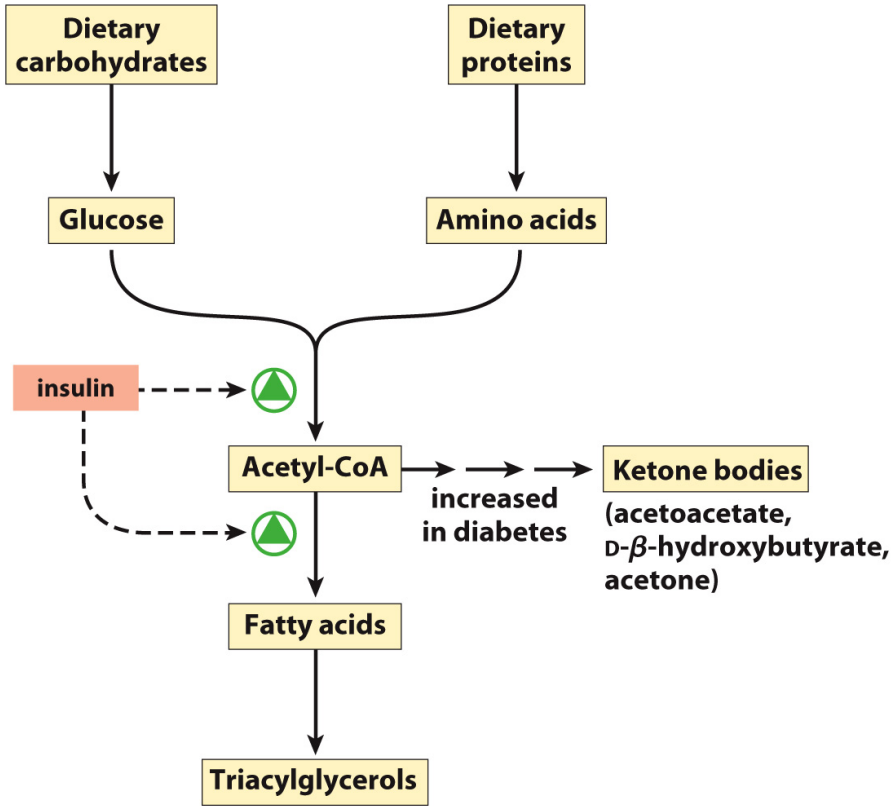

Figure 21-19
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Triacylglycerol Breakdown and Resynthesis create a Futile Cycle

- Seventy-five percent of free fatty acids (FFAs) released by lipolysis are reesterified to form TAGs, rather than be used for fuel.
  - Some recycling occurs in adipose tissue.
  - Some FFAs from adipose cells are transported to the liver, remade into TAG, and redeposited in adipose cells.
- Although the distribution between these two paths may vary, overall, the percentage of FFAs being esterified remains at ~75%.

The Triacylglycerol Cycle

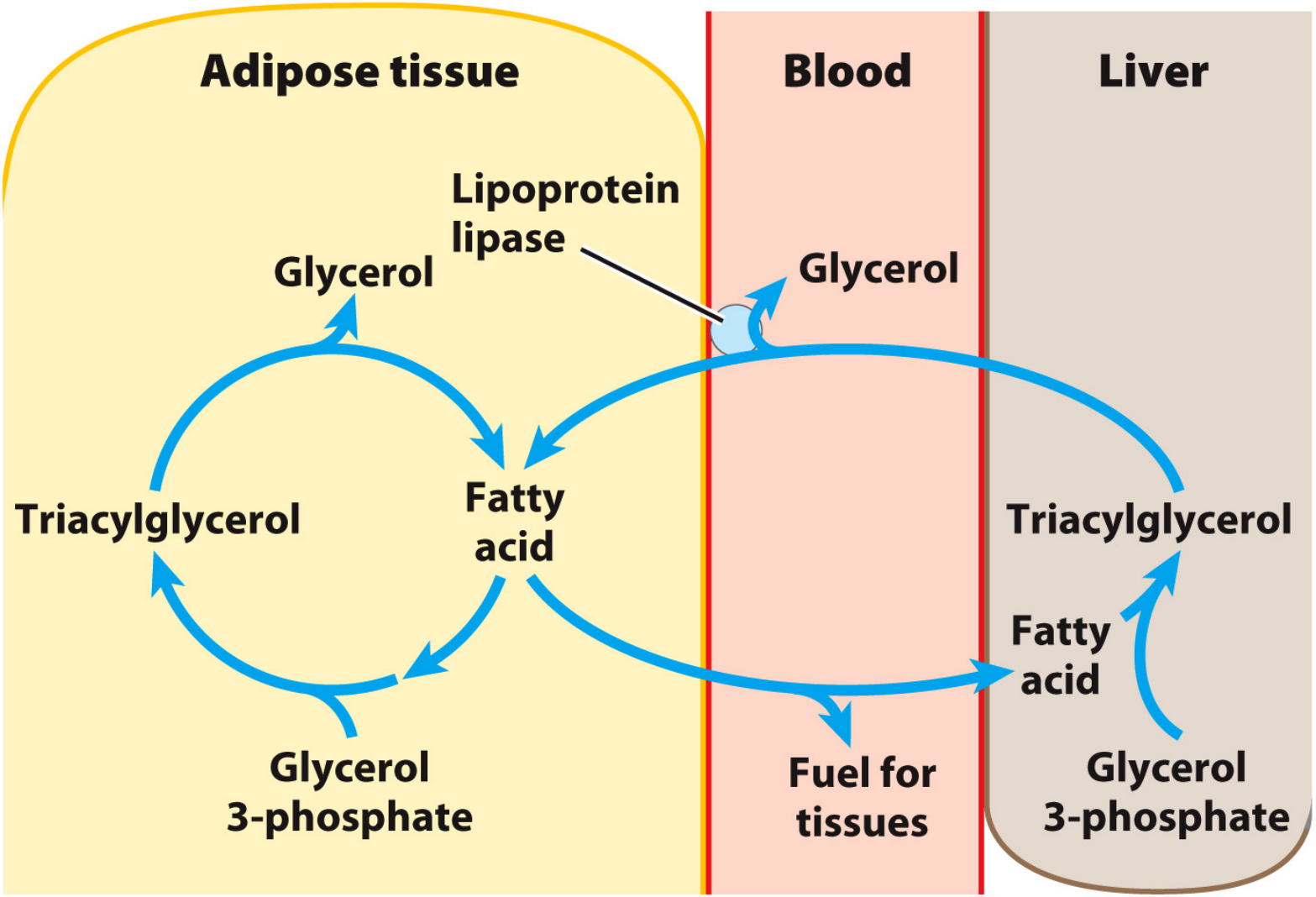

Figure 21-20
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What Is the Source of the Glycerol 3-Phosphate Needed for Fatty Acid Reesterification?

- During lipolysis (stimulated by glucagon or epinephrine), glycolysis is inhibited.
  - So DHAP is not readily available to make glycerol 3-phosphate.
- And adipose cells don't have glycerol kinase to make glycerol 3-phosphate on site.
- So cells make DHAP via glyceroneogenesis.
- See next slide.

Glyceroneogenesis Makes DHAP for Glycerol 3-Phosphate Generation During TAG Cycle

- During lipolysis (stimulated by glucagon or epinephrine), glycolysis is inhibited.
  - So DHAP is not readily available to make glycerol 3-phosphate.
  - And adipose cells don't have glycerol kinase to make glycerol 3-phosphate on site.
- *Glyceroneogenesis* contains some of the same steps of gluconeogenesis.
  - converts pyruvate → DHAP
  - basically, an abbreviated version of gluconeogenesis in the liver and adipose tissue

Glyceroneogenesis

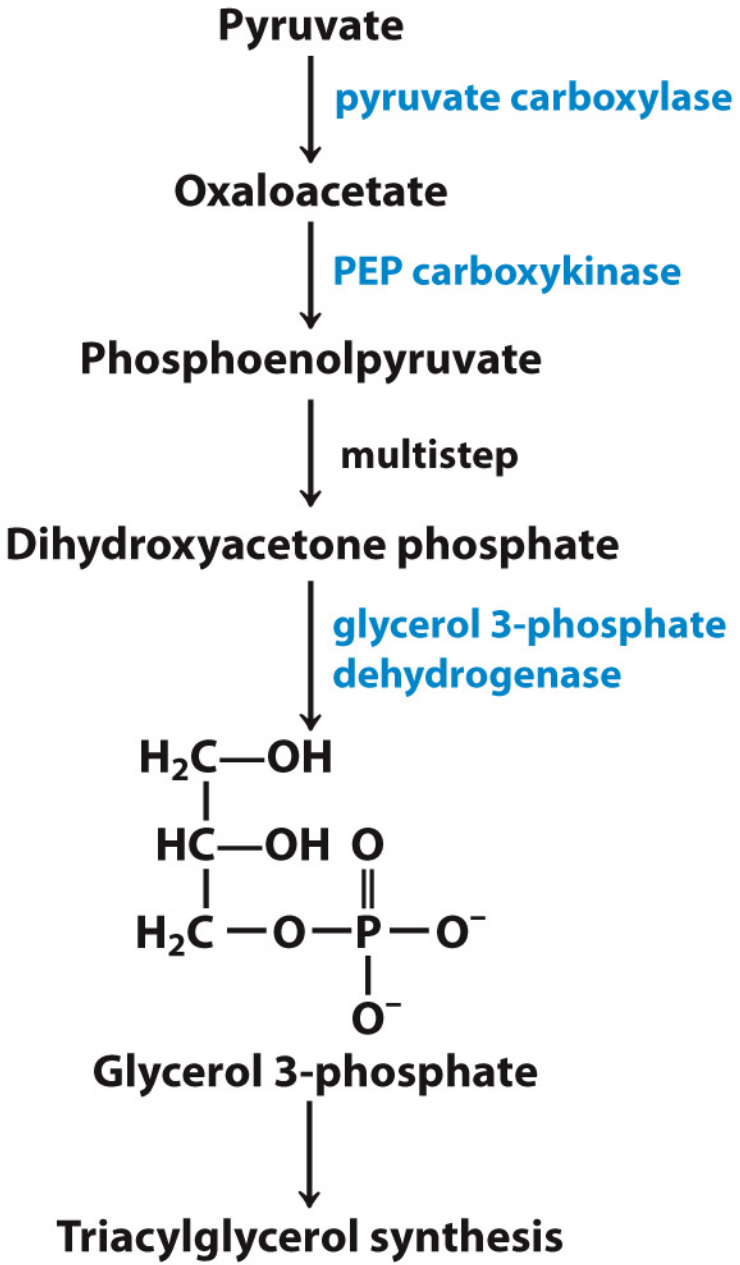

Figure 21-21
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Biosynthesis of Membrane Phospholipds

- Begin with phosphatidic acid or diacylglycerol
- Attach head group to C-3 OH group
  - C-3 has OH; head group has OH
  - new phospho-head group created when phosphoric acid condenses with these two alcohols
  - eliminates two H_2O

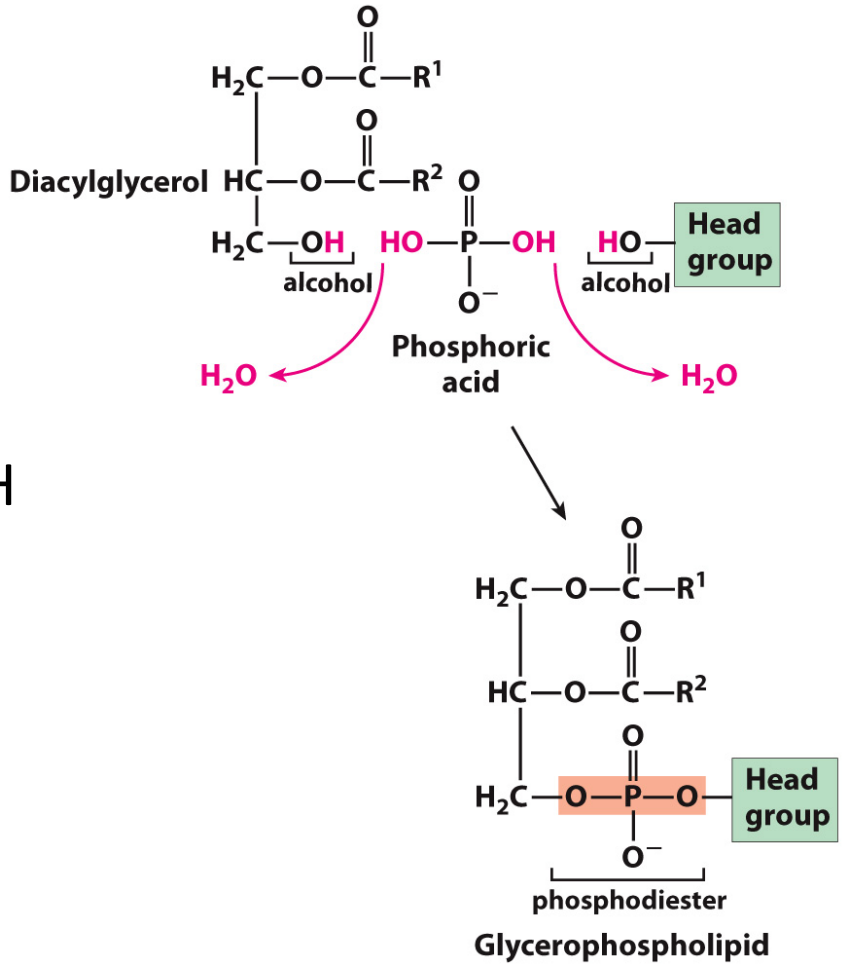

Figure 21-23
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Attaching Phospholipid Head Group Requires Activation by CDP

- Either one of the alcohols is activated by attaching to CDP (cytidine diphosphate).
- The free (not bound to CDP) alcohol then does a nucleophilic attack on the CDP-activated phosphate.

