Lehninger

SIXTH EDITION

Principles of Biochemistry

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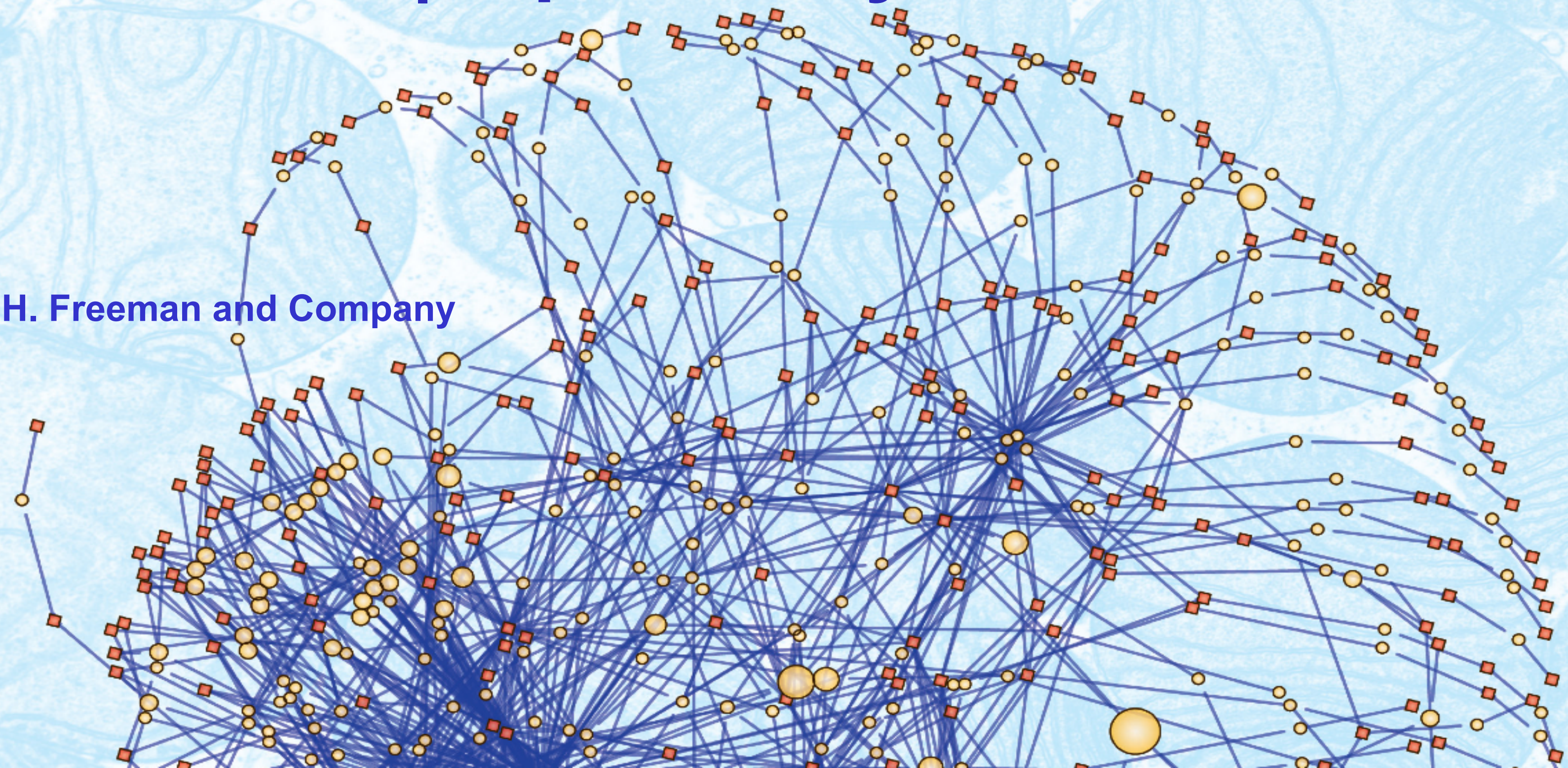
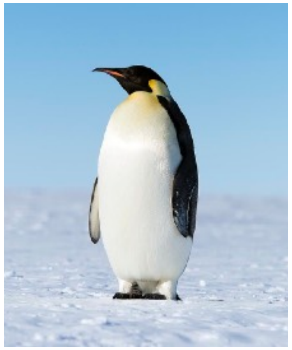
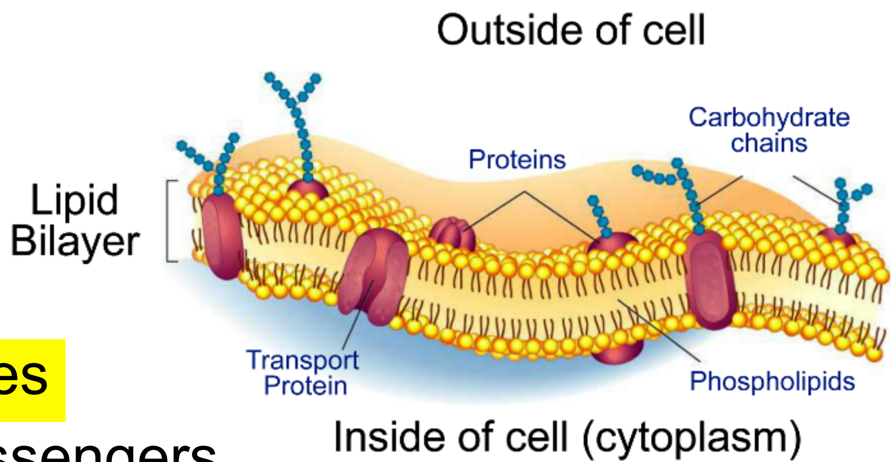
21| Lipid Biosynthesis

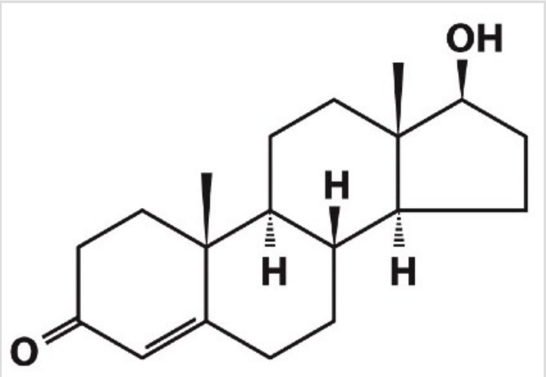


Biological Functions of Lipids

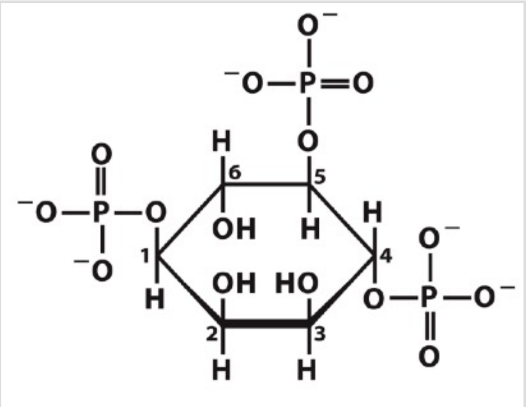
- Energy storage
- Pigments
- Cofactors
- Hormones
- Constituents of cellular membranes
- Extracellular and intracellular messengers







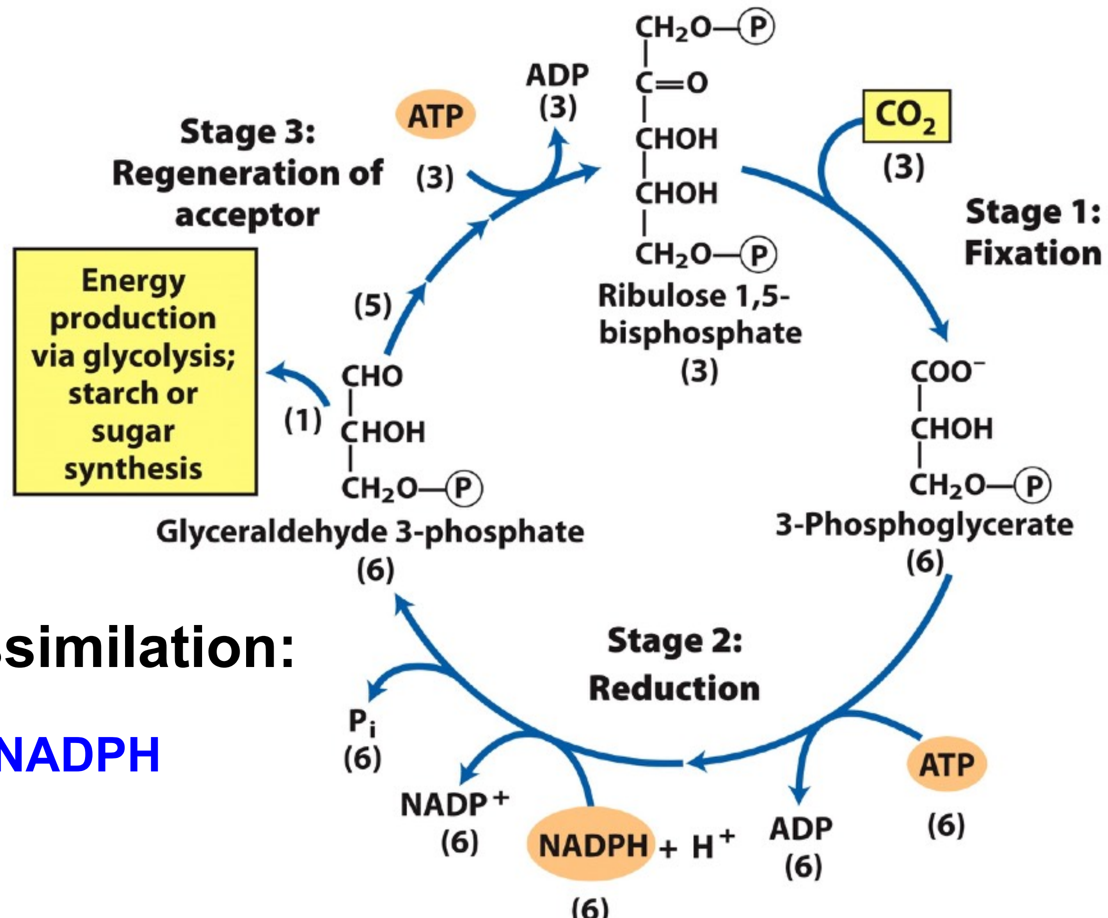
Testosterone



Inositol 1,4,5-trisphosphate (IP_3)

Biosynthesis is Endergonic and Reductive

- **ATP** as a source of metabolic energy.
- Reduced electron carrier as a reductant.
  - Usually **NADPH**.



Overall reaction of CO_2 assimilation:

$$3\ CO_2 + 9\ ATP + 6\ NADPH$$

$$\downarrow$$

$$\text{glyceraldehyde 3-phosphate} + 9\ ADP + 8\ P_i + 6\ NADP^+$$

Week 15 Lipid Biosynthesis

21.1 Biosynthesis of Fatty Acids and Eicosanoids

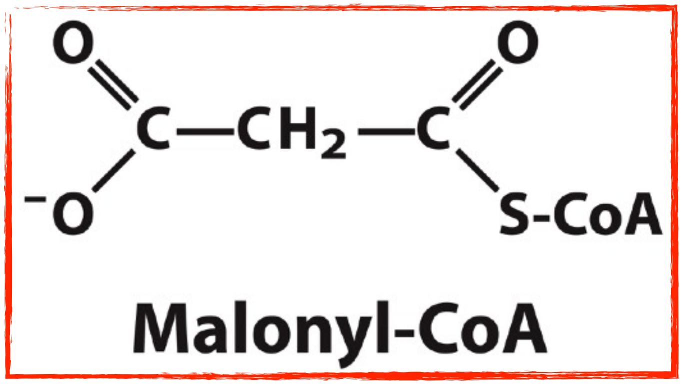
21.2 Biosynthesis of Triacylglycerols

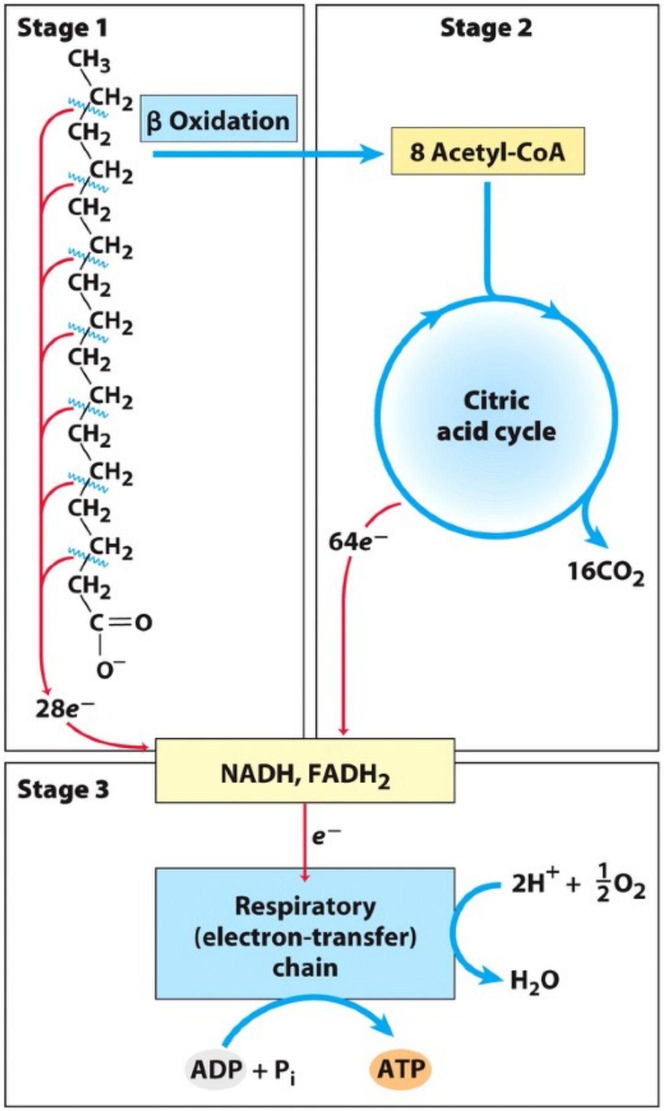
21.3 Biosynthesis of Membrane Phospholipids