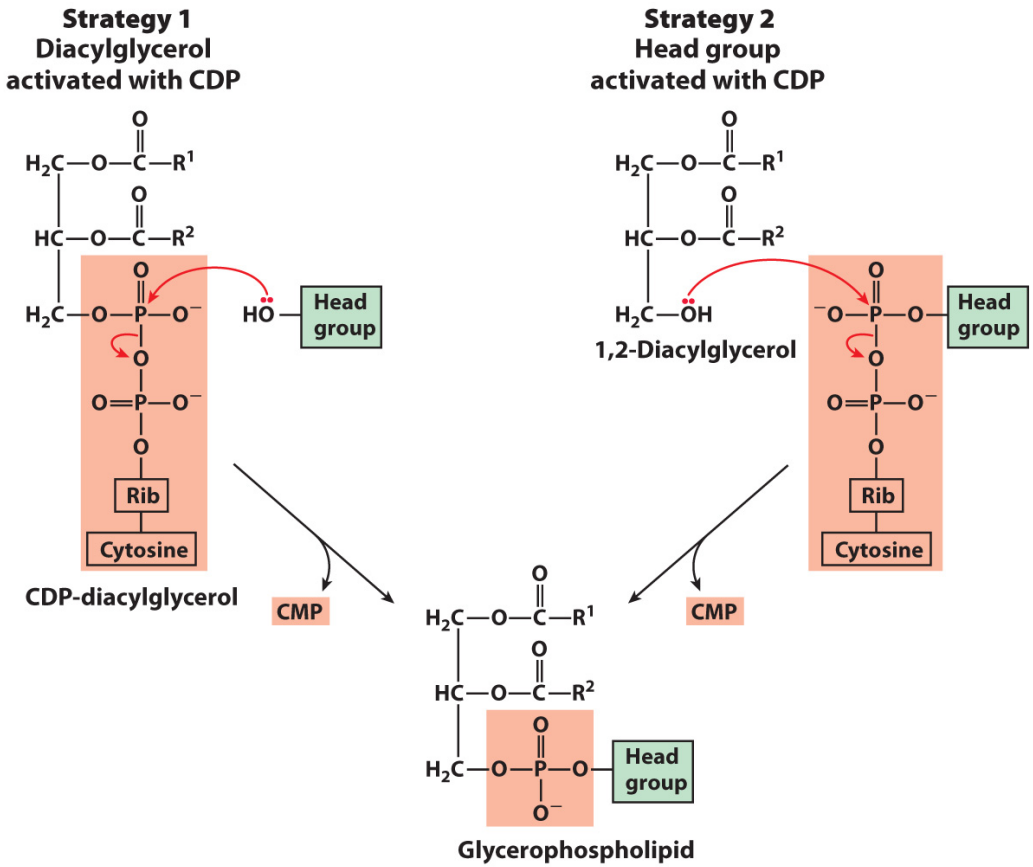

Figure 21-24
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Phospholipid Synthesis in *E. coli*

Two main pathways:

- Phosphatidylserine is synthesized and can be decarboxylated to phosphatidylethanolamine.
- Phosphatidylglycerol is synthesized by addition of a CDP-glycerol-3-phosphate.
  - Further modification to cardiolipin can be achieved by replacement of the glycerol head group with another phospholipid.

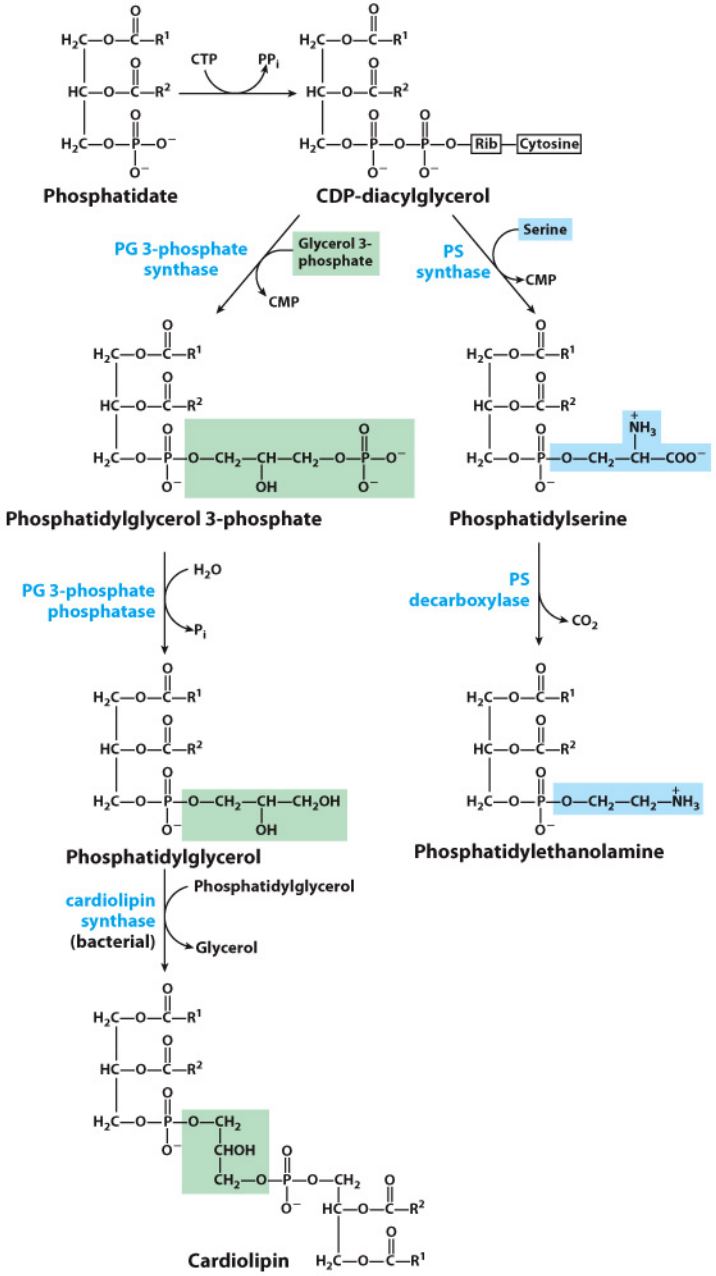

Figure 21-25

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Synthesis of Anionic Phospholipids in Eukaryotes Uses Similar Strategies to That of *E. coli*

Slightly different from bacterial synthesis strategy (e.g., replacement of CMP, rather than glycerol)

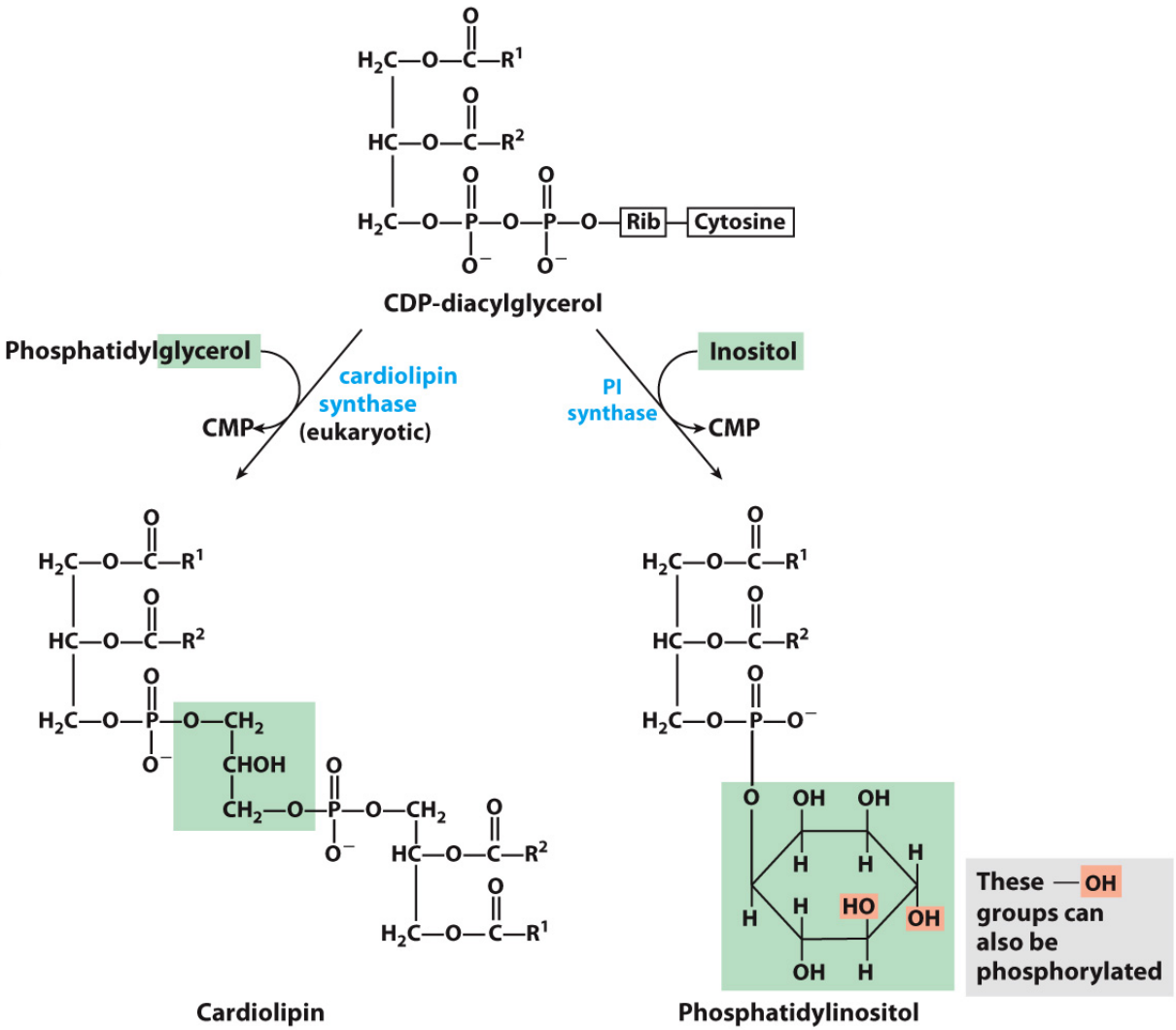

Figure 21-26
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Yeast Synthesize Phosphatidylcholine from Phosphatidylethanolamine

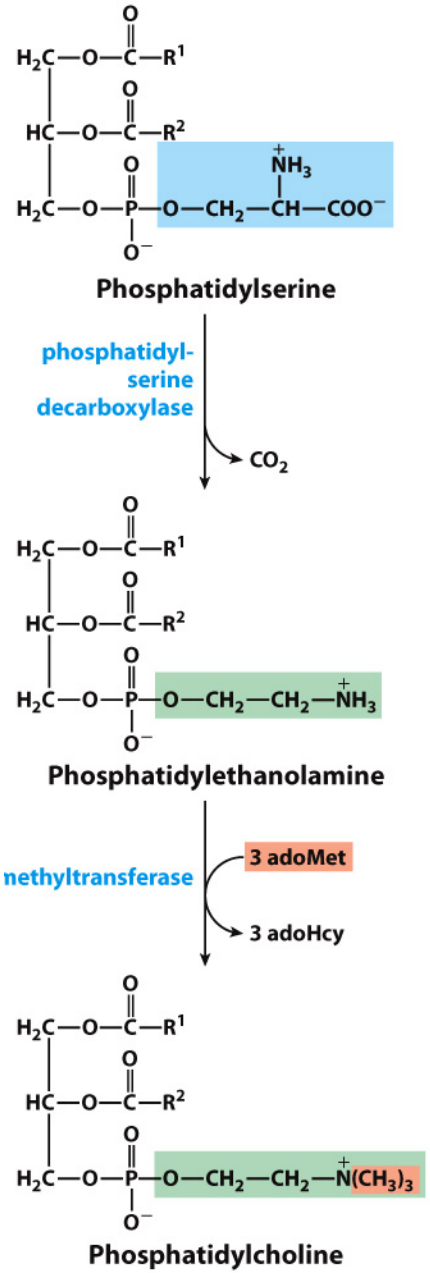

Figure 21-27
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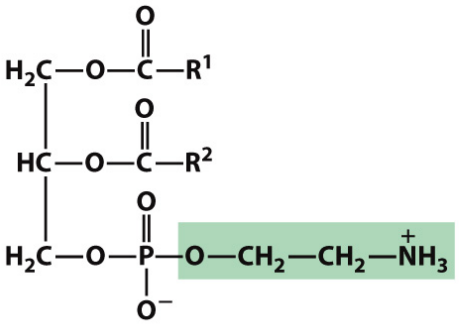
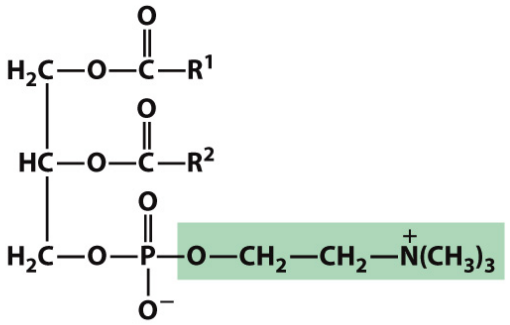
- Phosphatidylserine is decarboxylated to ***phosphatidylethanolamine.***
  - as in bacteria, but enzyme is phosphatidylserine decarboxylase
- Phosphatidylethanolamine acted on by *S*-adenosylmethione (methyl group donor) adds three methyl groups to amino group → ***phopshatidylcholine (lecithin).***
  - catalyzed by methyltransferase

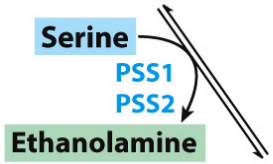
Synthesis of Phosphatidylserine and Phosphatidylcholine in Mammals Constitutes a Salvage Pathway

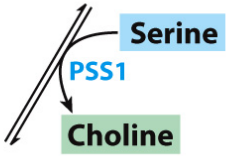


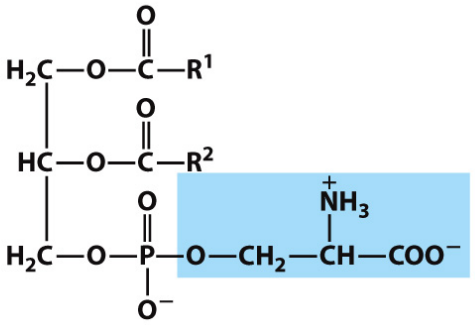
Phosphatidylethanolamine



Phosphatidylcholine







Phosphatidylserine

- Phosphatidylserine is made "backwards" from phosphatidyl-ethanolamine or phosphatidylcholine via head-group exchange reactions.
  - catalyzed by specific synthases
  - pathway "salvages" the choline

Figure 21-29a
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Summary of Phospholipid Biosynthesis Pathways in Eukaryotes

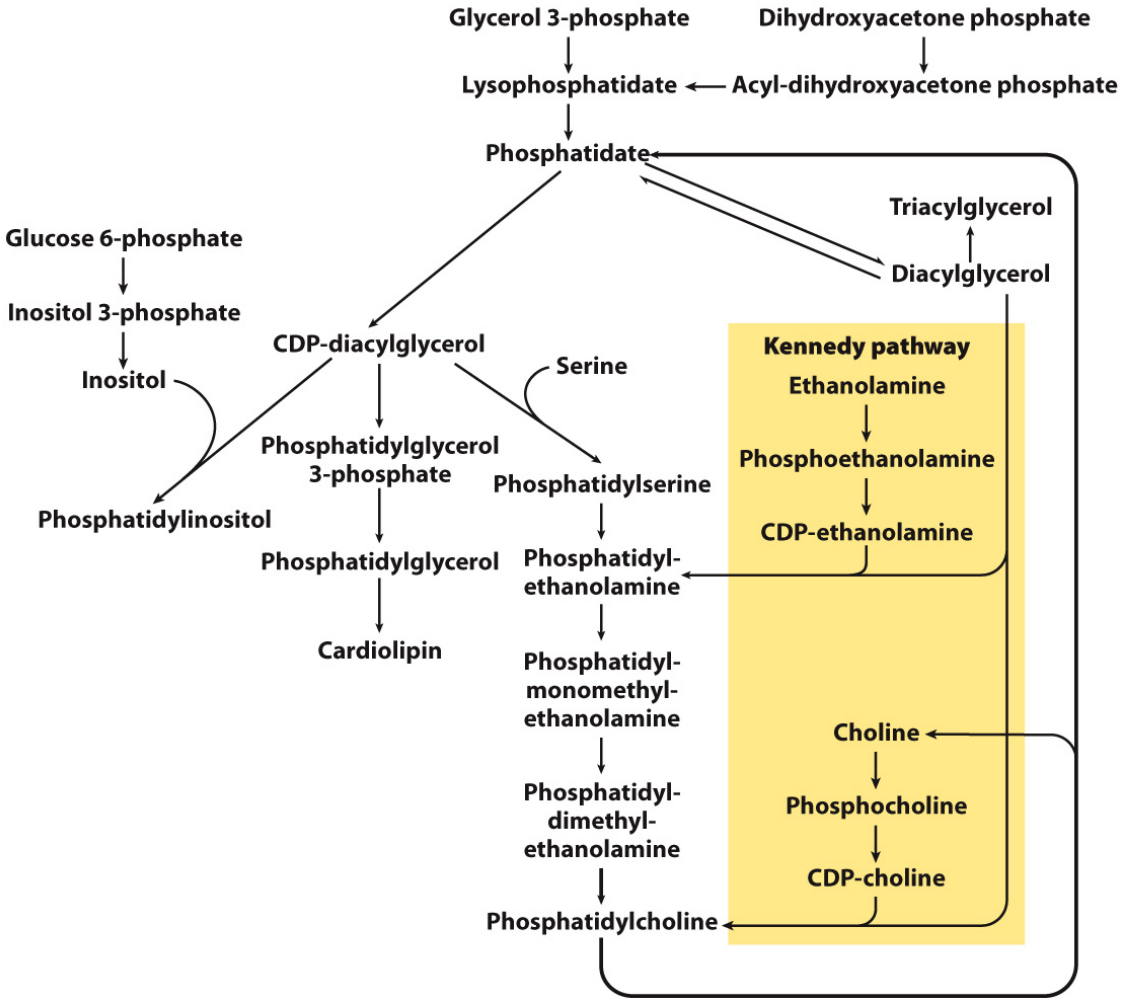

Figure 21-28
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Synthesis of Ether Lipids and Plasmalogens Use Similar Pathways

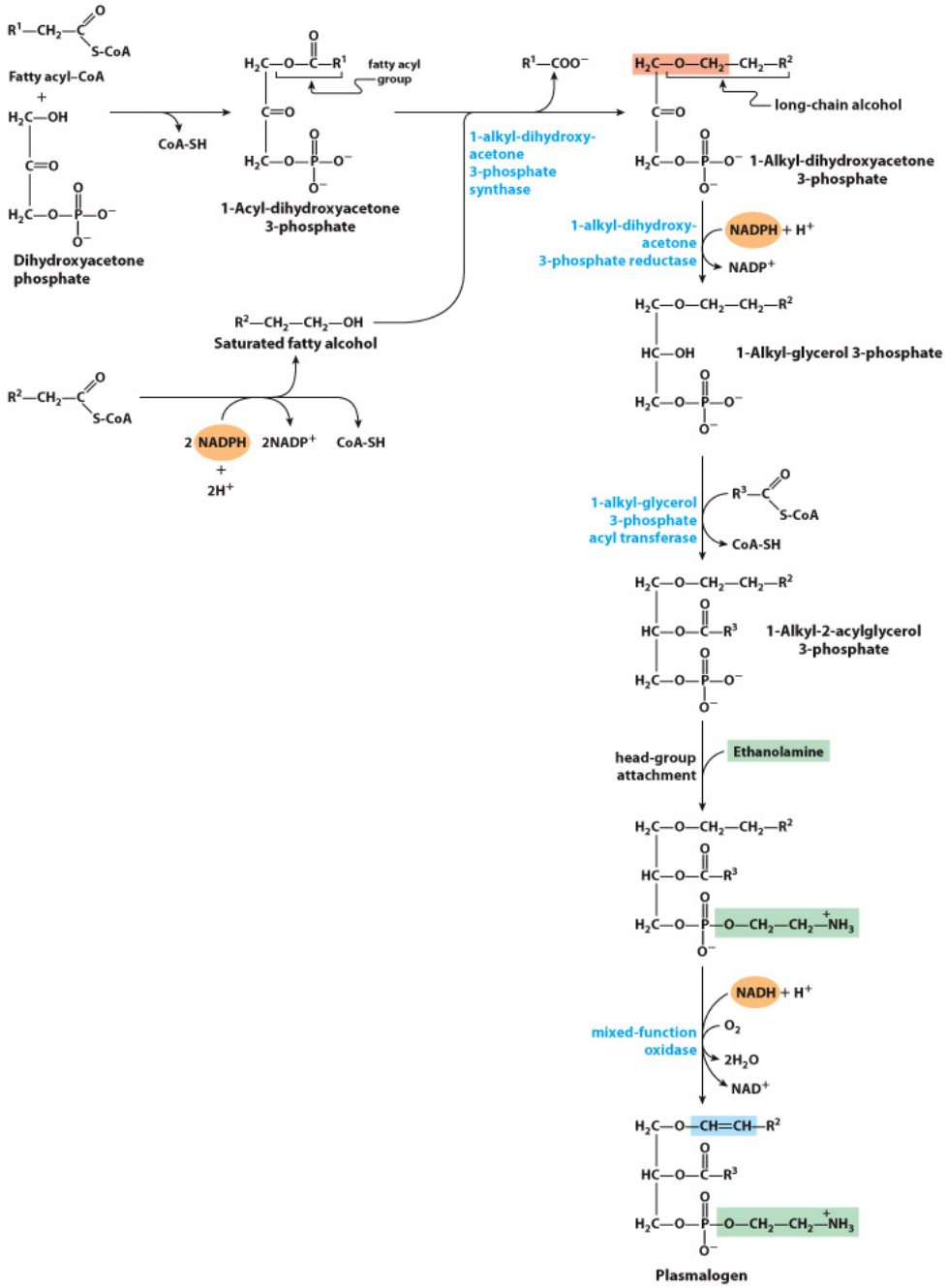

Figure 21-30
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Synthesis of Sphingolipids Use Similar Pathways

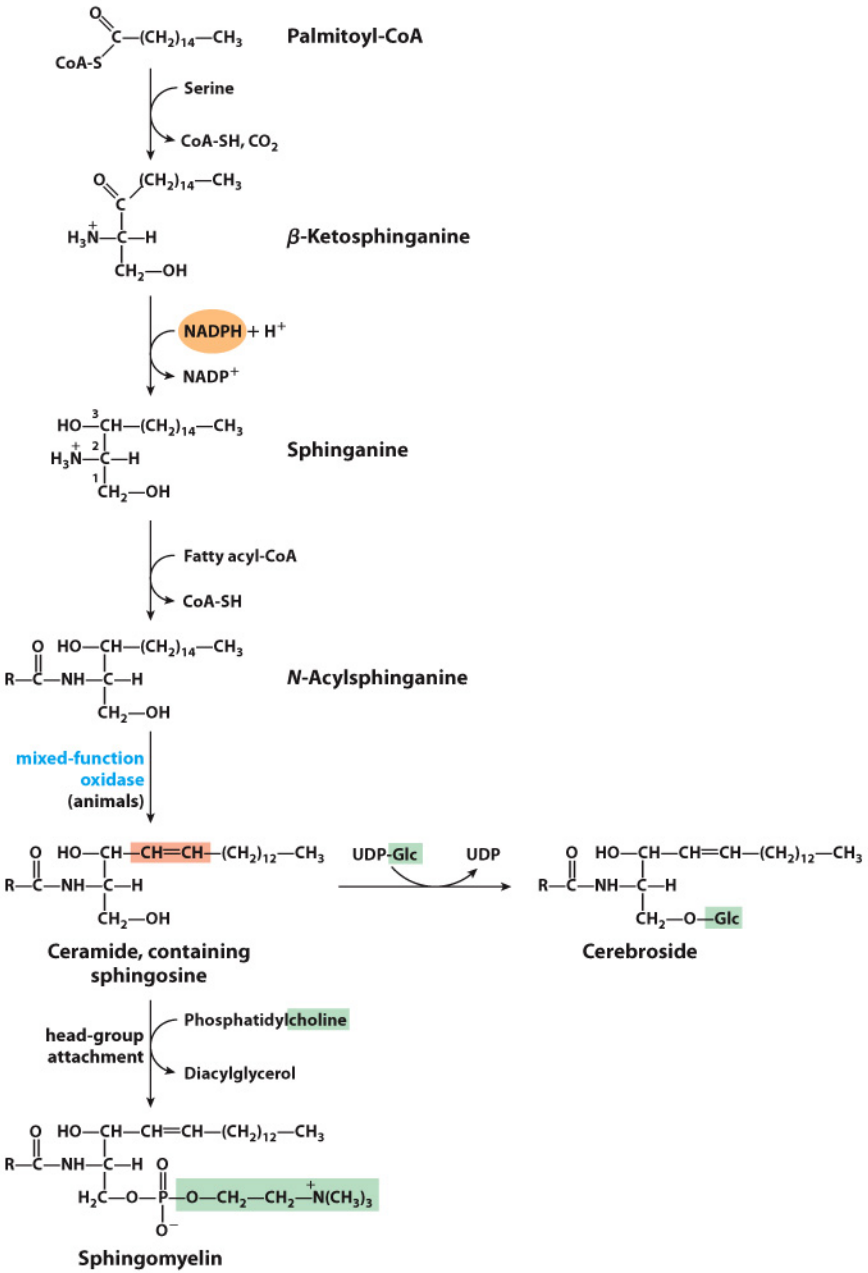

Figure 21-31

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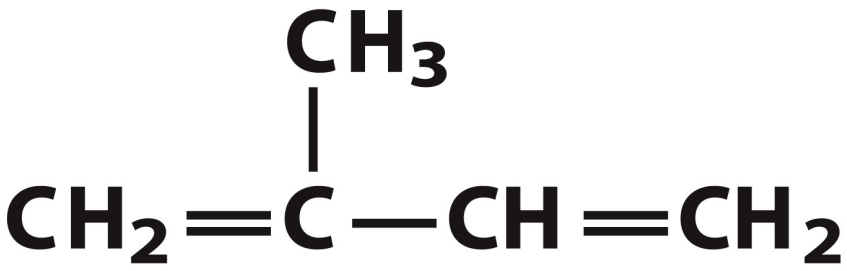
Synthesis and Transport of Cholesterol, Steroids, and Isoprenes

- Compounds are chemically related and distinct from TAGs, phospholipids, sphingolipids, and plasmalogens.
- Chemical relationship is built on biosynthesis using 5-carbon isoprene unit



Isoprene

Overview of Eukaryotic Cholesterol Biosynthesis

1. Three **acetates** condense to form **mevalonate.**
2. Mevalonate converts to phosphorylated **5-C isoprene.**
3. Six isoprenes polymerize to form the **30-C linear squalene.**
4. Squalene cyclizes to form the four rings that are modified to produce **cholesterol.**

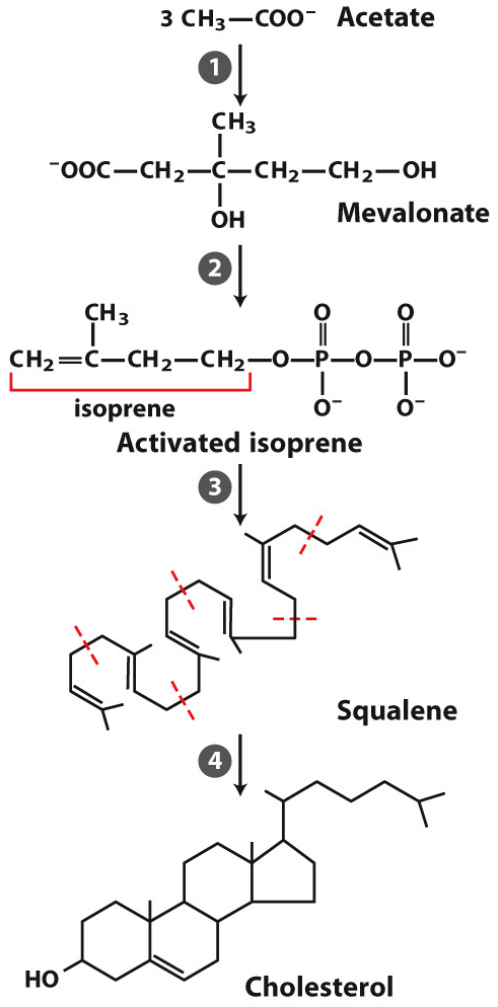


Figure 21-33
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Step 1: Formation of Mevalonate from Acetyl-CoA

- Three acetyl-CoA are condensed to form HMG-CoA.
- HMG-CoA is reduced to form mevalonate.
  - HMG-CoA reductase is a common target of cholesterol-lowering drugs.