21.4 Cholesterol, Steroids, and Isoprenoids

Catabolism and Anabolism Pathways

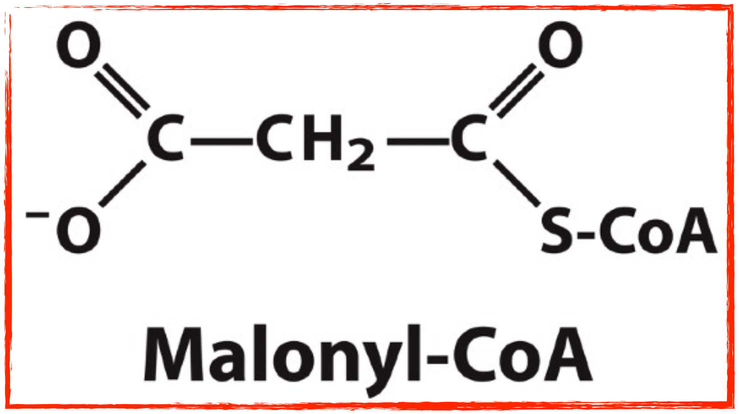
- Catabolism of fatty acids
  - Produces acetyl-CoA
  - Produces reducing power (NADH)
  - Takes place in **mitochondria** in animals, peroxisome in plants
- Anabolism of fatty acids
  - Requires acetyl-CoA and **malonyl-CoA**
  - Requires reducing power from **NADPH**
  - Takes place in **cytosol** in animals, chloroplast in plants

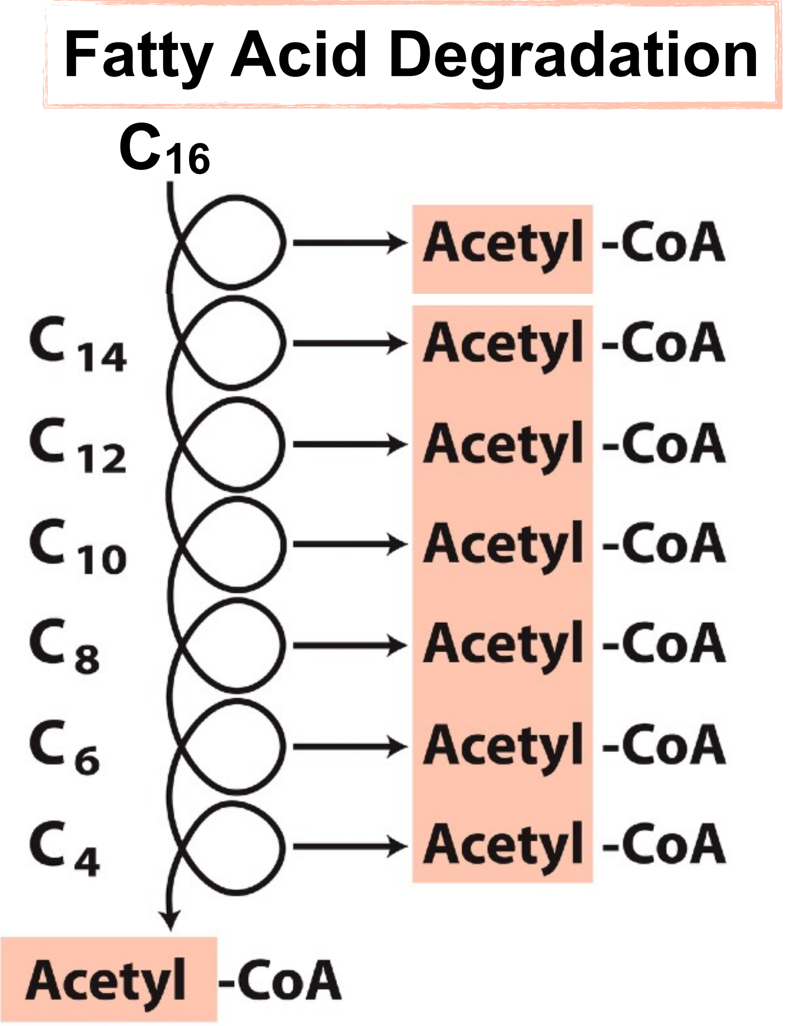




Overview of Fatty Acid Synthesis

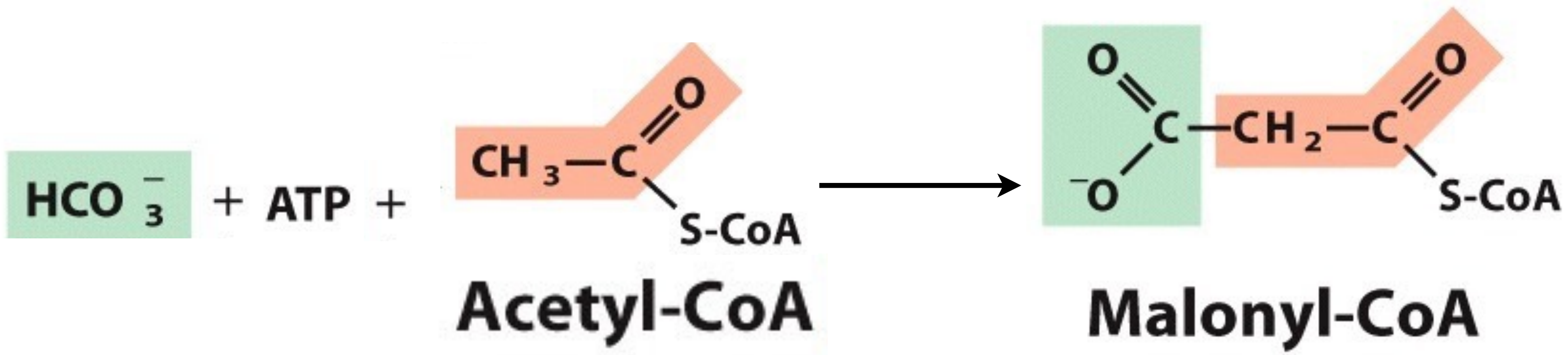
- Fatty acids are built in several passes, processing one **acetate unit** at a time
- Acetate comes from activated malonate in the form of **malonyl-CoA**
- Each pass involves **reduction** of a carbonyl carbon to a methylene carbon





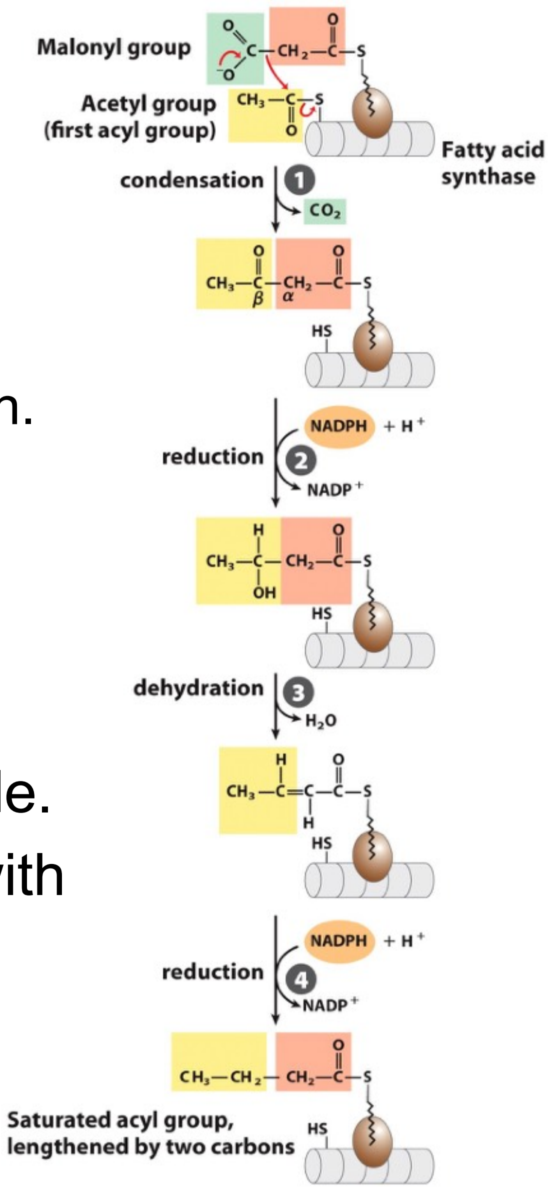
Malonyl-CoA from Acetyl-CoA + HCO_3^-

- Bicarbonate (HCO_3^-) is the source of CO_2.
- Catalyzed by acetyl-CoA carboxylase (ACC).
  - A single polypeptide in animal cells.
  - Three separate polypeptide subunits in bacterial cells.
  - Both types of acetyl-CoA carboxylase are present in plant cells.
- Consumes one ATP molecule per malonyl-CoA formed.

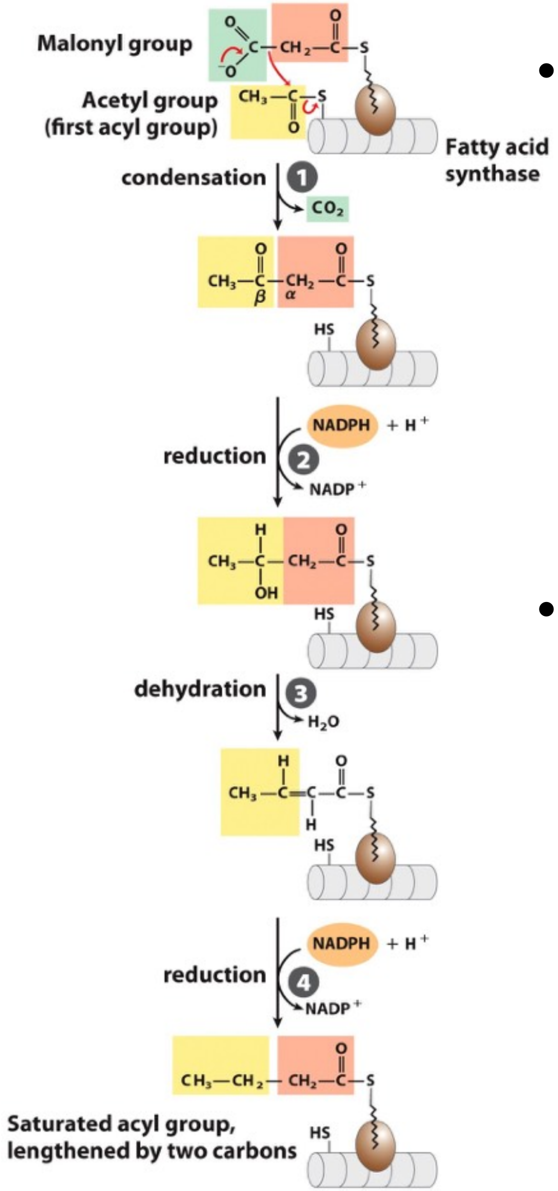


Fatty Acid Synthase (FAS)

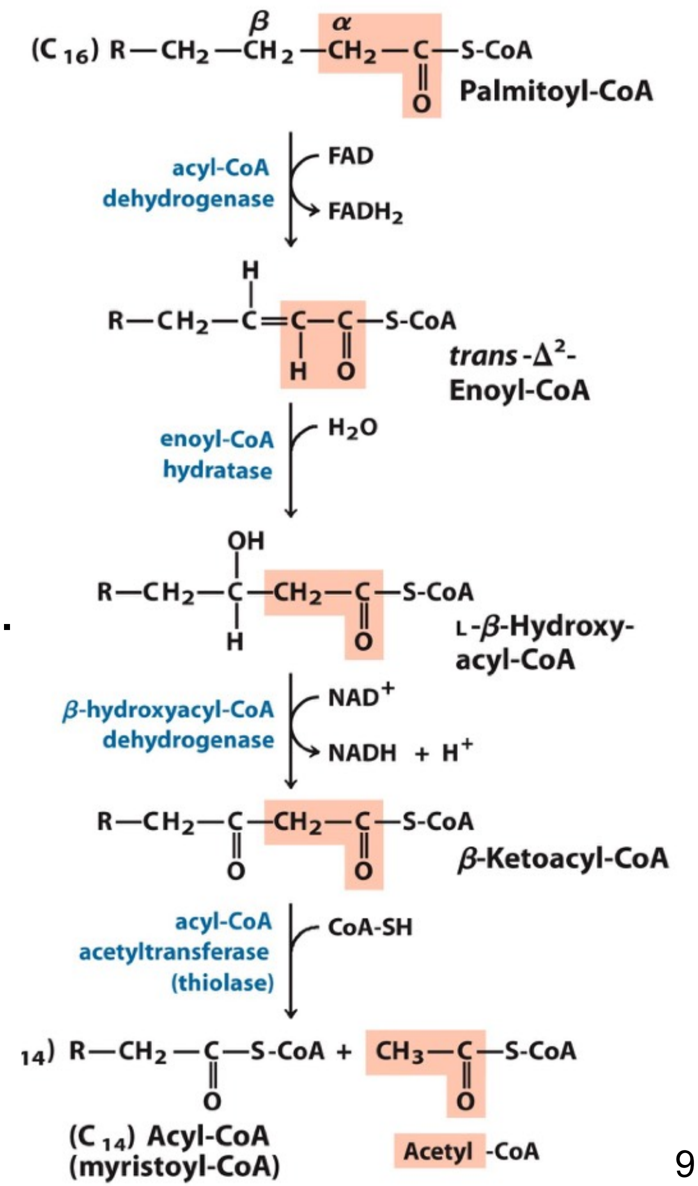
- Long carbon chain is assembled in a repeating four-step sequence.
  - Condensation. Reduction. Dehydration. Reduction.
  - β-oxidation of fatty acid also has four steps.
  - Dehydrogenation. Hydration. Dehydrogenation. Thiolysis.
- A saturated acyl group produced by each four-step sequence becomes substrate for next cycle.
- Fatty acyl chain is extended by **two carbons** with each passage through the cycle.



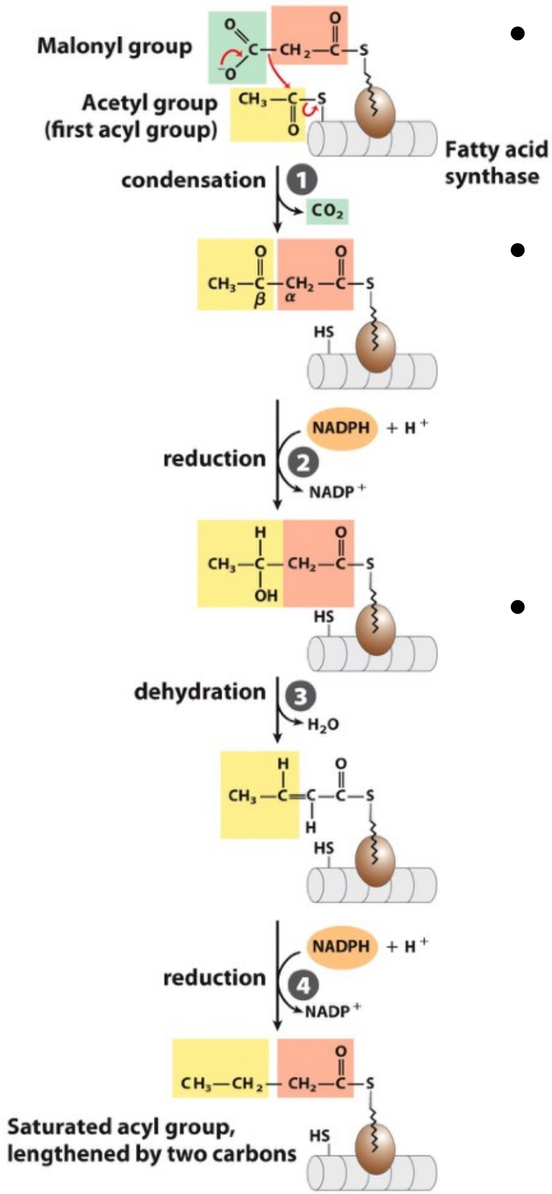
Fatty Acid Synthesis vs. Degradation



- Four-step synthesis.
  - Condensation.
    - Forms C-C bond.
  - Reduction.
    - Consumes **NADPH**.
  - Dehydration.
    - Loses H_2O.
  - Reduction.
    - Consumes **NADPH**.
- Four-step degradation.
  - Dehydrogenation.
    - Produces **$FADH_2$**.
  - Hydration.
    - Adds H_2O.
  - Dehydrogenation.
    - Produces **NADH**.
  - Thiolysis.
    - Breaks C-C bond.



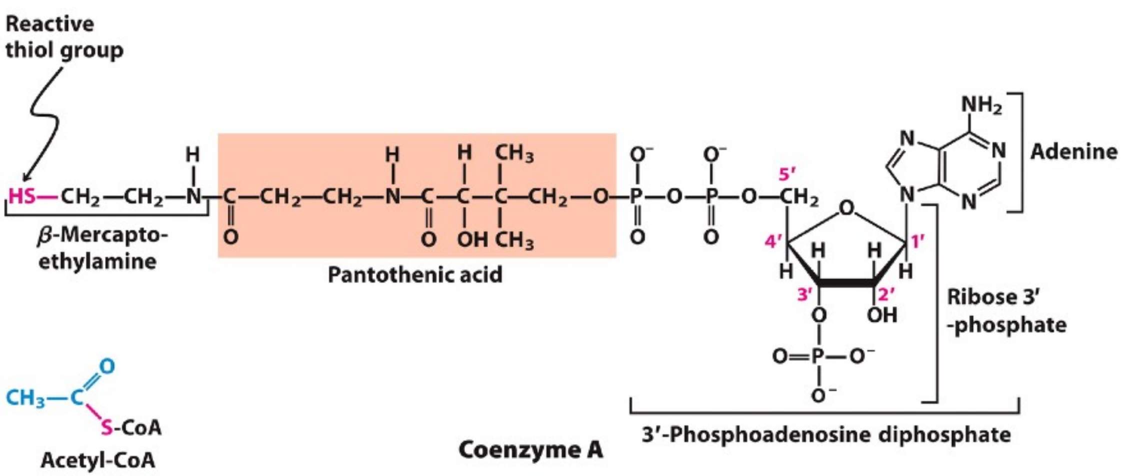
Fatty Acid Synthesis

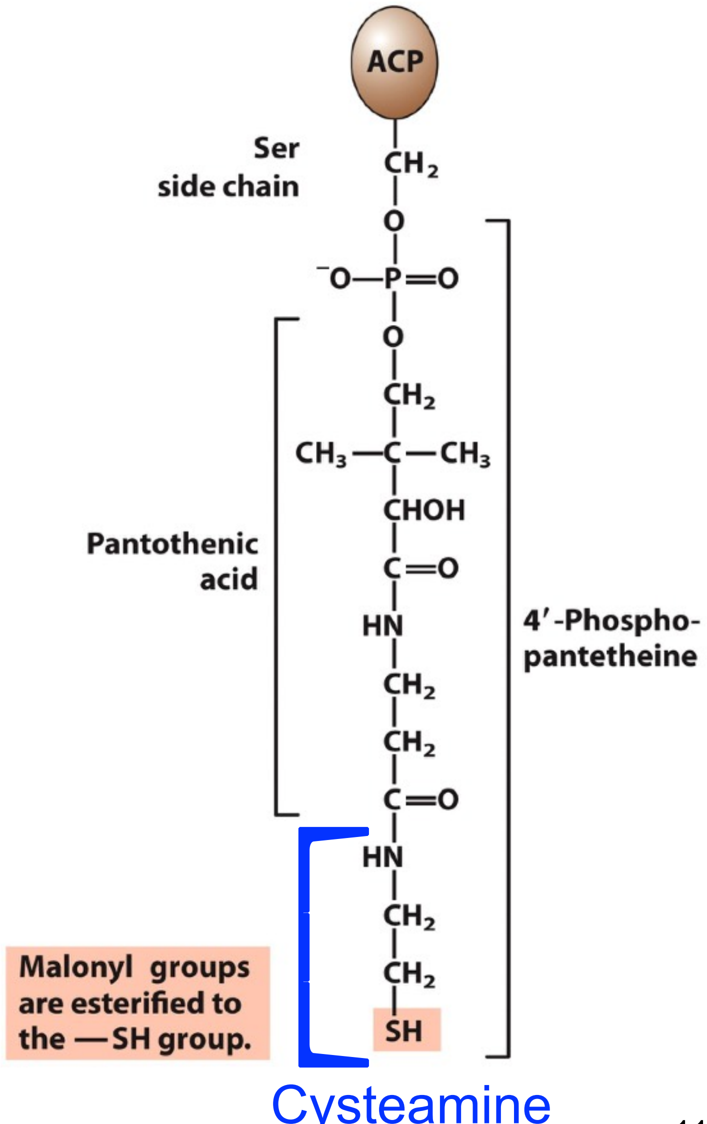


- Overall goal of one cycle
  - **Attach** two-carbon acetate unit from malonyl-CoA to a growing chain and then **reduce** it
- Involves four enzyme-catalyzed steps
  - Condensation of growing chain with activated acetate
  - Reduction of carbonyl oxygen to hydroxyl group
  - Dehydration of alcohol to alkene
  - Reduction of alkene to alkane
- **Acyl carrier protein (ACP)** is the shuttle
  - Growing chain is initially attached to fatty acid synthase enzyme (Cys residue)
  - During condensation, growing chain is transferred to acyl carrier protein (ACP)
  - After 2nd reduction (step 4), elongated chain is transferred back to fatty acid synthase (Cys residue)

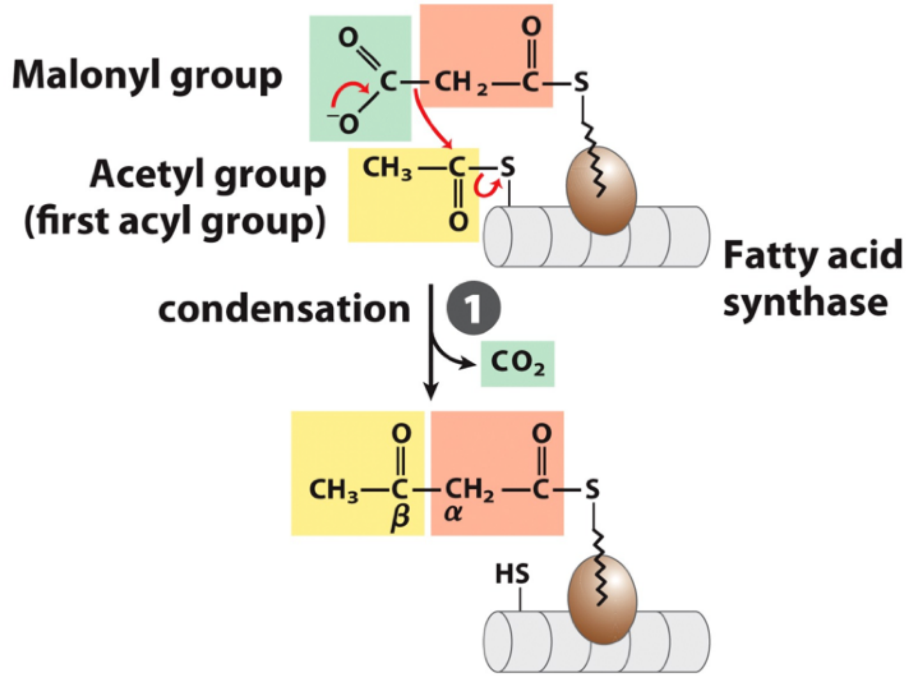
Acyl Carrier Protein (ACP)

- Contains a prosthetic group
  - 4’-phosphopantetheine
  - Has a thiol group
  - Carries and transfers fatty acyl chain
- Structure of prosthetic group
  - Attached to protein via Ser -OH group
  - Phosphodiester bond and amide bond
  - Compare with coenzyme A





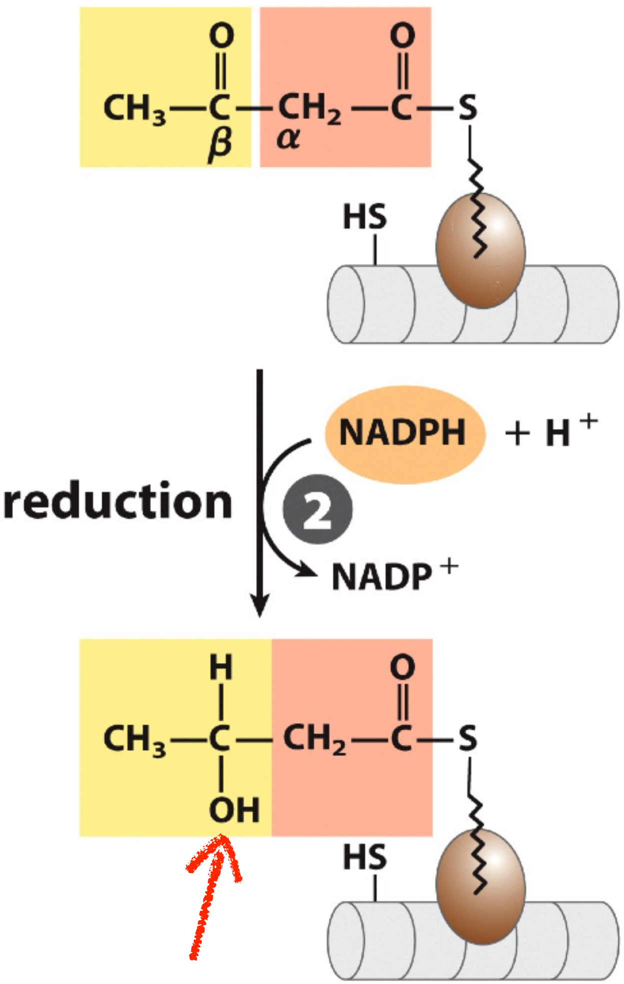
Fatty Acid Synthesis Step 1. Condensation



- Preparation
  - Acetyl group and malonyl group bind via **thioester** bond
- Condensation reaction attaches two carbons from malonyl group to acetyl group
  - Decarboxylation releases CO_2 from malonyl group
  - Condensation creates β-keto intermediate (acetoacetyl-ACP)

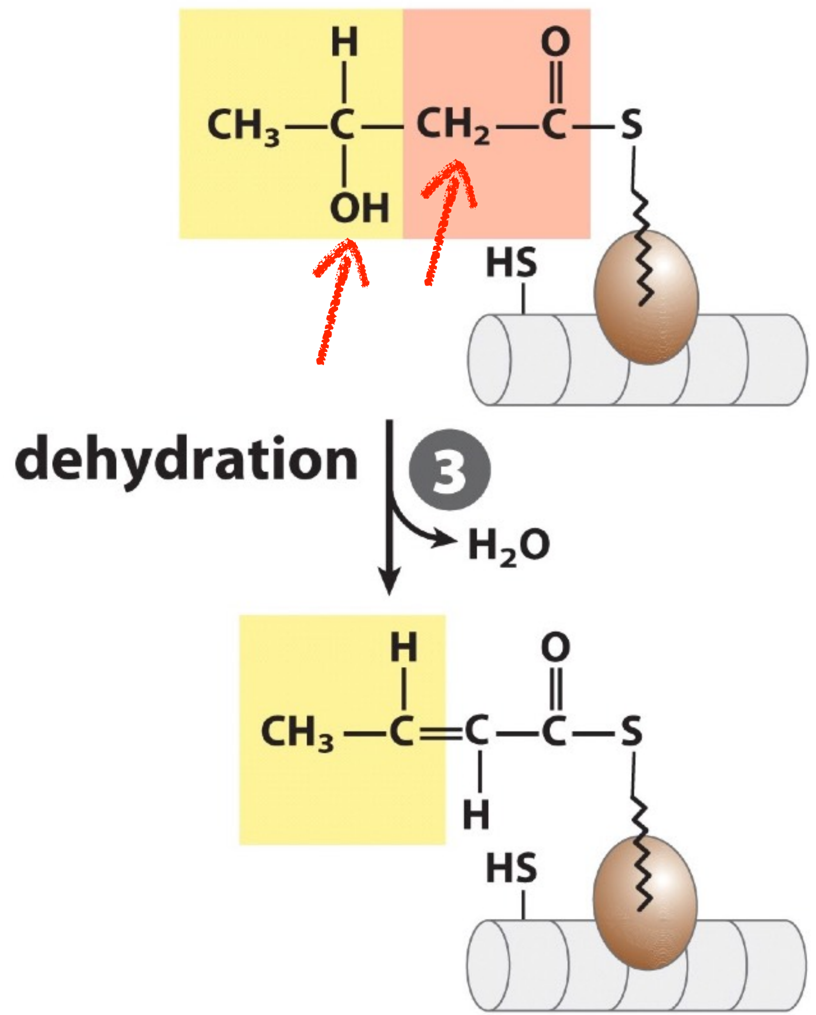
Fatty Acid Synthesis Step 2. Reduction

- This and next two steps are almost identical to β oxidation reactions, but in reverse direction
  - Reduction (2) vs. dehydrogenation (3)
  - Dehydration (3) vs hydration (2)
  - Reduction (4) vs. dehydrogenation (1)
- 1st reduction
  - NADPH reduces β-keto intermediate to an alcohol