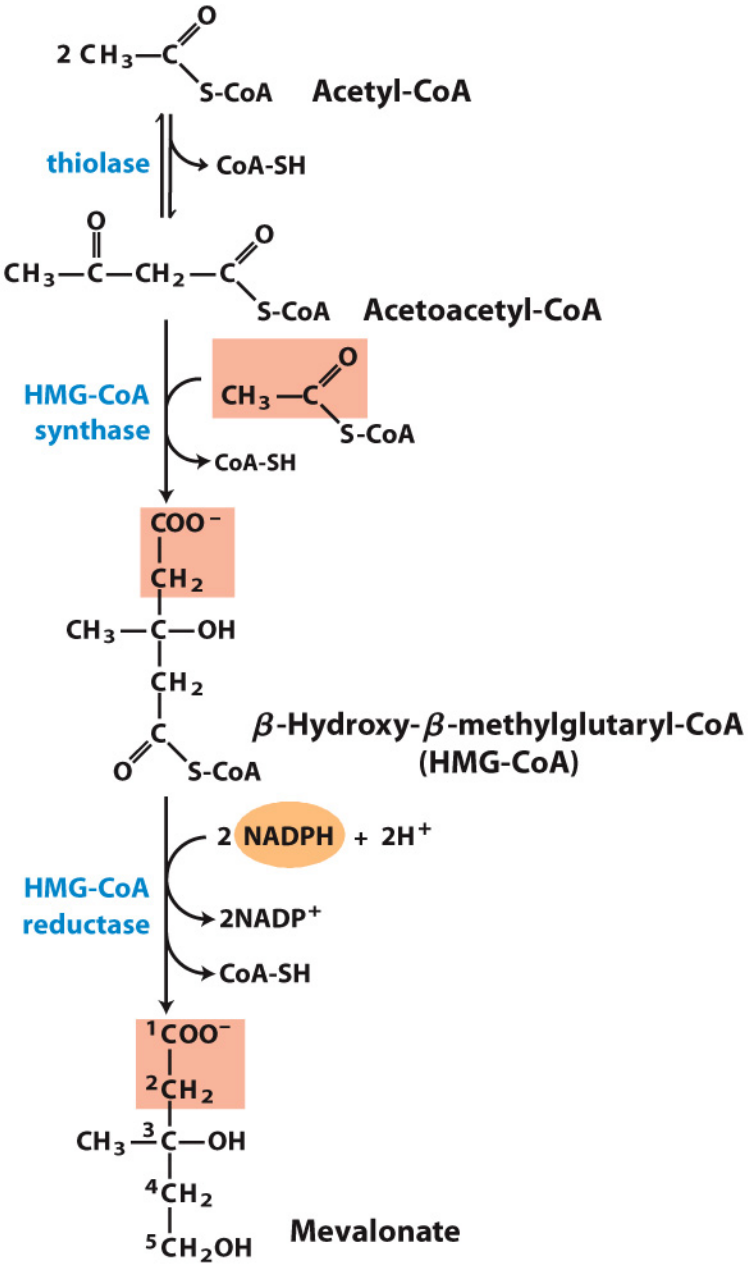

Figure 21-34
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Step 2: Conversion of Mevalonate to Activated Isoprenes

- Three phosphates are transferred stepwise from ATP to mevalonate.
- Decarboxylation and hydrolysis creates a diphosphorylated 5-C product **(isoprene)** with a double bond.
- Isomerization to a second isoprene
  - *Δ^3-isopentyl pyrophosphate (IPP)*
  - *dimethylallylpyrophosphate (DMAPP)*

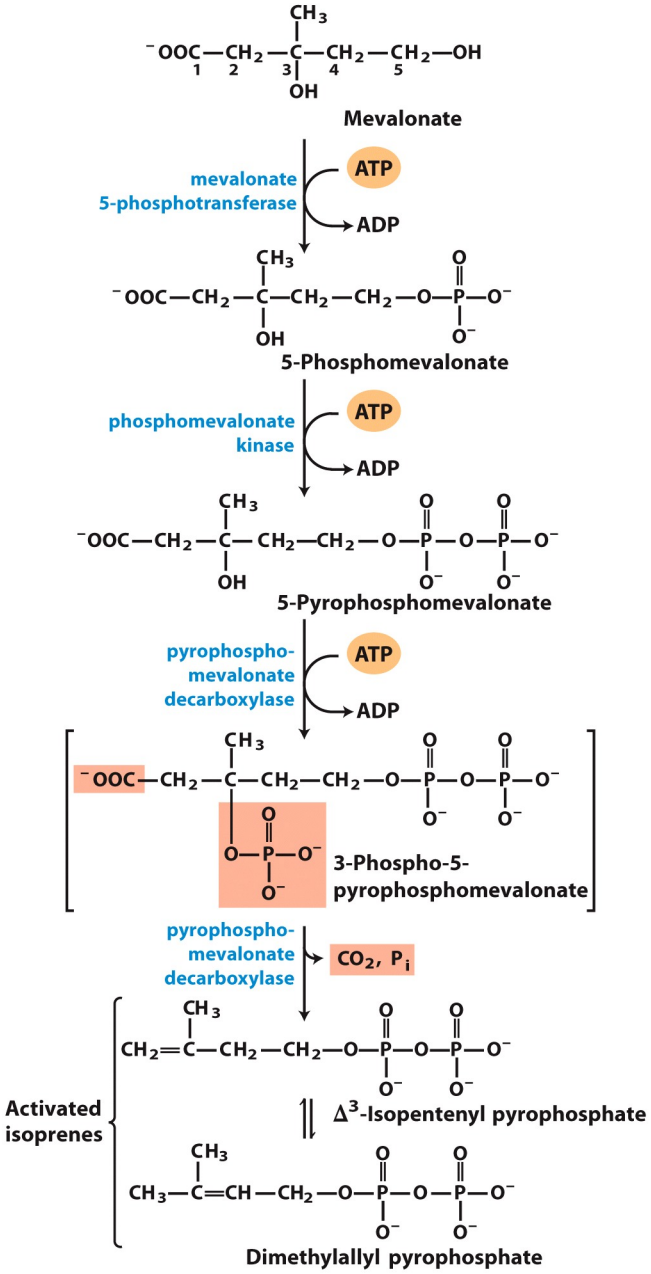

Figure 21-35
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Step 3: Six Activated Isoprene Units Condense to Form Squalene

- The two isoprenes join **head-to-tail**, displacing one set of diphosphates.
  → forms ***geranyl pyrophopshate***
- Geranyl pyrophosphate joins to another isopentenyl pyrophosphate.
  → forms 15-C ***farnesyl pyrophosphate***
- Two farnesyl pyrophosphates join **head-to-head** to form phosphate-free ***squalene.***

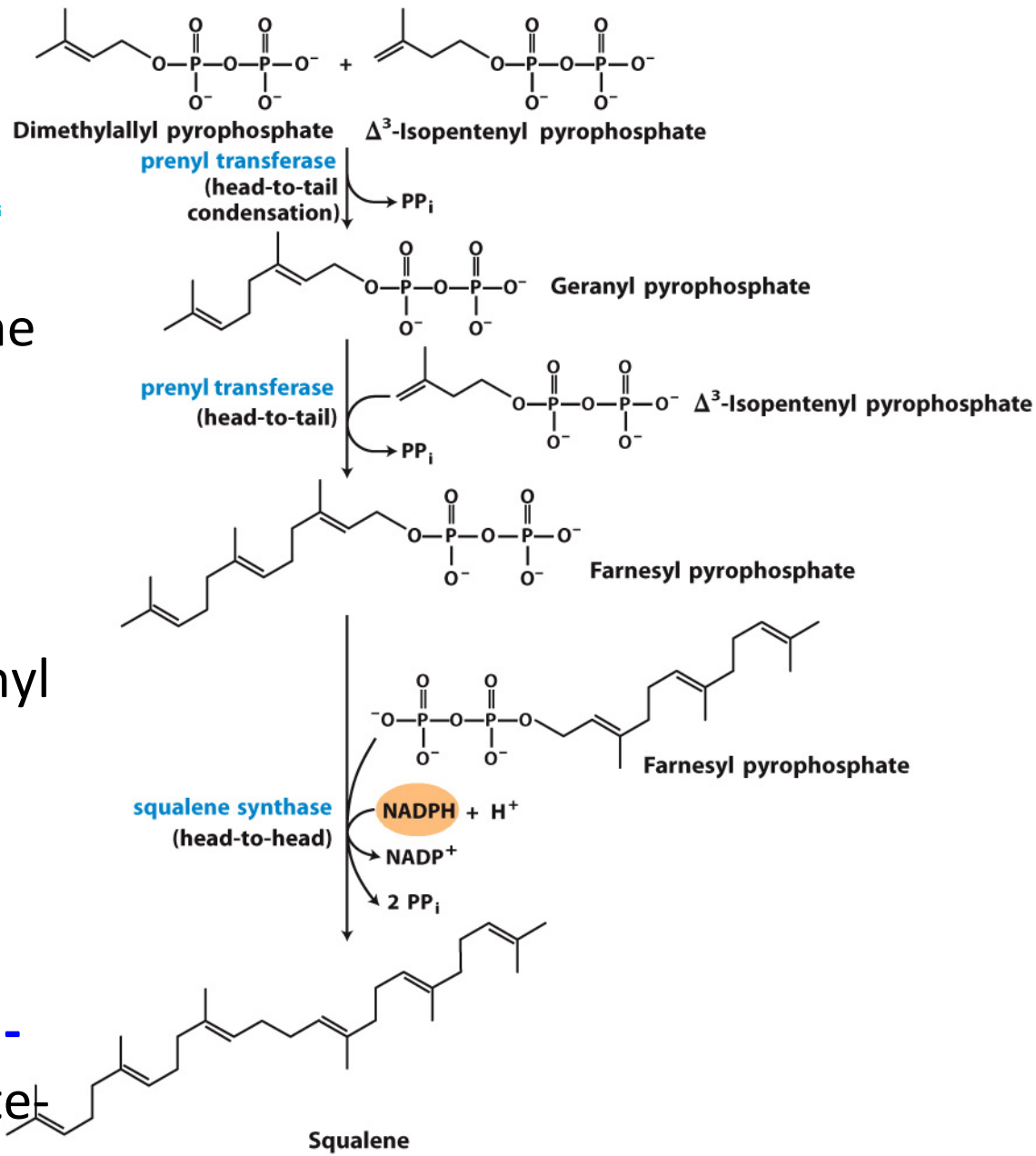

Figure 21-36
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Step 4: Conversion of Squalene to Four-Ring Steroid Nucleus

- Squalene monooxygenase adds one oxygen to the end of the squalene chain.

  → forms squalene 2,3-epoxide

- Here, pathways diverge in animal cells versus plant cells.
- The cyclization product in animals is lanosterol, which converts to cholesterol.
- In plants, the epoxide cyclizes to other sterols, such as ergosterol.