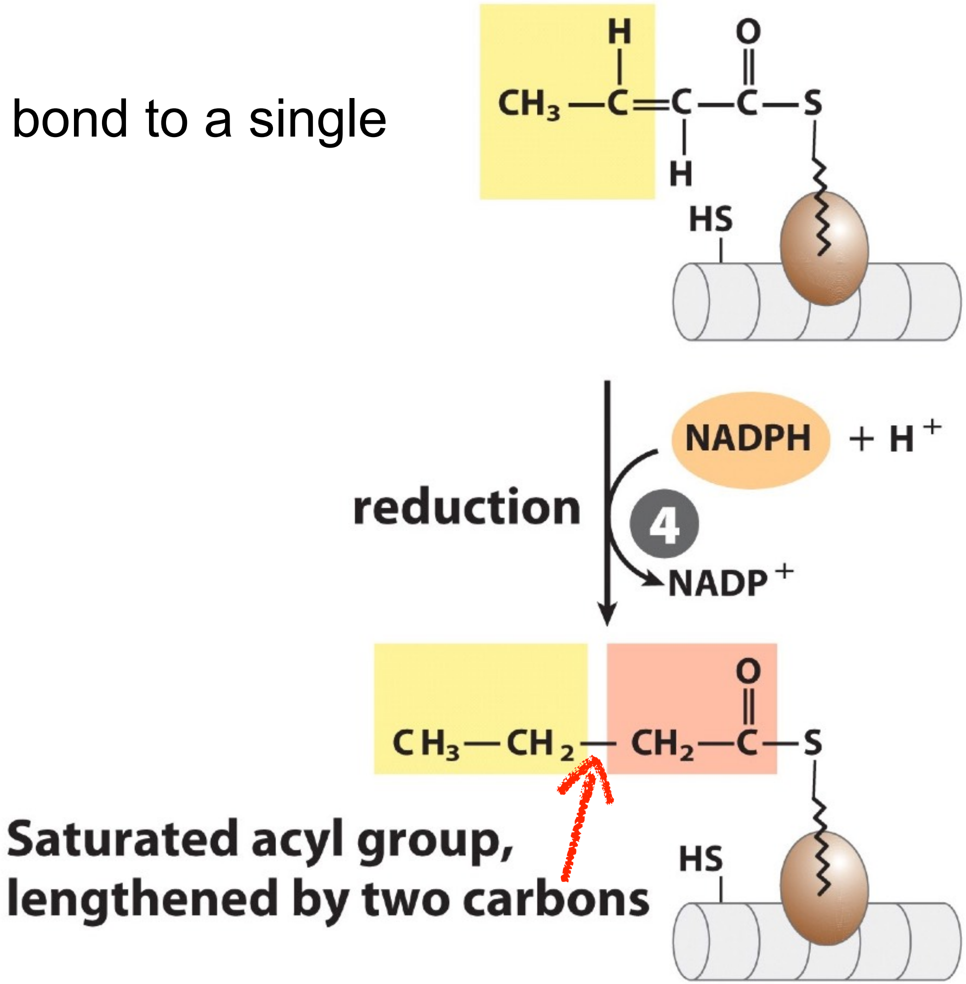
Fatty Acid Synthesis Step 3. Dehydration

- Dehydration
  - OH group from C-3
  - H from C-2 are eliminated
  - Creates a double bond (trans-alkene)



Fatty Acid Synthesis Step 4. Reduction

- 2^{nd} reduction
  - NADPH reduces double bond to a single bond (saturated alkane)

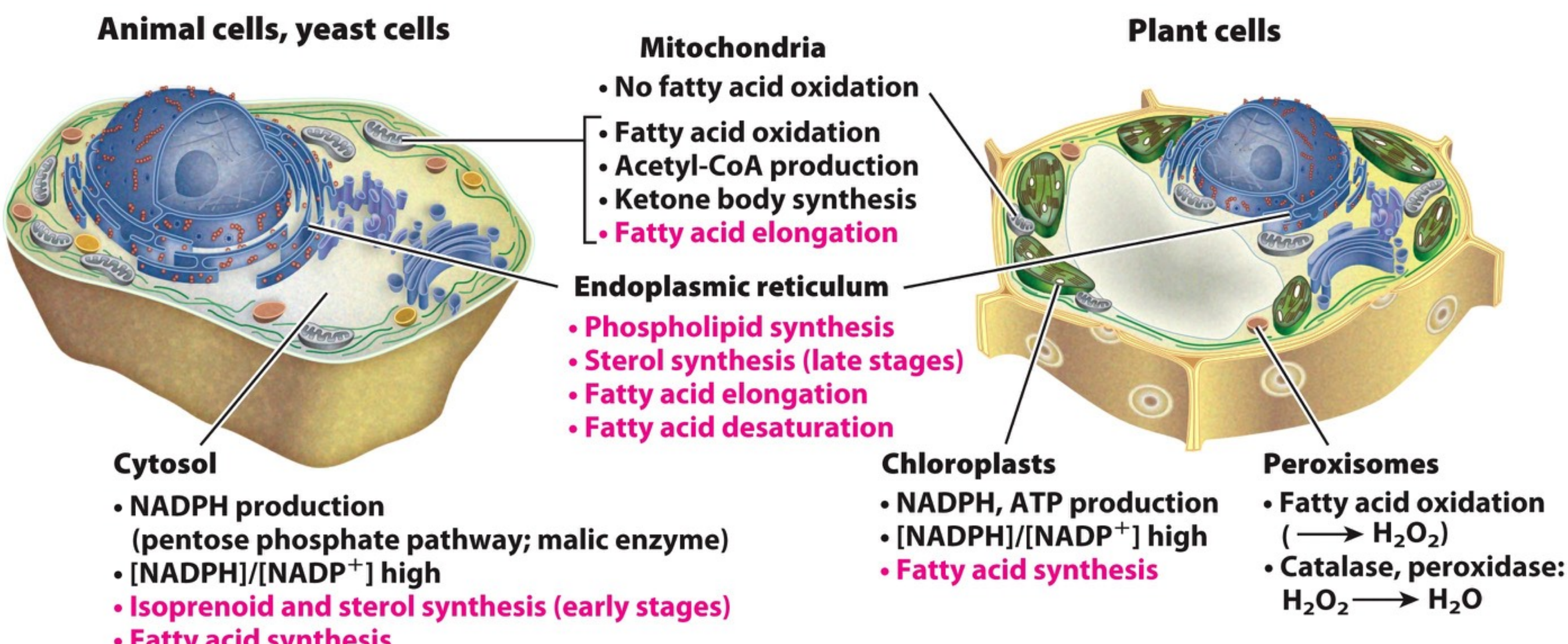


Overall Palmitate Synthesis

- **Seven** cycles of condensation and reduction are required to produce saturated palmitate (16:0)
- First part is formation of seven malonyl-CoA molecules
  - 7 Acetyl-CoA + 7 CO_2 + 7 ATP -> 7 malonyl-CoA + 7 ADP + 7 P_i
  - Energy cost is one ATP per two-carbon unit
- Second part is seven cycles of condensation and reduction
  - Acetyl-CoA + 7 malonyl-CoA + 14 NADPH -> palmitate + 7 CO_2 + 14 $NADP^+$
- **Overall process**
  - 8 Acetyl-CoA + 7 ATP + 14 NADPH -> palmitate + 7 ADP + 7 P_i + 14 $NADP^+$

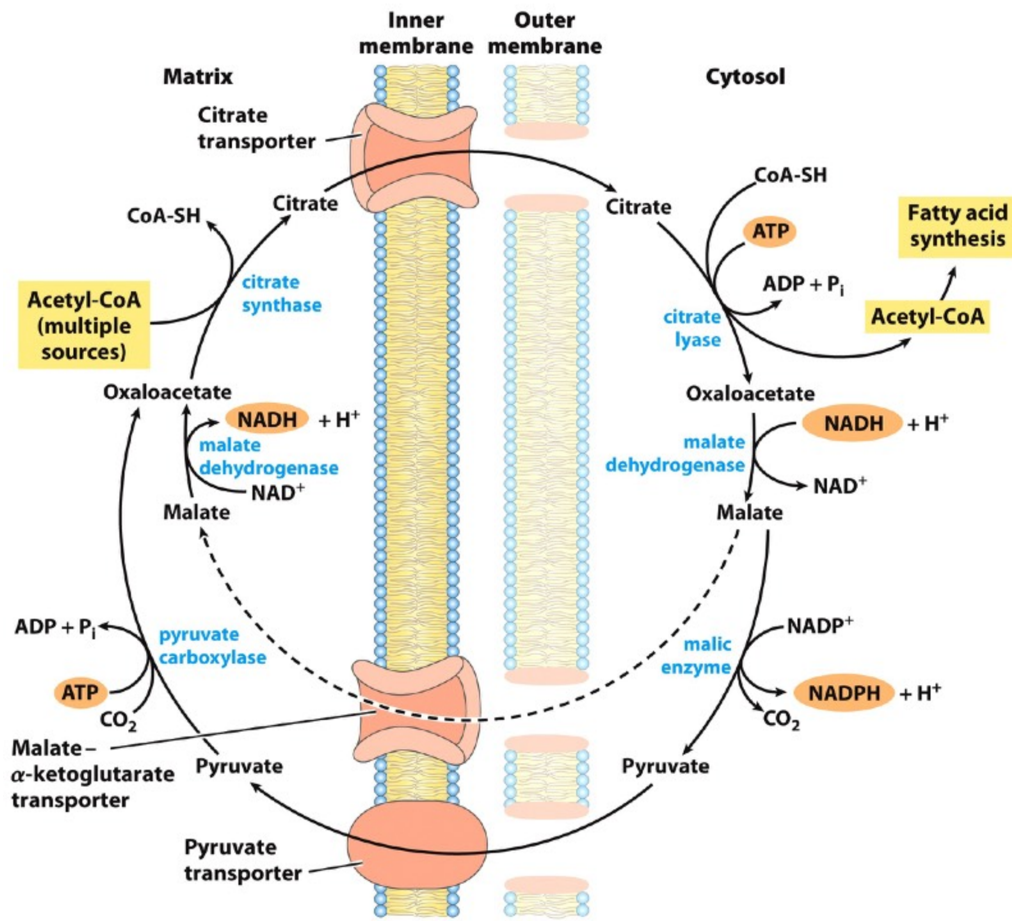
Cellular location of Fatty Acid Metabolism

- Fatty acid metabolism in animal cells
  - Synthesis occurs in cytosol, where [NADPH]/[NADP$^+$] ratio is high
  - Oxidation occurs in mitochondria
- In plant cells, synthesis in chloroplast and oxidation in peroxisome



Extra Energy Cost of Acetyl-CoA Transport

- In animal cells, acetyl-CoA is produced in mitochondria. But fatty acid synthesis occurs in cytosol. **Transport consumes two ATPs**
- Acetyl-CoA is shuttled out of mitochondria as **citrate**
  - Citrate synthase (1st step in CAC)
  - **Citrate transporter**
- Acetyl-CoA is regenerated in cytosol
  - Citrate lyase
  - **Consumes ATP**
- Oxaloacetate -> malate -> pyruvate -> oxaloacetate
  - **Another ATP consumed**
  - Pyruvate transporter



Three ATP molecules per two-carbon unit

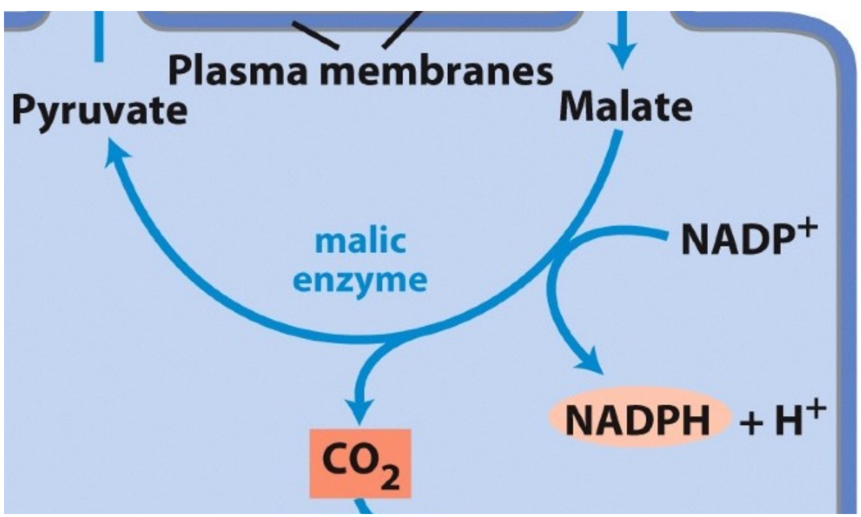
Reducing Power: NADPH and NADH

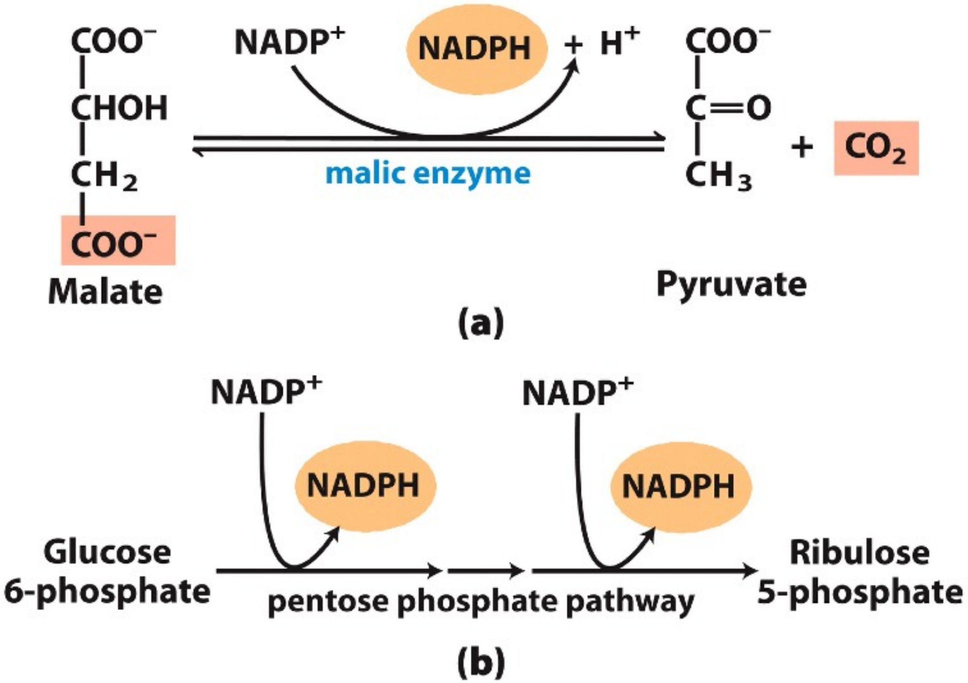
- Usually NADPH is electron donor in **anabolic reactions**
  - $3\ CO_2$ + 9 ATP + 6 **NADPH** -> glyceraldehyde 3-P + 9 ADP + 6 $NADP^+$
  - 8 Acetyl-CoA + 7 ATP + 14 **NADPH** -> palmitate + 7 ADP + 14 $NADP^+$
- NAD^+ is electron acceptor in catabolic reactions
  - Glucose + 2 ADP + 2 NAD^+ -> 2 pyruvate + 2 ATP + 2 NADH
  - Pyruvate + Co-A + NAD^+ -> acetyl-CoA + CO_2 + NADH
  - Acetyl-CoA + 3 NAD^+ + FAD + GDP -> 2 CO_2 + CoA + 3 NADH + $FADH_2$ + GTP
  - Palmitoyl-CoA + 7 NAD^+ + 7 FAD-> 8 acetyl-CoA + 7 NADH + 7 $FADH_2$

Cytosol	Glycolysis Fatty acid synthesis	[NADH]/[NAD^+] ratio low [NADPH]/[$NADP^+$] ratio high
Mitochondria	Pyruvate -> CO_2 Citric acid cycle Fatty acid oxidation	[NADH]/[NAD^+] ratio high

Pathways for NADPH Production

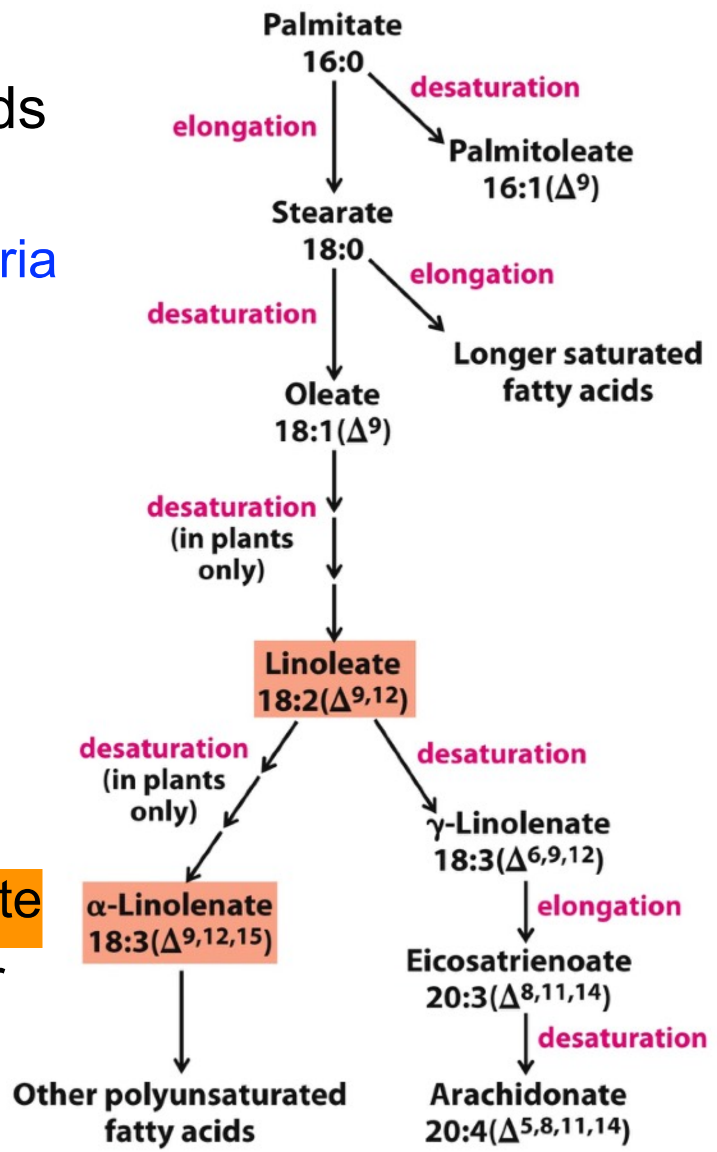
- Cytosolic NADPH is largely generated by malic enzyme and pentose phosphate pathway
  - Malic enzyme: similar reaction in carbon assimilation pathway of C_4 plants
  - PPP: Glucose 6-P + 2 $NADP^+$ -> ribose 5-P + CO_2 + 2 NADPH





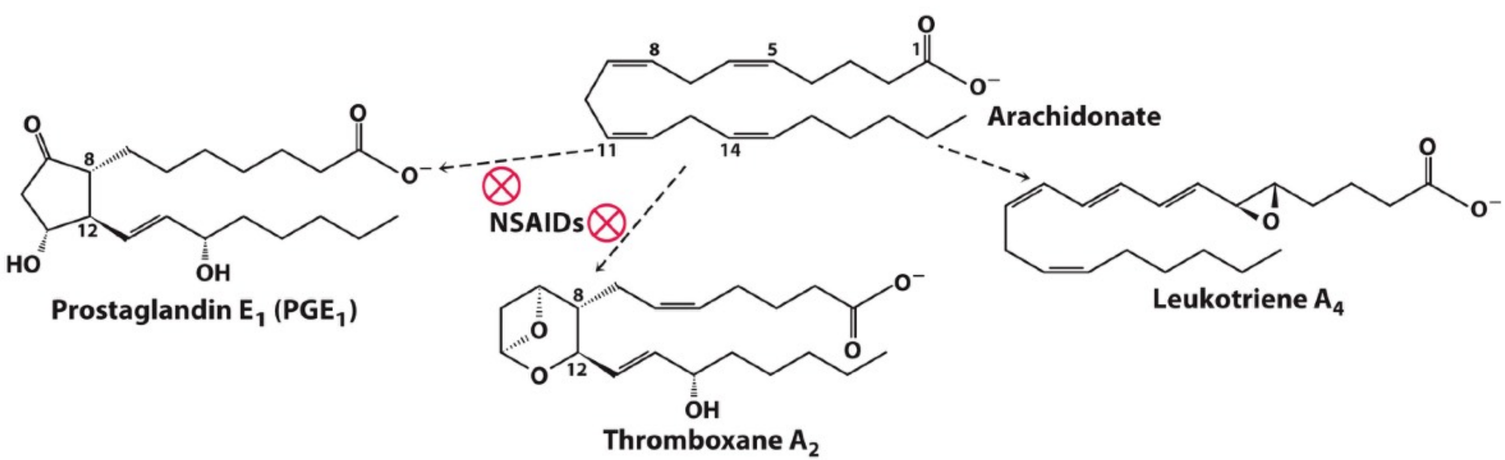
Long-Chain and Desaturated Fatty Acids

- Palmitate may be lengthened to form stearate (18:0) or even longer fatty acids
  - Fatty acid elongation system in endoplasmic reticulum and in mitochondria
  - Each step adds a two-carbon unit
- Palmitate and stearate may be desaturated to form palmitoleate, 16:1(Δ^9) and oleate, 18:1(Δ^9)
  - Catalyzed by fatty acyl-CoA desaturase
- Mammals cannot introduce double bonds between C-10 and methyl end
  - Both linoleate 18:2 ($\Delta^{9,12}$) and α-linolenate 18:3 ($\Delta^{9,12,15}$) are essential fatty acids for mammals



Three Classes of Eicosanoids

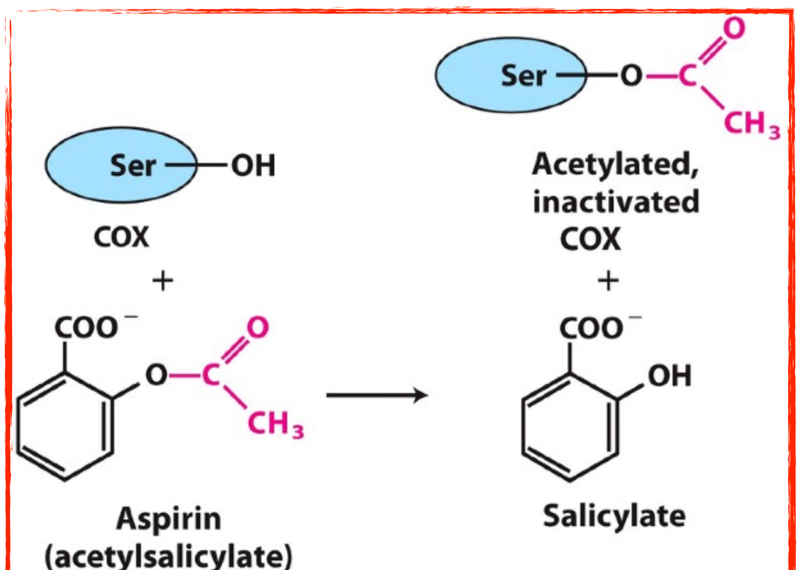
- Prostaglandins contain a five-carbon ring
  - Elevate body **temperature** and cause inflammation and **pain**
- Thromboxanes have a six-membered ring containing an ether
  - Act in formation of blood clots
- Leukotrienes contain three conjugated double bonds
  - Overproduction causes asthmatic attacks

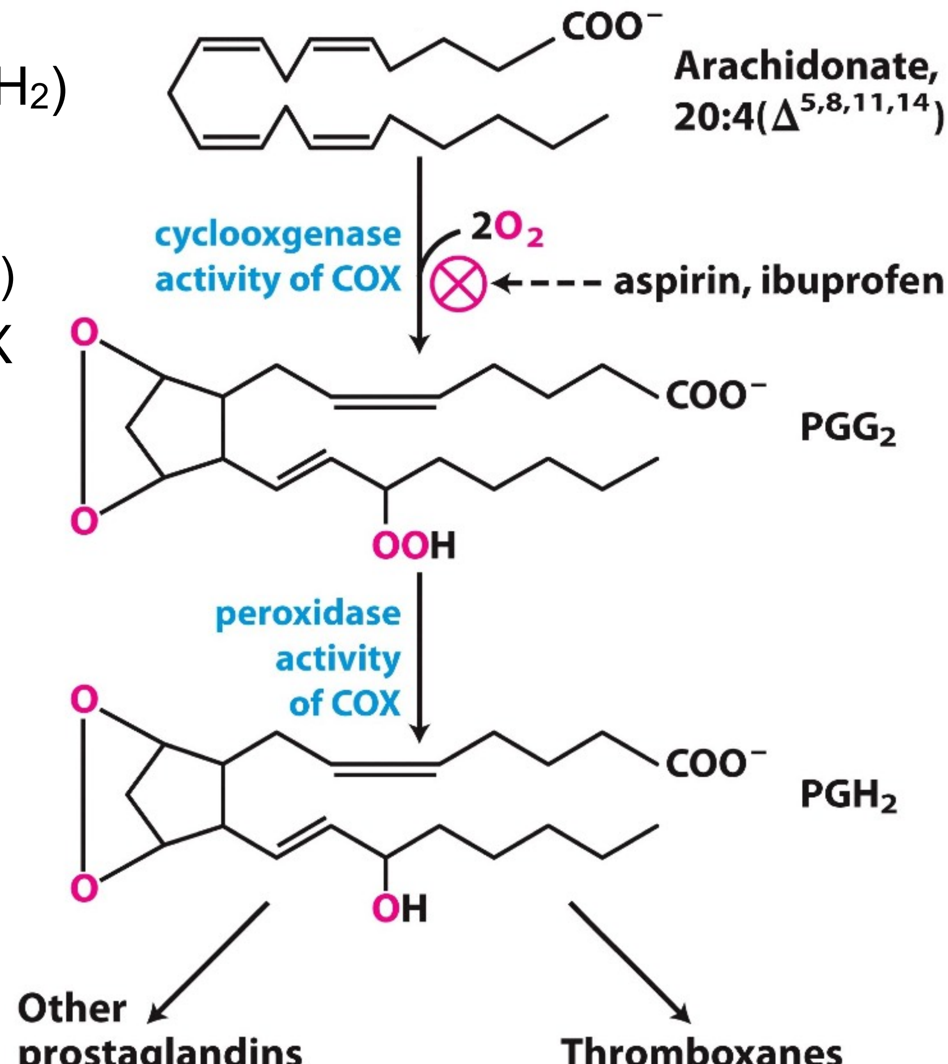


Nonsteroidal anti-inflammatory drugs (NSAIDs) such as **aspirin** and **ibuprofen** inhibit an enzyme involved in the conversion of arachidonate to prostaglandin and thromboxane

Aspirin and Ibuprofen

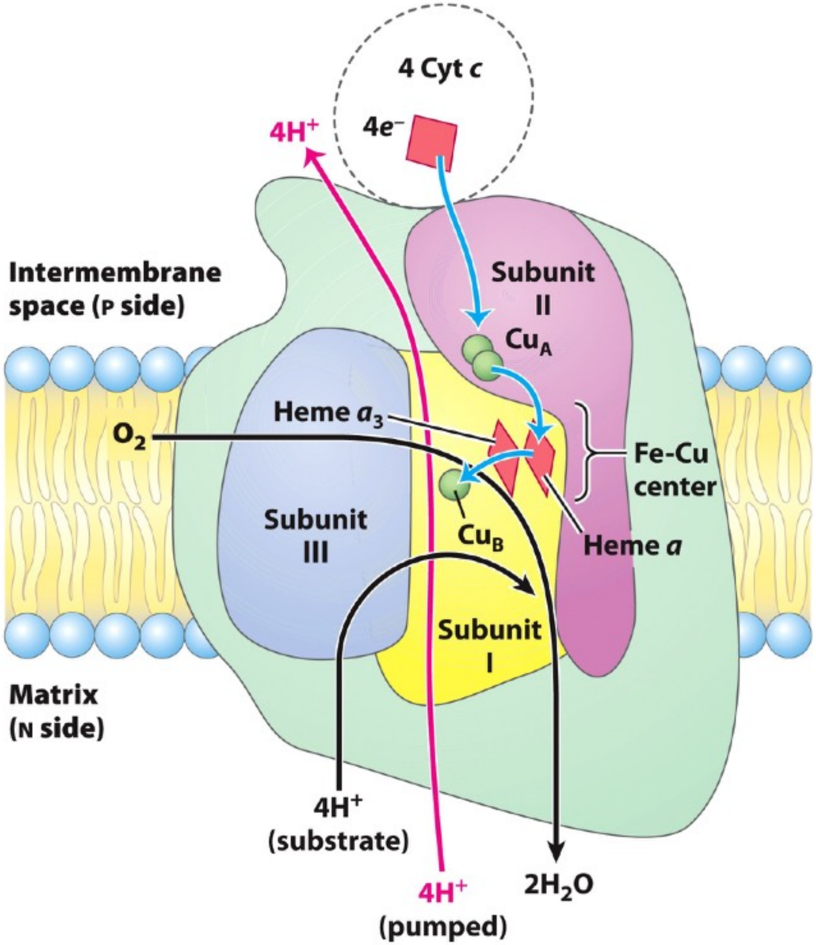
- Arachidonate 20:4($\Delta^{5,8,11,14}$) is converted to prostaglandin H_2 (PGH_2)
  - PGH_2 is precursor of many other prostaglandins and thromboxanes
  - Catalyzed by cyclooxygenase (COX)
- Aspirin irreversibly inactivates COX
  - Acetylates active-site Ser residue
- Ibuprofen is a competitive inhibitor