Conversion of Squalene to Cholesterol

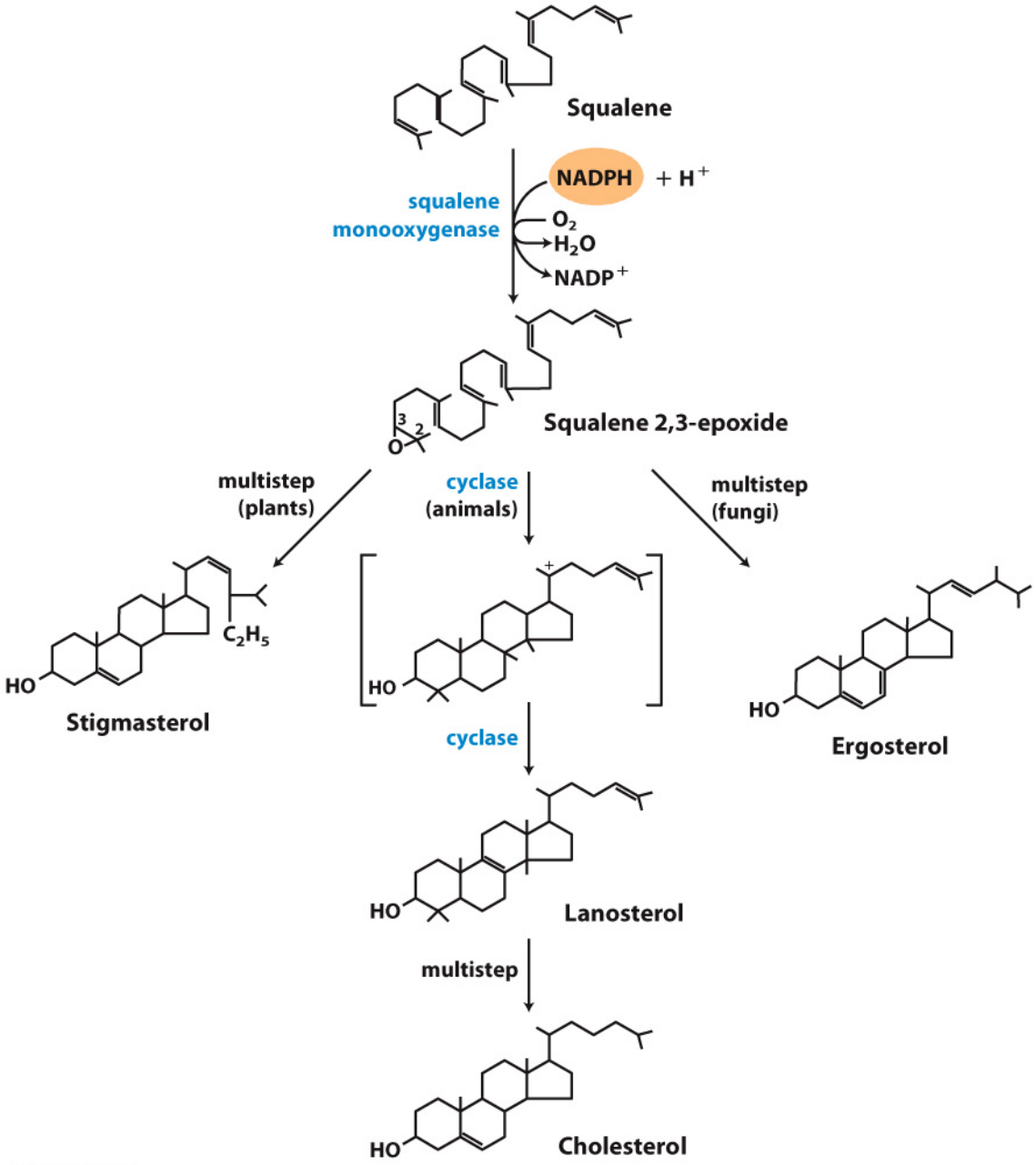

Figure 21-37

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Fates of Cholesterol After Synthesis

- In vertebrates, most cholesterol is synthesized in the liver, then exported.
  - They are exported as bile acids, biliary cholesterol, or cholesteryl esters.
  - Bile is stored in the gall bladder and secreted into the small intestine after fatty meal.
  - Bile acids such as taurocholic acid emulsify fats.
  - They surround droplets of fat, increasing surface area for attack by lipases.
- Other tissues convert cholesterol into steroid hormones and so on.

Fates of Cholesterol After Synthesis

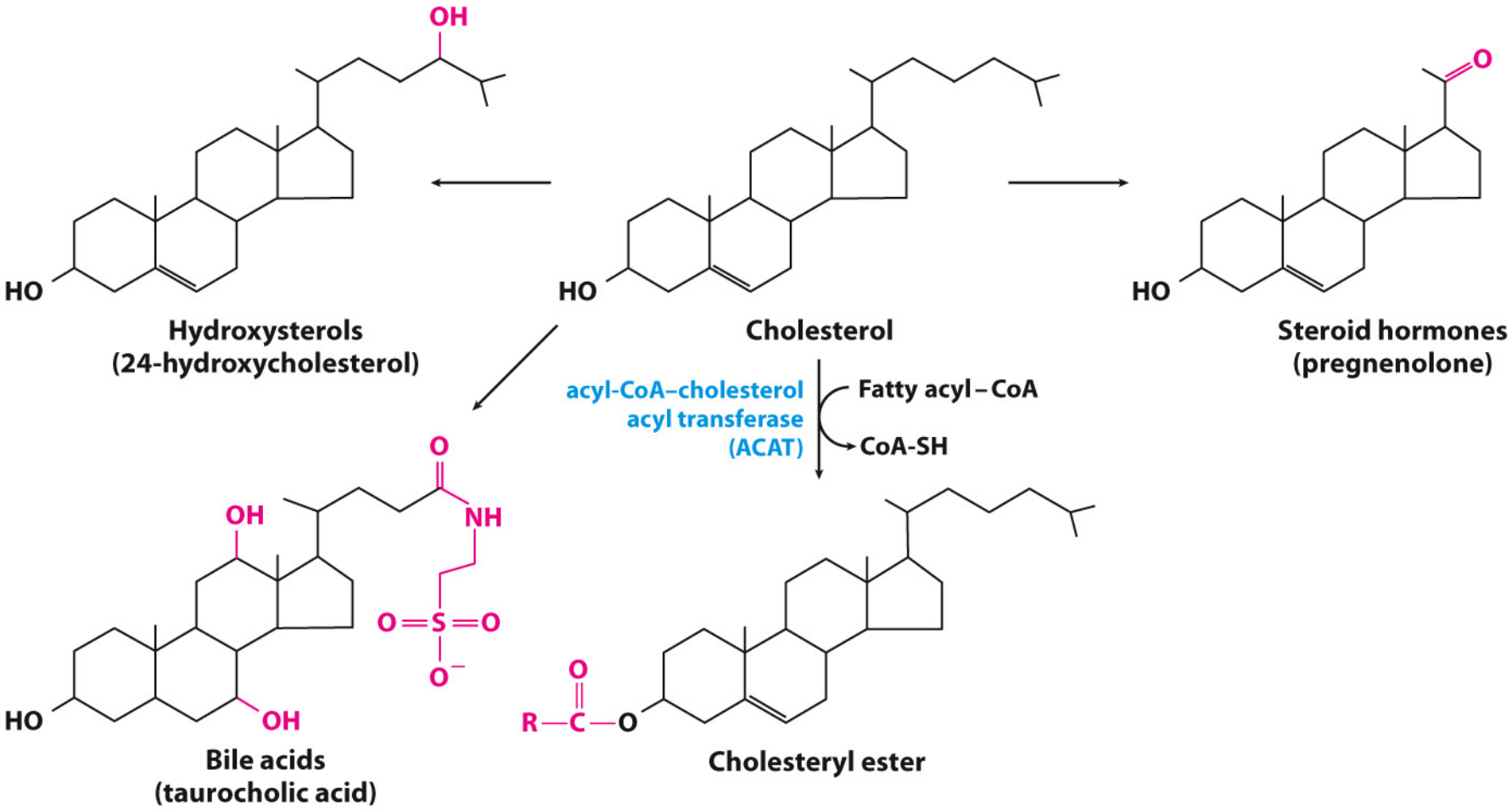

Figure 21-38

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Cholesterol and Other Lipids Are Carried on Lipoprotein Particles

- Lipids are carried through the plasma on spherical particles.
  - surface is made of protein (called apolipoprotein) and a phospholipid monolayer
  - interior contains cholesterol, TAGs, and cholesteryl esters, which are more nonpolar than cholesterol

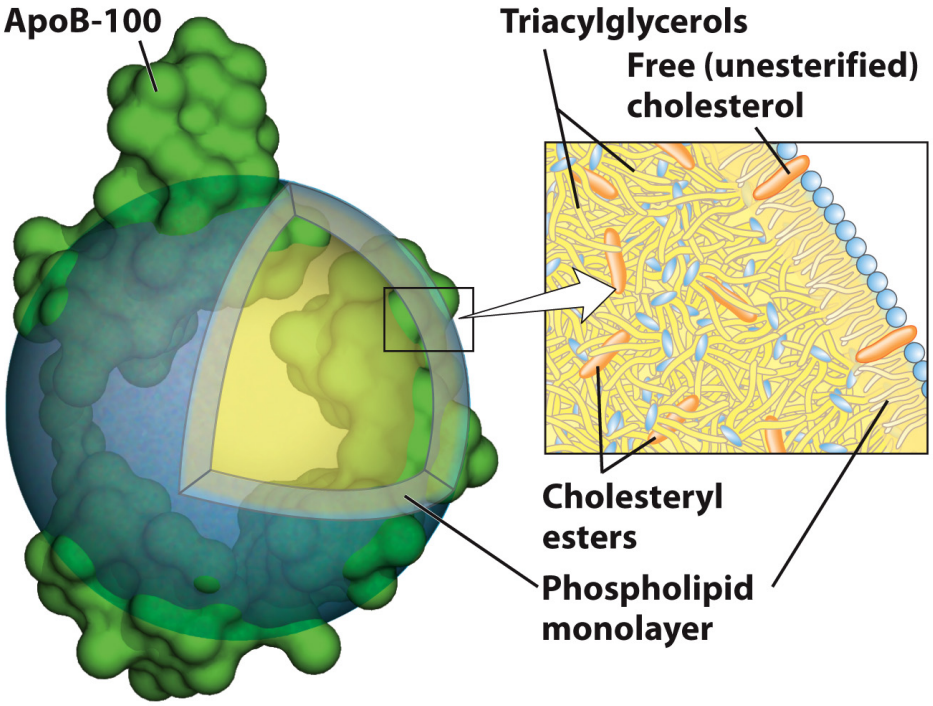

Figure 21-39a
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Four Major Classes of Lipoprotein Particles

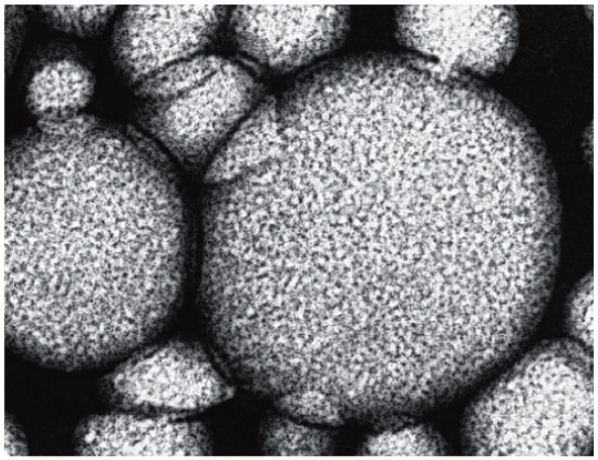
- Named based on position of sedimentation (density) in centrifuge
- Composition varies between class of lipoprotein
- Includes four major classes:

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

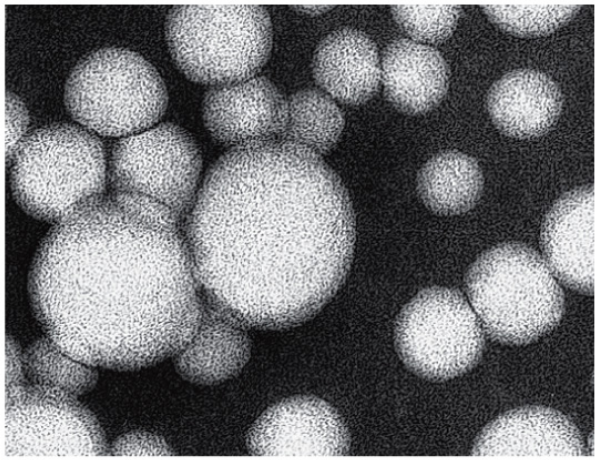
Lipoprotein	Density (g/ml)	Composition (wt %)				
		Protein	Phospholipids	Free cholesterol	Cholesteryl esters	Triacylglycerols
Chylomicrons	<1.006	2	9	1	3	85
VLDL	0.95–1.006	10	18	7	12	50
LDL	1.006–1.063	23	20	8	37	10
HDL	1.063–1.210	55	24	2	15	4

Source: Data from D. Kritchevsky, *Nutr. Int.* 2:290, 1986.

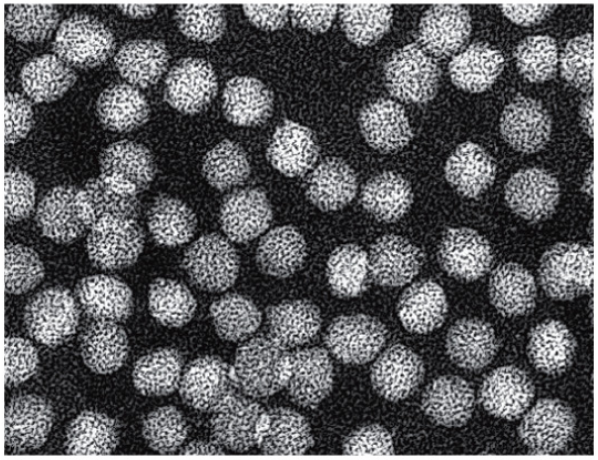
Electron Microscope Pictures of Lipoproteins



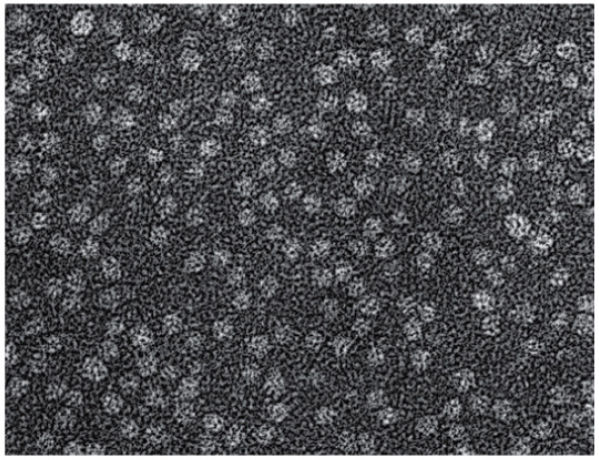
Chylomicrons (×60,000)



VLDL (×180,000)



LDL (×180,000)



HDL (×180,000)

Robert Hamilton, Jr., PhD

Figure 21-39b
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Apolipoproteins in Lipoproteins

- "Apo" for "without"…
  - So "apolipoprotein" refers to the protein part of a lipoprotein particle.

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

Source: Information from D. E. Vance and J. E. Vance (eds), *Biochemistry of Lipids and Membranes*, 5th edn, Elsevier Science Publishing, 2008.