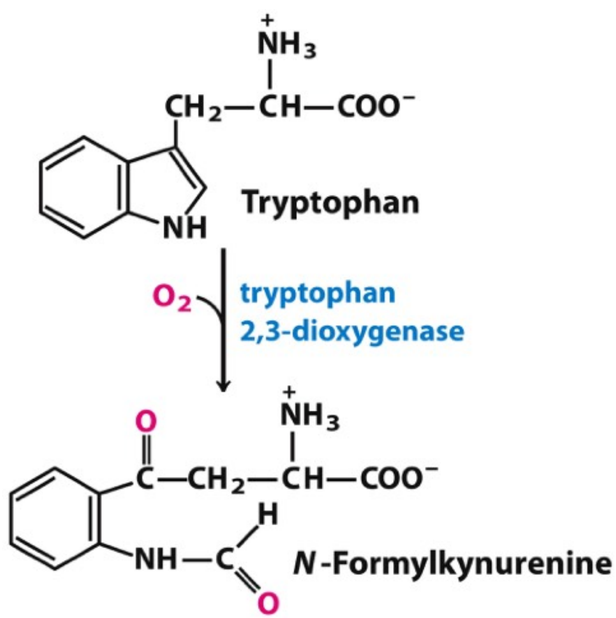
Oxidase vs. Oxygenase

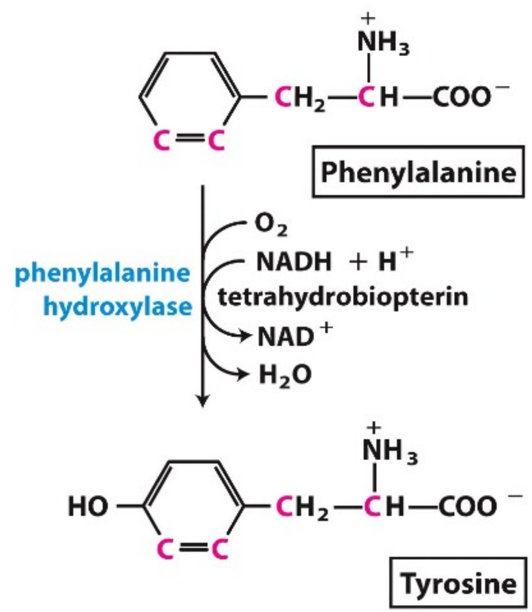
- Oxidase: O_2 is electron acceptor, but O atom not in oxidized product
  - Cytochrome oxidase (complex IV) of mitochondrial electron transfer chain
  - O_2 accepts four electrons and is reduced to H_2O
  - Cytochrome *c* is oxidized
- Oxygenase. O atoms are directly incorporated into product
  - Forms a new hydroxyl or carboxyl group, for example
  - Dioxygenase and monooxygenase



Oxygenase

- Oxygenase catalyzes oxidative reactions in which O atoms are directly incorporated into product
  - Dioxygenase. Both O atoms are incorporated into organic product
    - Tryptophan 2,3-dioxygenase catalyzes ring-opening in Trp catabolism
  - Monooxygenase. One O atom goes to organic product. The other to H_2O
    - $AH + BH_2 + O_2 \rightarrow A\text{-}OH + B + H_2O$. Both substrates (A and B) are oxidized
    - Also called hydroxylase, or mixed-function oxygenase
    - Phenylalanine hydroxylase catalyzes conversion of Phe to Tyr





Summary 21.1 Biosynthesis of Fatty Acids

- Long-chain saturated fatty acids are synthesized from acetyl-CoA by fatty acid synthase
  1. Malonyl-CoA is formed from acetyl-CoA and CO_2
  2. Malonyl-CoA condenses with an acetyl group, releasing CO_2
  3. Acetoacetyl group is reduced to β-hydroxy derivative
  4. Dehydration to form *trans*-Δ^2-unsaturated acyl group
  5. Reduction to butyryl group. NADPH is electron donor
- Six more malonyl groups react to form palmitate 16:0. Palmitate can be elongated to stearate 18:0. Palmitate and stearate can be desaturated to palmitoleate 16:1 and oleate 18:1.
- Aspirin inhibits COX enzyme that catalyzes synthesis of prostaglandins and thromboxanes.

Week 15 Lipid Biosynthesis

21.1 Biosynthesis of Fatty Acids and Eicosanoids

21.2 Biosynthesis of Triacylglycerols

21.3 Biosynthesis of Membrane Phospholipids

21.4 Cholesterol, Steroids, and Isoprenoids

Triacylglycerols Provide More Energy

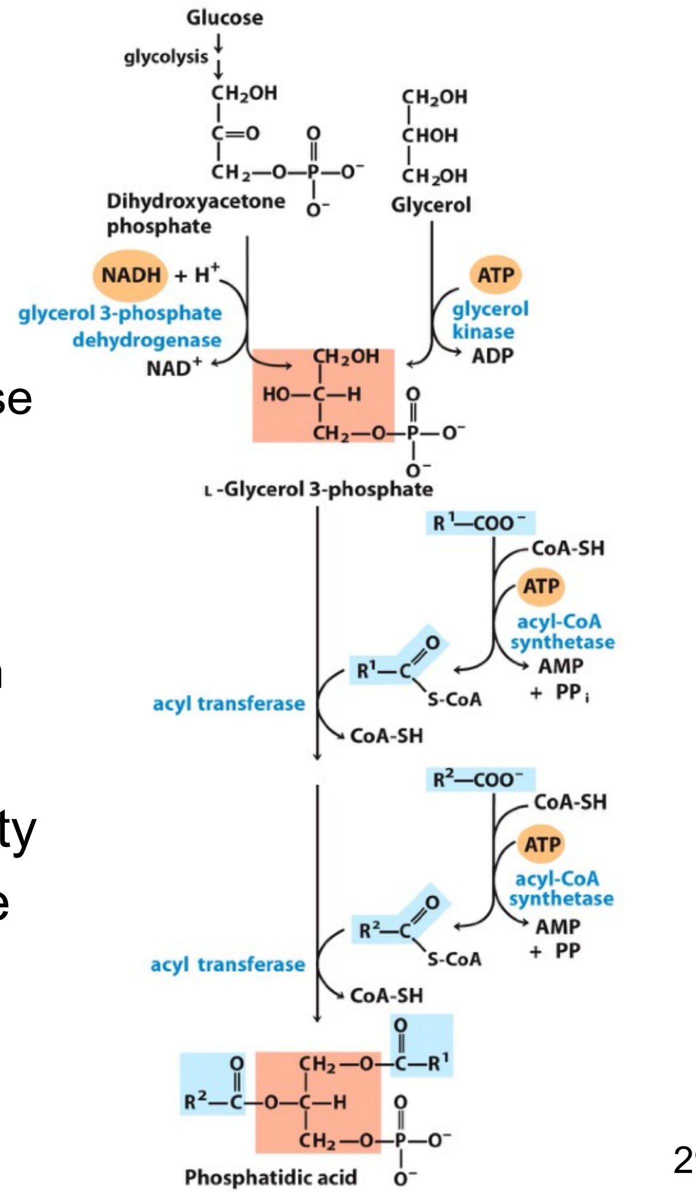
- Human can only store a few hundred grams of glycogen.
  - Supply energy needs for **12 hours**.
- A 70 kg man can store 15 kg of triacylglycerols.
  - Supply energy needs for **12 weeks**.

TABLE 23–5 **Available Metabolic Fuels in a Normal-Weight, 70 kg Man and in an Obese, 140 kg Man at the Beginning of a Fast**

Type of fuel	Weight (kg)	Caloric equivalent (thousands of kcal (kJ))	Estimated survival (months)*
Normal-weight, 70 kg man			
Triacylglycerols (adipose tissue)	15	140 (590)	
Proteins (mainly muscle)	6	24 (100)	
Glycogen (muscle, liver)	0.23	0.90 (3.8)	
Circulating fuels (glucose, fatty acids, triacylglycerols, etc.)	0.023	0.10 (0.42)	
Total		165 (690)	3
Obese, 140 kg man			
Triacylglycerols (adipose tissue)	80	750 (3,100)	
Proteins (mainly muscle)	8	32 (130)	
Glycogen (muscle, liver)	0.23	0.92 (3.8)	
Circulating fuels	0.025	0.11 (0.46)	
Total		783 (3,200)	14

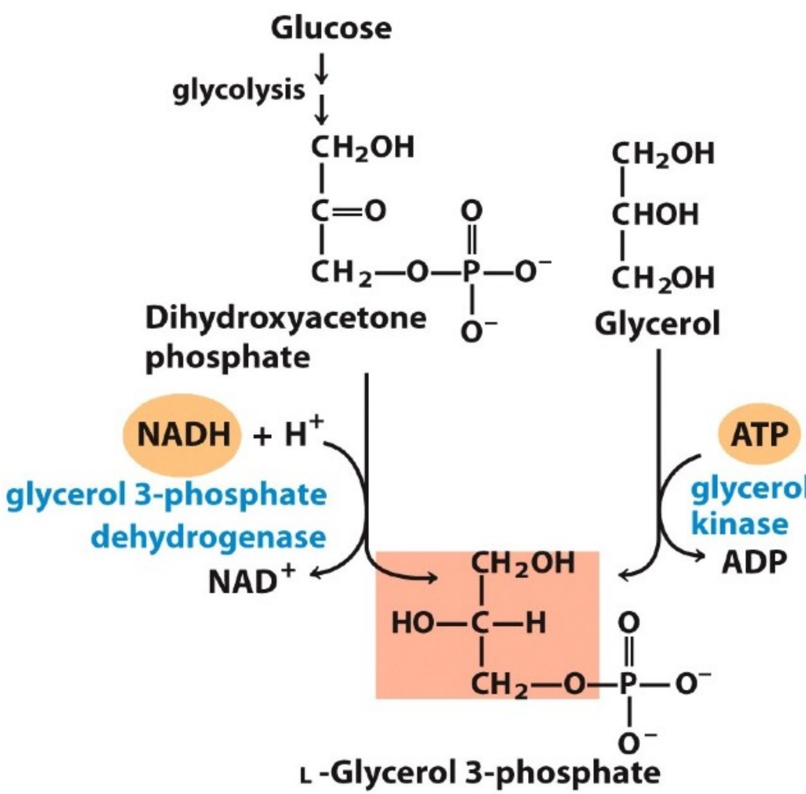
Two Precursors: Glycerol 3-P and Acyl-CoA

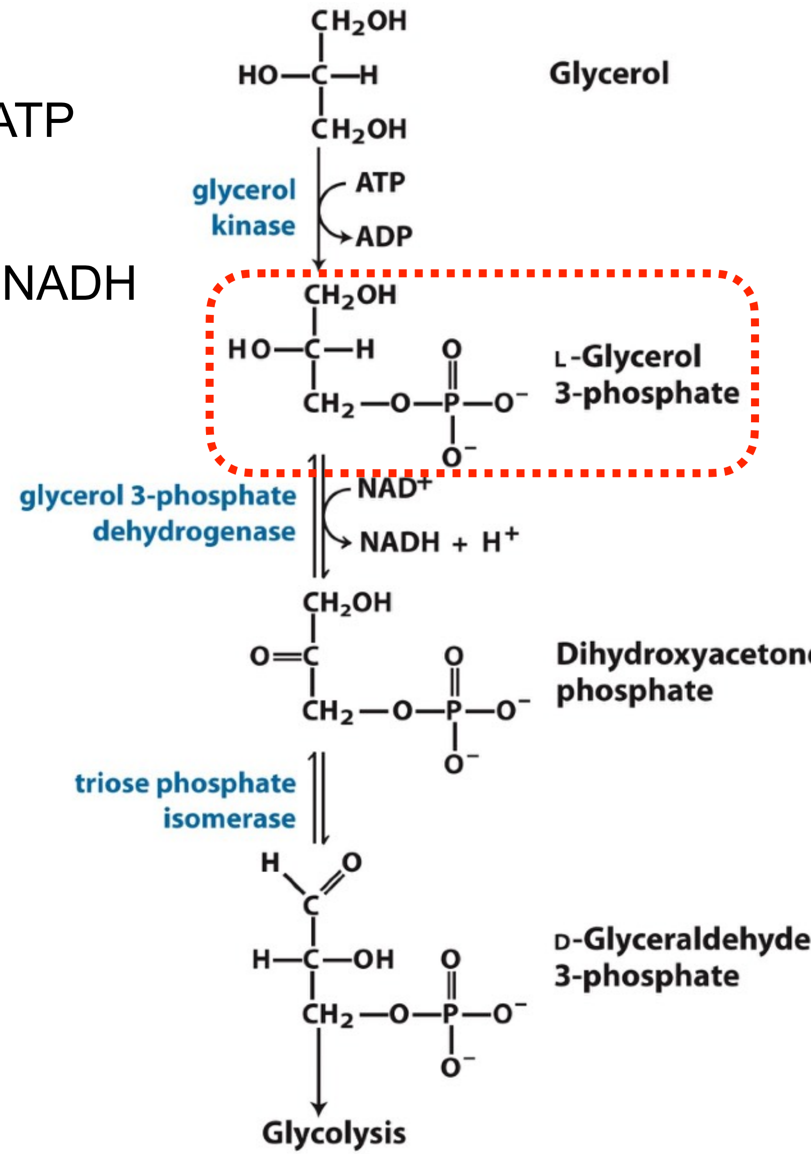
- Triacylglycerols and glycerophospholipids share two precursors (fatty acyl-CoA and glycerol 3-phosphate)
  - Glycerol 3-phosphate
    - Major: from DHAP catalyzed by dehydrogenase
    - Minor: from glycerol catalyzed by kinase
  - Fatty acyl-CoA
    - Catalyzed by acyl-CoA synthetase
    - Same as activation of fatty acids in β oxidation
- 1st stage of triacylglycerols
  - Acylation of glycerol 3-phosphate by two fatty acyl-CoA to yield diacylglycerol 3-phosphate
  - Product is also called phosphatidic acid
  - Catalyzed by acyl transferase



Production of Glycerol 3-Phosphate

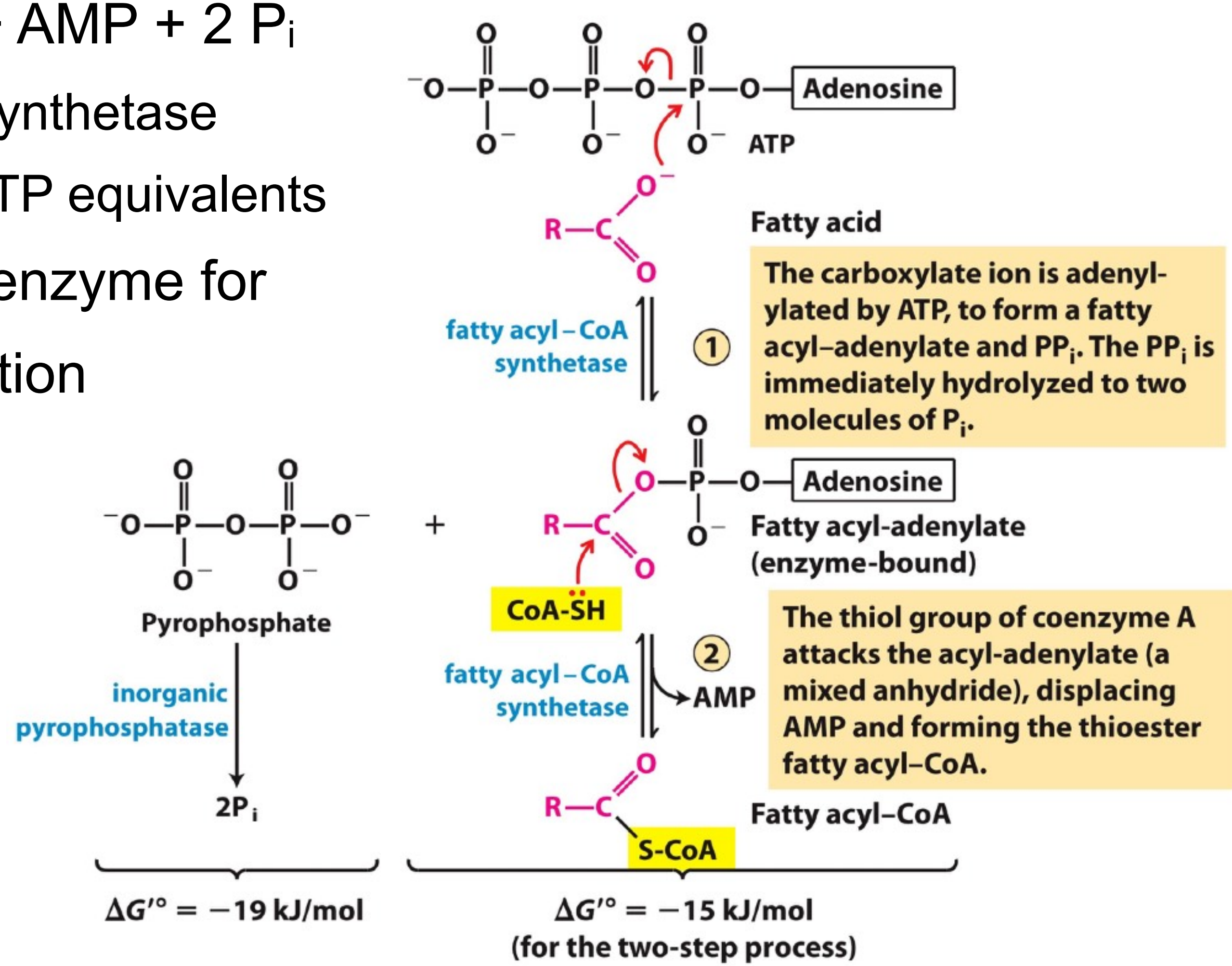
- Glycerol -> glycerol 3-phosphate
  - Catalyzed by glycerol kinase. Consumes ATP
- DHAP <-> glycerol 3-phosphate
  - Catalyzed by dehydrogenase. Consumes NADH





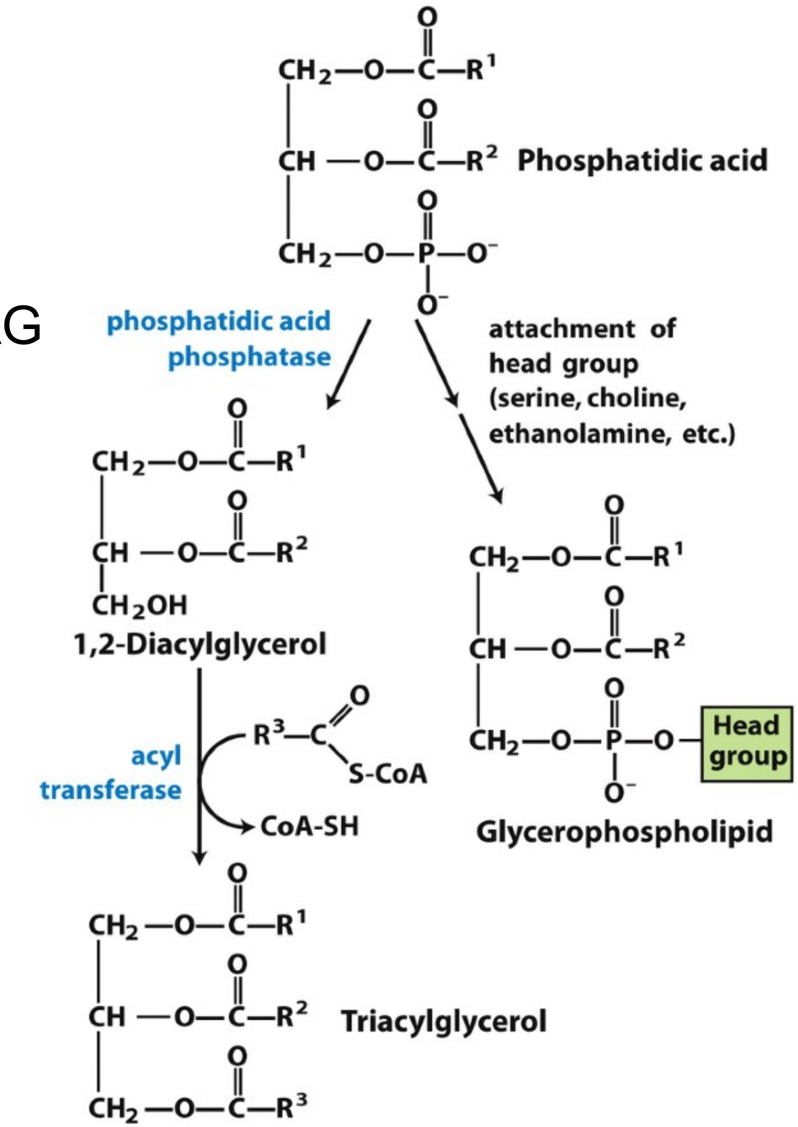
Production of Fatty Acyl-CoA

- Fatty acid + CoA + ATP -> fatty acyl-CoA + AMP + 2 P_i
  - Catalyzed by synthetase
    Consumes 2 ATP equivalents
- Same reaction/enzyme for fatty acid activation



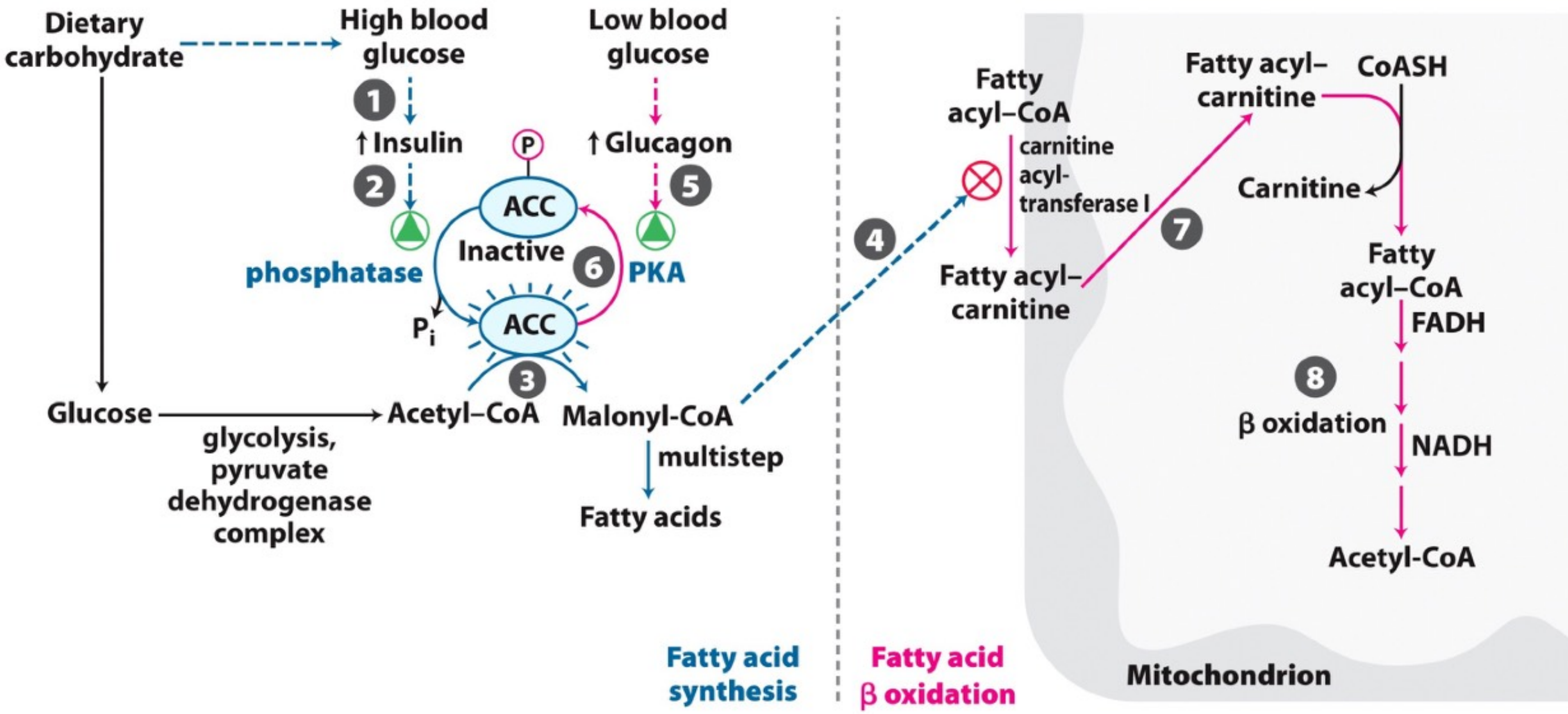
Phosphatidic Acid is Common Precursor

- **Phosphatidic acid** is a central intermediate in lipid biosynthesis
- Pathway to **triacylglycerol**
  - Hydrolyzed by phosphatase to form DAG
  - DAG is converted to TAG by transesterification with a third acyl-CoA
- Pathway to **glycerophospholipid**
  - Attachment of polar head group



Regulation of Synthesis and Breakdown

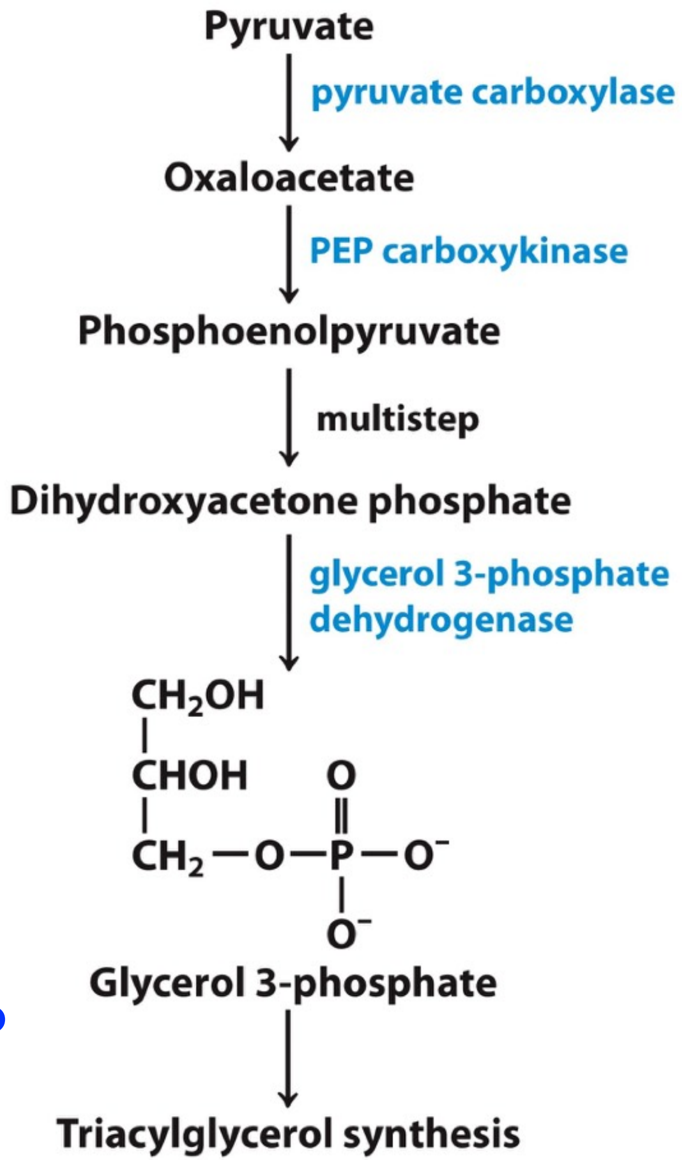
- High [glucose] -> activation of ACC -> production of malonyl-CoA
  - Malonyl-CoA is precursor of fatty acid synthesis
  - Malonyl-CoA also inhibits transportation of fatty acyl-CoA into mitochondria
- Low [glucose] -> inactivation of ACC -> low [malonyl-CoA]
  - Inhibition relieved and fatty acids are oxidized. Fatty acid synthesis still occurs