Biological Roles and Characteristics of Lipoproteins

Chylomicrons

- Least dense of lipoproteins (contains most TAG)
- Have apoB-48, apoE, and apoC-II

VLDL

- Contains TAG and cholesteryl esters in high concentrations
- Contain apoB-100, apoC-I, apoC-II, apoC-III, and apoE

LDL

- Produced by removal of TAG from VLDL
- LDL is enriched in cholesterol/ chloesteryl esters.
- ApoB-100 is the major apolipoprotein.

HDL

- Produced from enzymatic conversion of LDL and VLDL cholesterol to cholesteryl esters
- HDLs are high in protein, including apoA-I.

Activation and Mobilization of Lipoprotein Contents (1)

Chylomicrons

- ApoC-II activates lipoprotein lipase to allow free fatty acid release for fuel in adipose tissue, heart, and skeletal muscle.
- When fats are depleted, remnants go to the liver for absorption via apoE-mediated endocytosis.

VLDL

- Again, apoC-II activates lipoprotein lipase to release free fatty acids.
- Adipocytes take up the FFAs, reconvert them to TAGs, and store them in lipid droplets.
- Muscle uses the TAG for energy.

Activation and Mobilization of Lipoprotein Contents (2)

LDL

- Muscle and adipose tissue have LDL receptors and recognize apoB-100.
- Myocytes and adipocytes take up cholesterol via receptor-mediated endocytosis.

HDL

- HDL picks up cholesterol from the cells and returns to liver, where it can be metabolized (e.g., bile salts).
- Also catalyzes conversion of remnant cholesterol of LDL and VLDL to cholesteryl esters

Lecithin-Cholesterol Acyl Transferase-Catalyzed Reaction Occurs in HDL

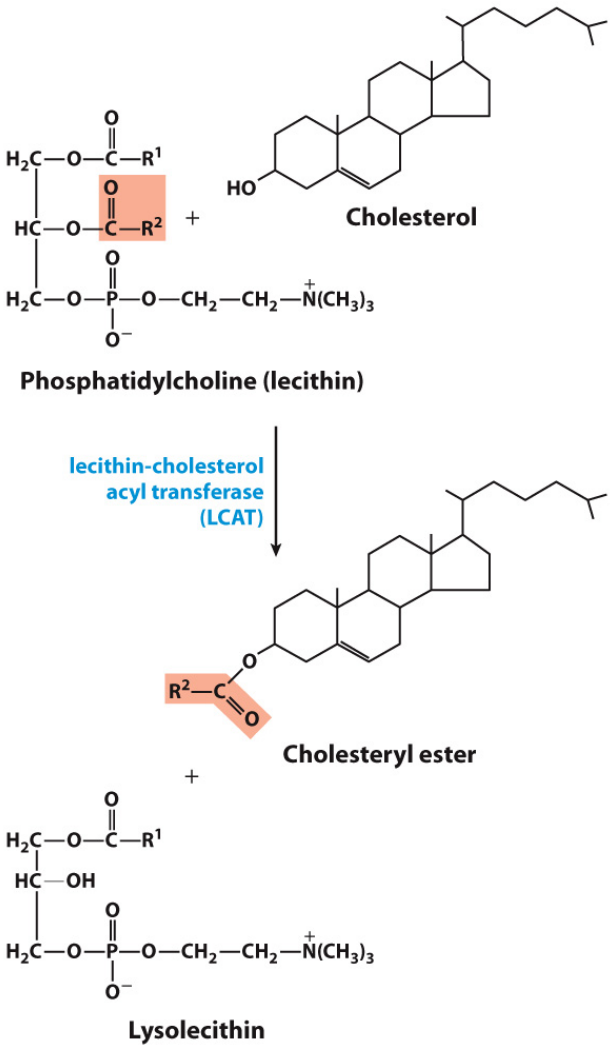

Figure 21-42
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Biological Roles of Lipoproteins in Trafficking Cholesterol and TAGs

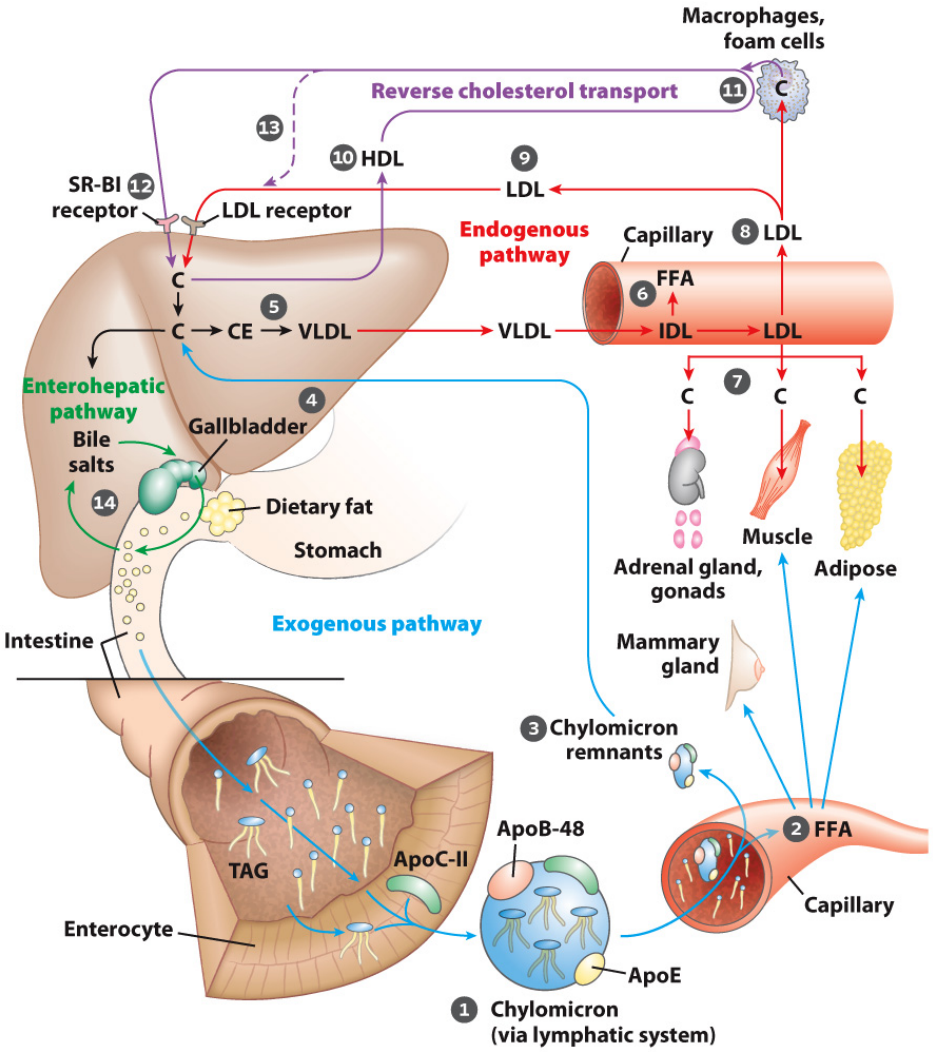

Figure 21-40
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Cholesterol Uptake by Receptor-Mediated Endocytosis

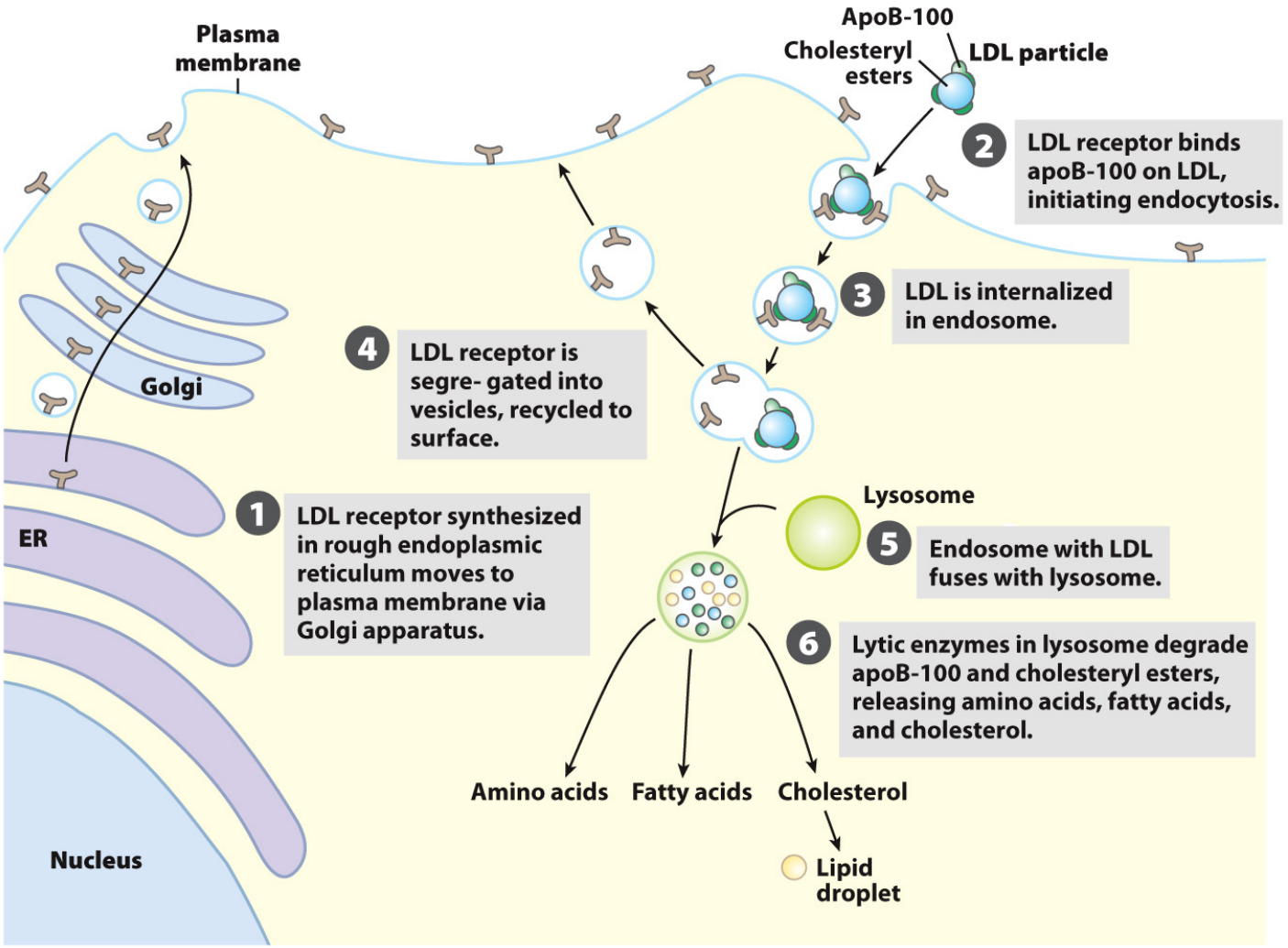

Figure 21-41
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Five Modes of Regulation of Cholesterol Synthesis and Transport

1. Covalent modification of HMG-CoA reductase
2. Transcriptional regulation of HMG-CoA gene
3. Proteolytic degradation of HMG-CoA reductase
4. Activation of ACAT, which increases esterification for storage
5. Transcriptional regulation of the LDL receptor

HMG-CoA Reductase Is Most Active When Dephosphorylated

1. AMP-dependent protein kinase
   - when AMP rises, kinase phosphorylates the enzyme → activity ↓, cholesterol synthesis ↓
2. Glucagon, epinephrine
   - cascades lead to phosphorylation, ↓ activity
3. Insulin
   - cascades lead to dephosphorylation, ↑ activity

Covalent modification provides short-term regulation.

Regulation of Cholesterol Metabolism

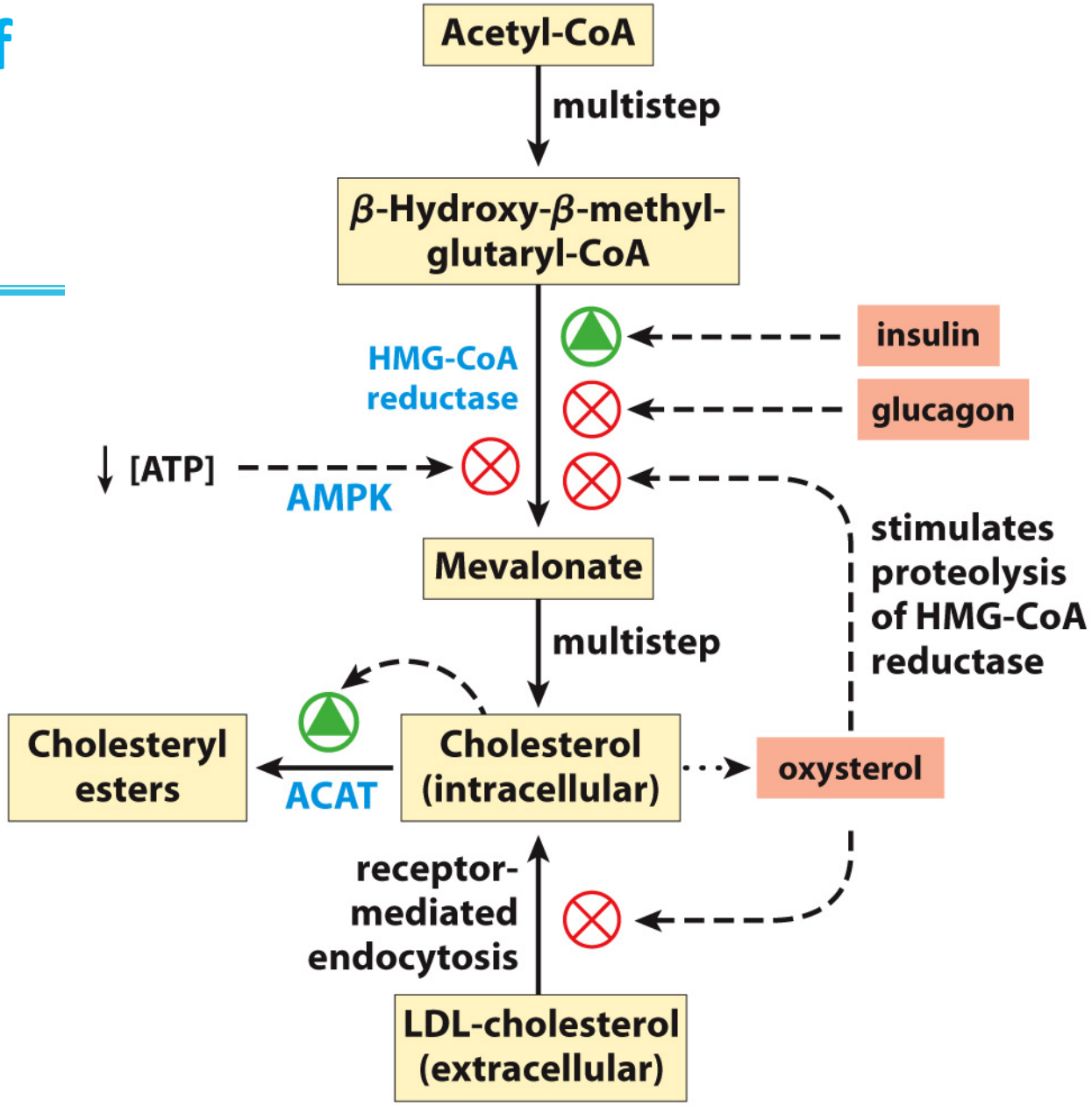

Figure 21-43
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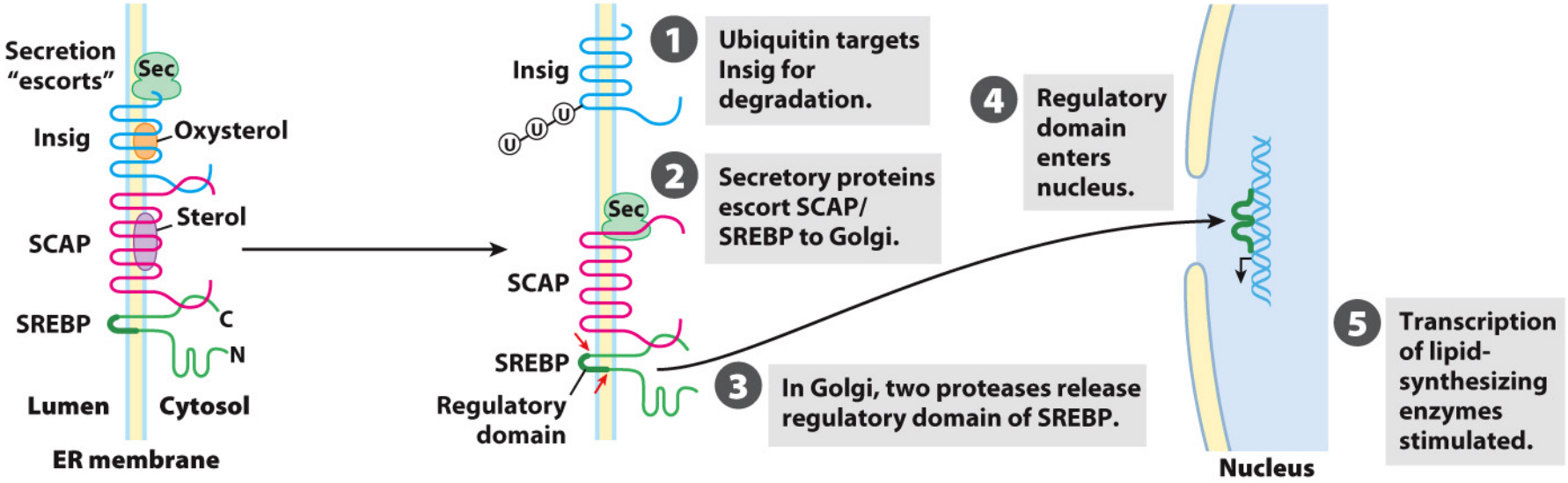
Longer-Term Regulation of HMG-CoA Reductase Through Transcriptional Control

- Sterol regulatory element-binding proteins (SREBPs)
  - When sterol levels are high, SREBPs are in the ER membrane with other proteins.
  - When sterol levels fall, the complex is cleaved and moves to the nucleus.
  - It activates transcription of HMG-CoA reductase and LDL receptor, as well as other genes.

Regulation of Cholesterol Synthesis by SREBP



(a) High [sterol] in ER SCAP/SREBP retained in ER, bound to Insig

(b) Low [sterol] in ER Regulatory domain of SREBP released by proteolysis

(c) Increased cholesterol synthesis in ER

Figure 21-44

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Regulation of HMG-CoA Reductase by Proteolytic Degradation

- Insig (***ins***ulin-***i***nduced ***g***ene ***p***rotein) senses cholesterol levels.
  - triggers ubiquination of HMG-CoA reductase
  - targets the enzyme for degradation by proteasomes

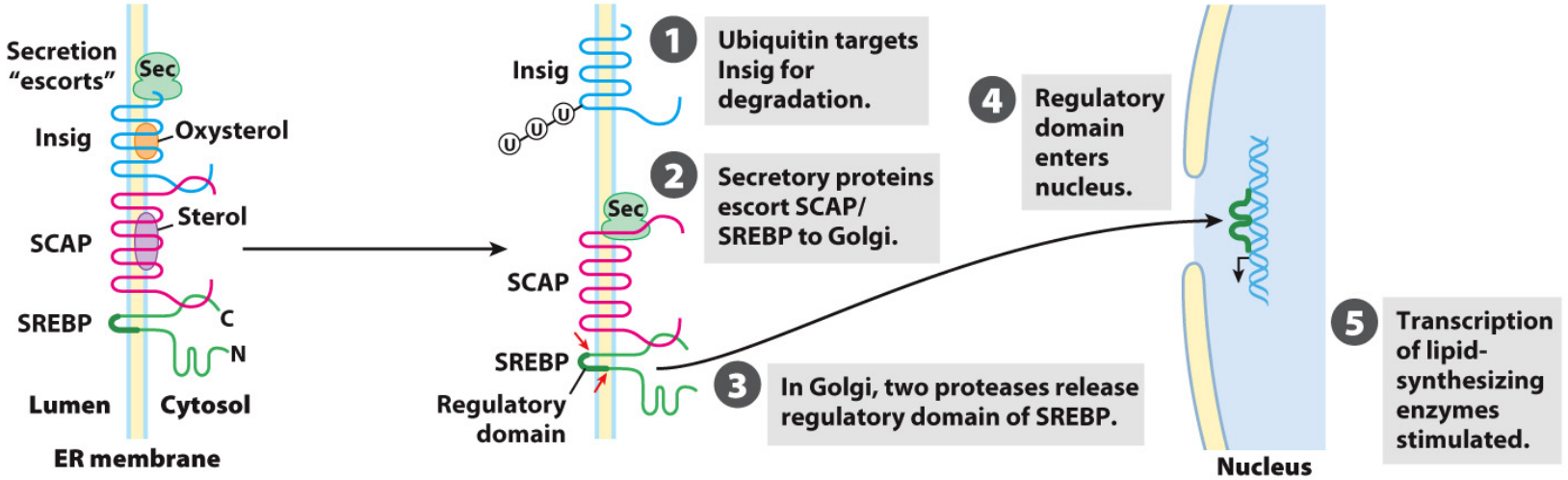

Figure 21-44
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Regulation by LXR-Mediated Transcription

- Liver X receptor (LXR) – a transcription factor activated by cholesterol
- Binds to retinoid X receptor (RXR)
- LXR-RXR dimer activates transcription of a host of genes.

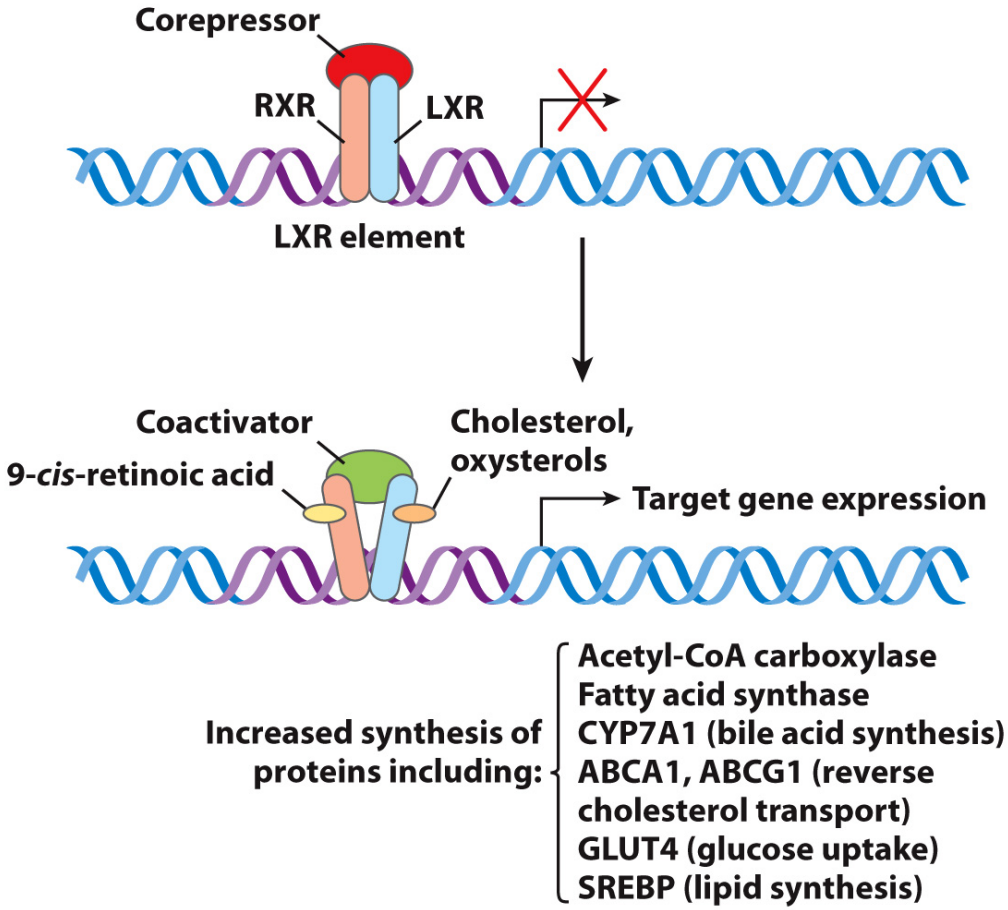

Figure 21-45
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The Genes Activated by LXR-RXR Are Largely for Cholesterol Transport

- Acetyl-CoA carboxylase
  - first enzyme in fatty acid synthesis
- Apoproteins (C1, C2, D, and E)
  - for cholesterol transport
- GLUT4
- ABC transporters
  - for reverse cholesterol transport

Cardiovascular Disease (CVD) Is Multifactorial

- **Very high LDL-cholesterol** levels tend to correlate with atherosclerosis.
  - although many heart attack victims have normal cholesterol, and many people with high cholesterol do not have heart attacks
- **Low HDL-cholesterol** levels are negatively associated with heart disease.

How Plaques Form

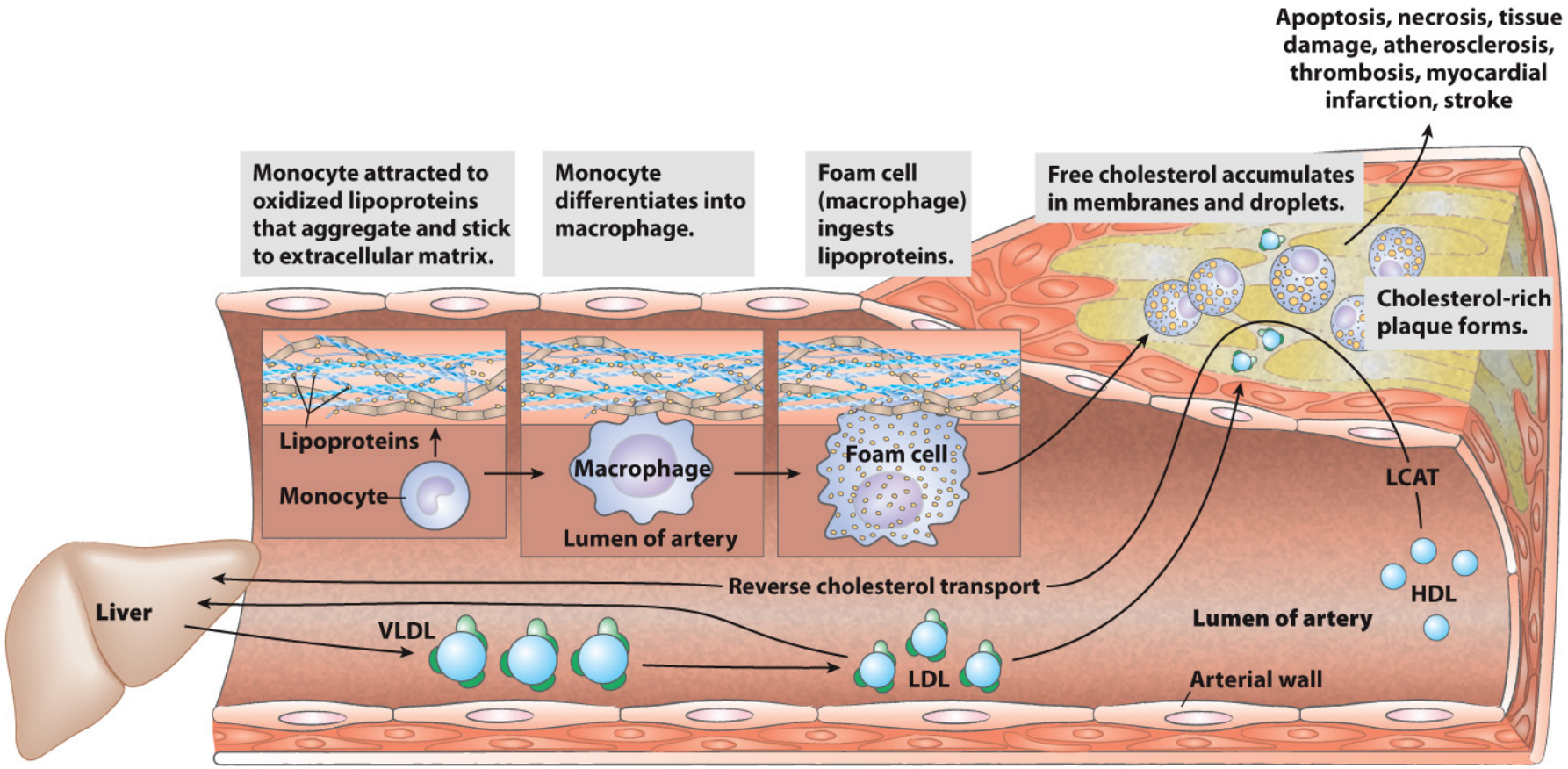

Figure 21-46
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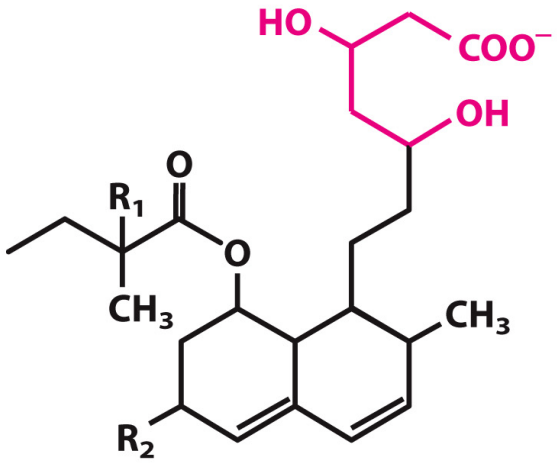
Familial Hypercholesterolemia

- Due to genetic mutation in LDL receptor
- Impairs receptor-mediated uptake of cholesterol from LDL
- Cholesterol accumulates in the blood and in foam cells.
- Regulation mechanisms based on cholesterol sensing inside the cell don’t work.
- Homozygous individuals can experience severe CVD as youths.

Statin Drugs Inhibit HMG-CoA Reductase to Lower Cholesterol Synthesis

- Statins resemble mevalonate → competitive inhibitors of HMG-CoA reductase
- First statin, lovastatin, found in fungi
  - lowers serum cholesterol by tens of percent
- Also reported to improve circulation, stabilize plaques by removing cholesterol from them, and reduce vascular inflammation



Reverse Cholesterol Transport by HDL Explains Why HDL Is Cardioprotective

- HDL picks up cholesterol from nonliver tissues, including foam cells at growing plaques.
- HDL carries cholesterol back to the liver.

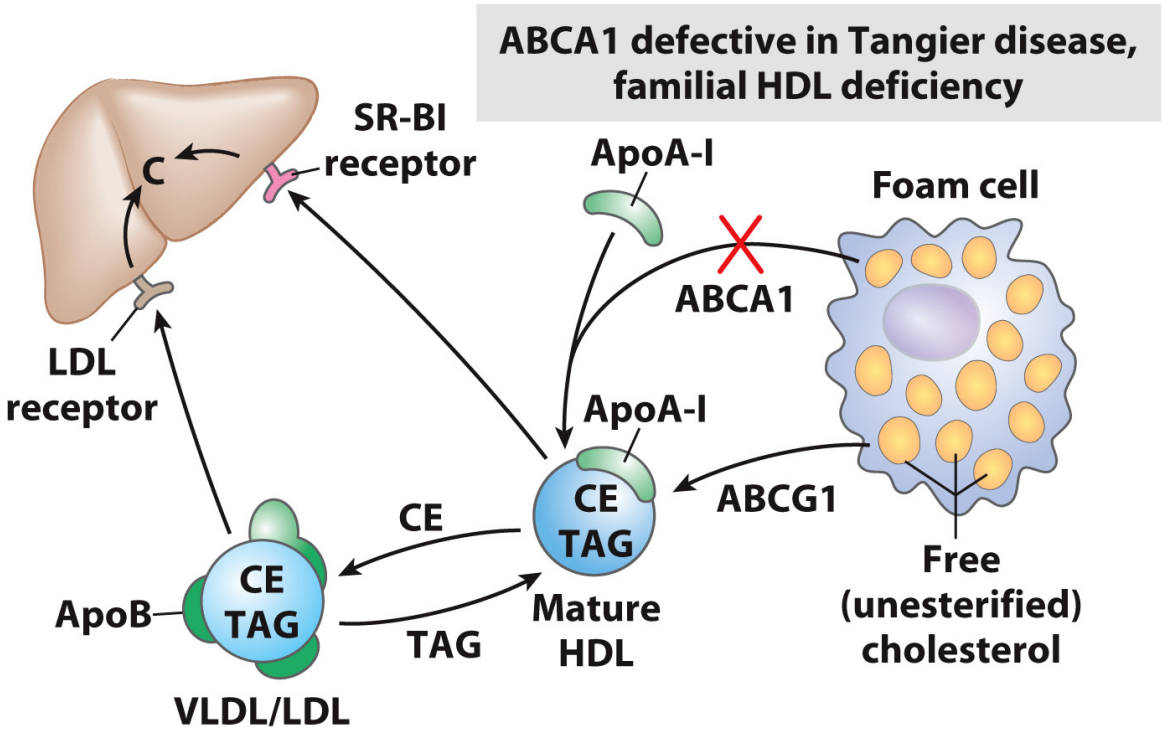


Figure 21-47
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There Are Several Classes of Cholesterol-Derived Steroids

- Adrenal gland-synthesized steroids:
  - mineralcorticoids
    - control electrolyte balance, reabsorption of Na^+, Cl^-, HCO_3^- from kidney
  - glucocorticoids
    - regulate gluconeogenesis, reduce inflammation
- Gonad-synthesized steroids:
  - progesterone, androgens, estrogems

Steroid Hormones Derived from Cholesterol

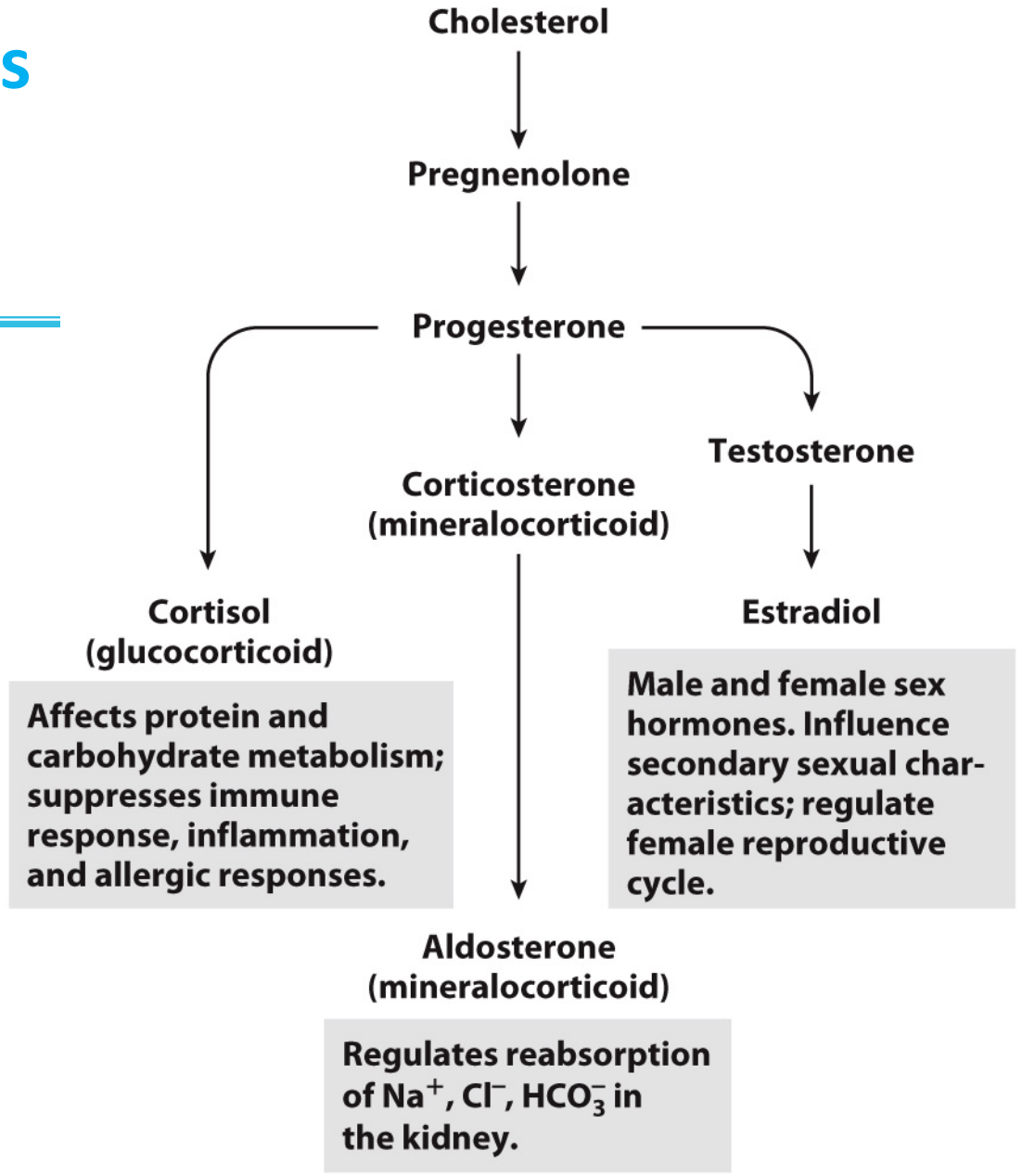

Figure 21-48
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Side-Chain Cleavage in Steroid Synthesis

- Takes place in mitochondria
- The “side chain” on C-17 of the D ring is modified or cleaved.
- Two adjacent carbons are hydroxylated.
- Uses mixed-function oxidases, NADPH and cytochrome P450

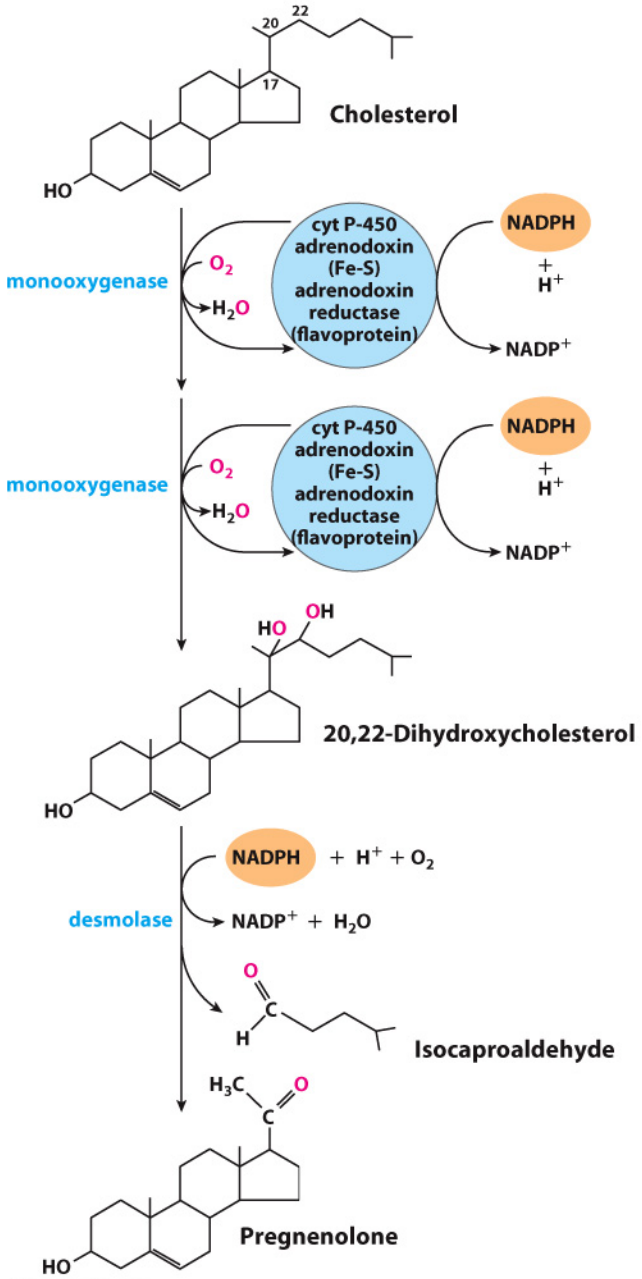

Figure 21-49

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Chapter 21 Summary

In this chapter, we learned that:

- synthesis of fatty acids is a multistep process starting from acetyl-CoA and its carboxylated product, malonyl-CoA
- phospholipids are a precursor to TAGs
- phospholipids and TAGs are built on a glycerol backbone that can be derived from dihydroxyacetone phosphate or glycerol
- head groups are attached using one of two methods, both of which use a CDP label
- pathways to the synthesis of specific head groups vary by organism and may use salvage pathways
- cholesterol is derived from the isoprene unit
- production of isoprene for cholesterol biosynthesis occurs via the mevalonate pathway and starts with multiple acetyl-CoA
- cholesterol can be metabolized and modified in a variety of ways
- cholesterol and TAGs are trafficked in lipoproteins that are classified by density
- incorrect trafficking of cholesterol and TAGs is correlated to multiple human diseases