Glyceroneogenesis

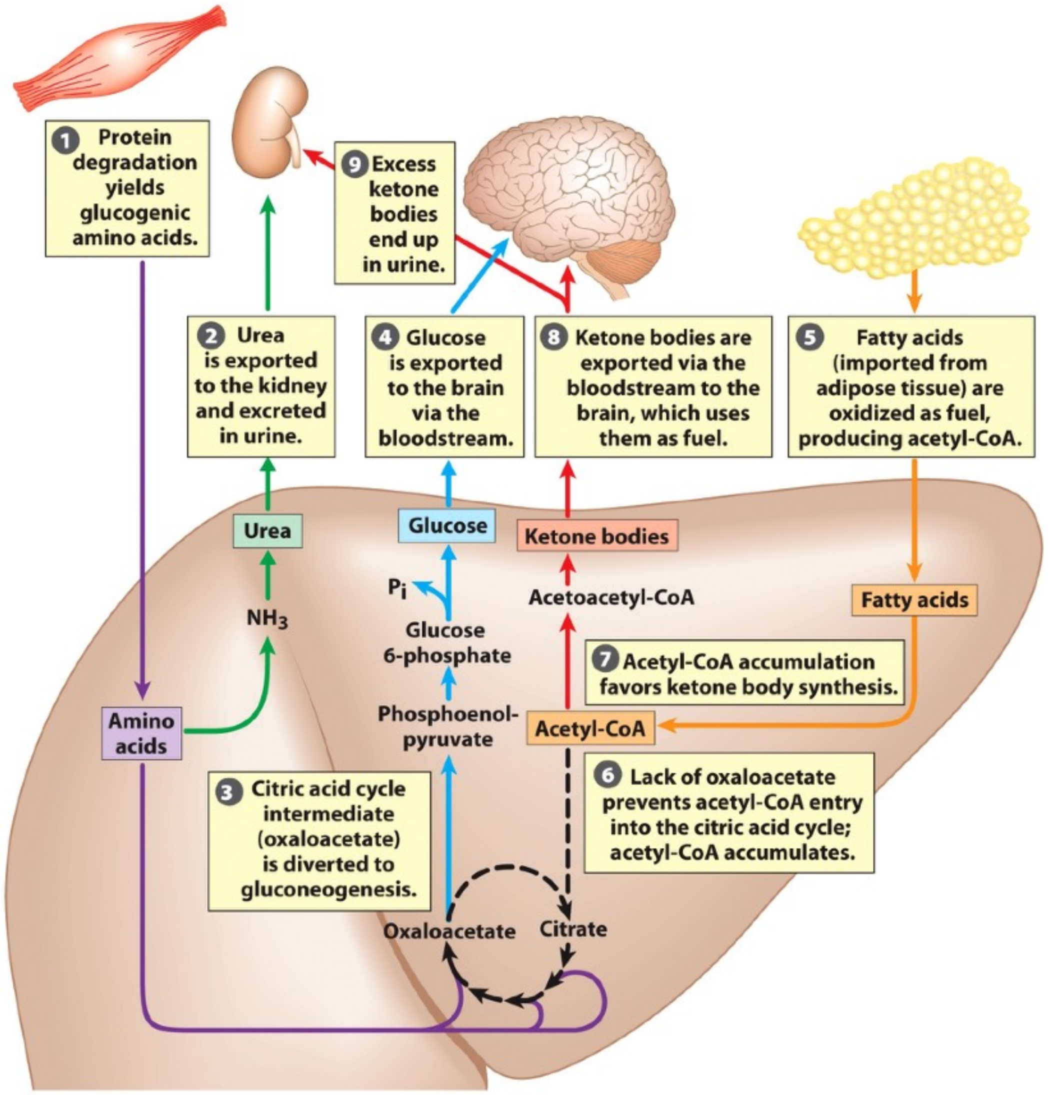
- Usually glycerol 3-P is generated from glucose by glycolysis
  - Low [glucose] -> glycolysis inhibited
  - Adipocytes lack glycerol kinase
- Glyceroneogenesis is a shortened version of gluconeogenesis
  - From pyruvate to DHAP (same)
  - DHAP to glycerol 3-P by dehydrogenase
- Pyruvate to PEP
  - Pyruvate to oxaloacetate by carboxylase
  - Oxaloacetate to PEP by carboxykinase

Explains why adipocytes express pyruvate carboxylase and PEPCK even though they do not make glucose.



Fuel Metabolism During Prolonged Fasting

- Depletion of glycogen
- Gluconeogenesis becomes main source of glucose
  - Degradation of proteins provides glucogenic amino acids for gluconeogenesis
  - CAC intermediates are consumed in gluconeogenesis
- Fatty acids cannot be converted to glucose
  - Degradation of fatty acids provides acetyl-CoA for ketone body formation
  - Acetyl-CoA cannot enter CAC



Summary 21.2 Biosynthesis of TAG

- Triacylglycerols are formed by:
  1. Transesterification of 2 fatty acyl-CoAs with glycerol 3-P
  2. Product phosphatidic acid is dephosphorylated
  3. Diacylglycerol is acylated by a third fatty acyl-CoA
- Synthesis and degradation of triacylglycerols are tightly regulated by hormones (insulin and glucagon)
- Triacylglycerols are synthesized from fatty acids and glycerol 3-P even during starvation. DHAP precursor of glycerol 3-P is derived from pyruvate via glyceroneogenesis

Week 15 Lipid Biosynthesis

21.1 Biosynthesis of Fatty Acids and Eicosanoids

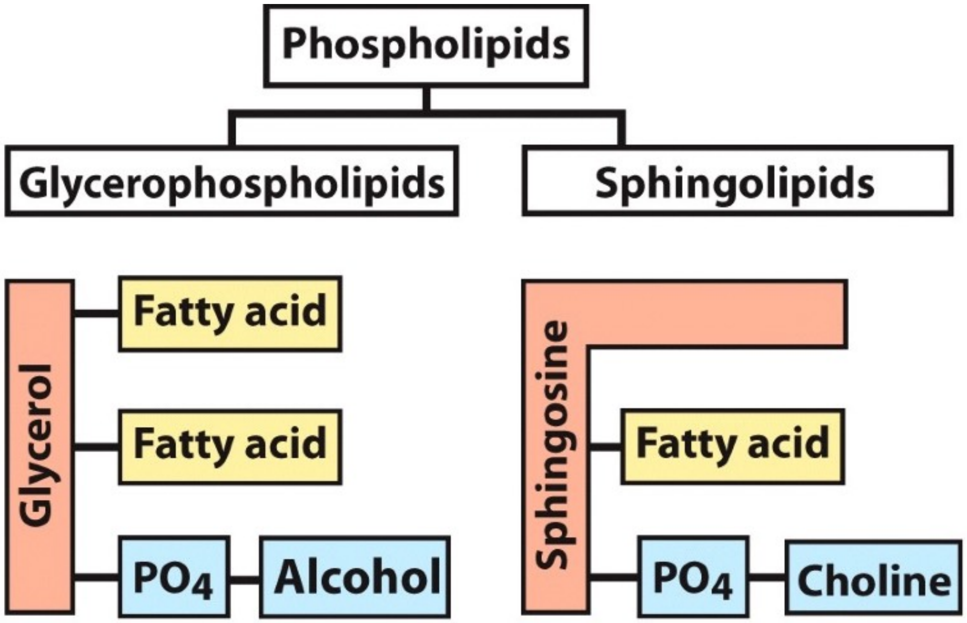
21.2 Biosynthesis of Triacylglycerols

21.3 Biosynthesis of Membrane Phospholipids

21.4 Cholesterol, Steroids, and Isoprenoids

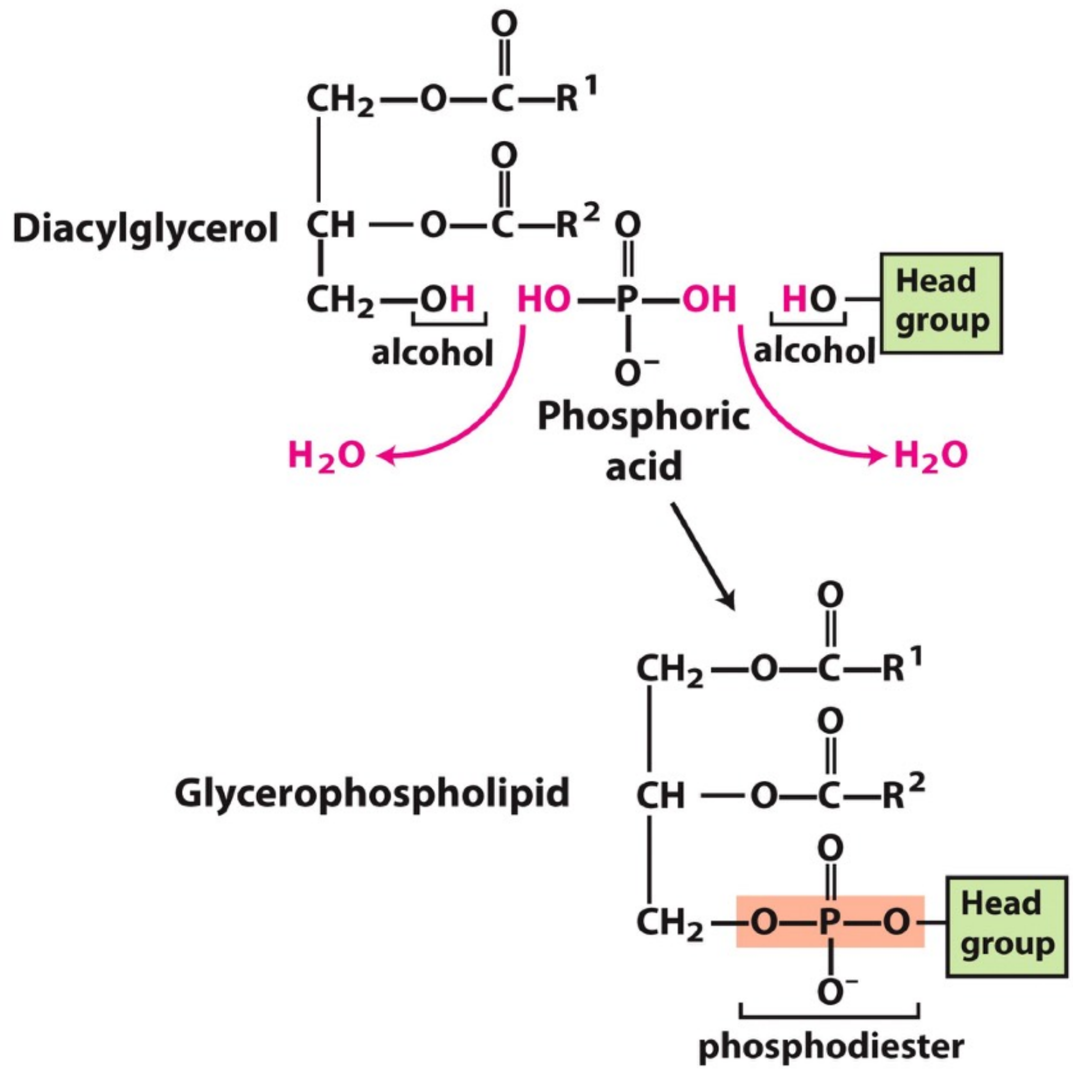
Membrane Lipids Are Amphipathic

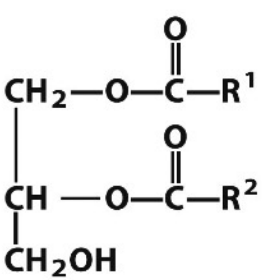
- Possess **both hydrophilic and lipophilic** properties
  - Hydrophilic (water-loving, polar) head
  - Lipophilic (fat-loving, nonpolar) fatty acid tail
- Linkage
  - Phosphodiester bond (phospholipids)
  - Glycosidic bond (glycolipids)



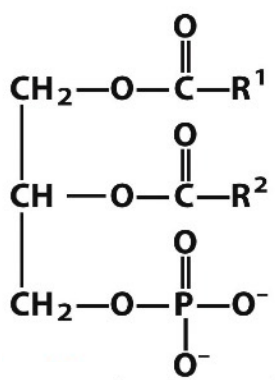
Attachment of Head Group

- Begin with diacylglycerol or phosphatidic acid
  - Both C-3 and head group has an -OH group
  - Phosphoric acid condenses with these two alcohols
  - Two H_2O are eliminated
  - Head group is attached by a phosphodiester bond





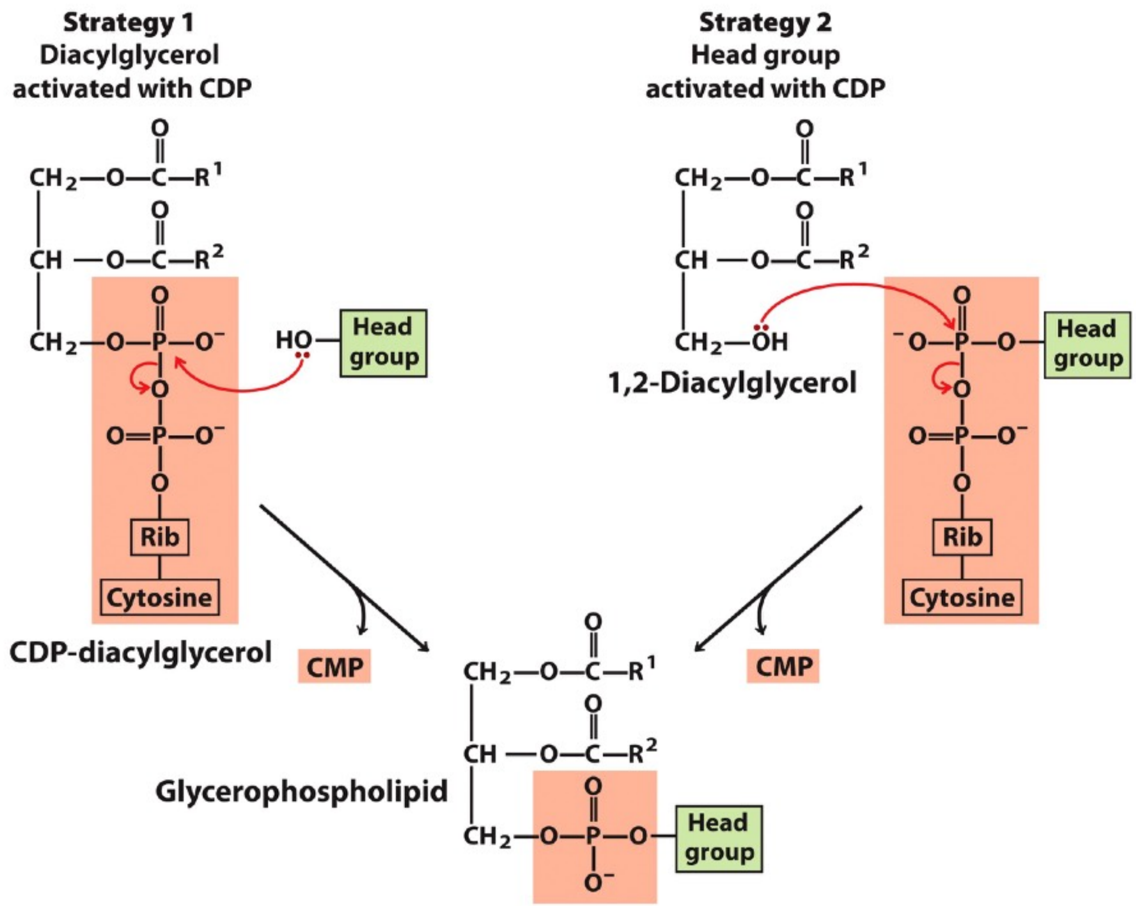
1,2-Diacylglycerol



Phosphatidic acid

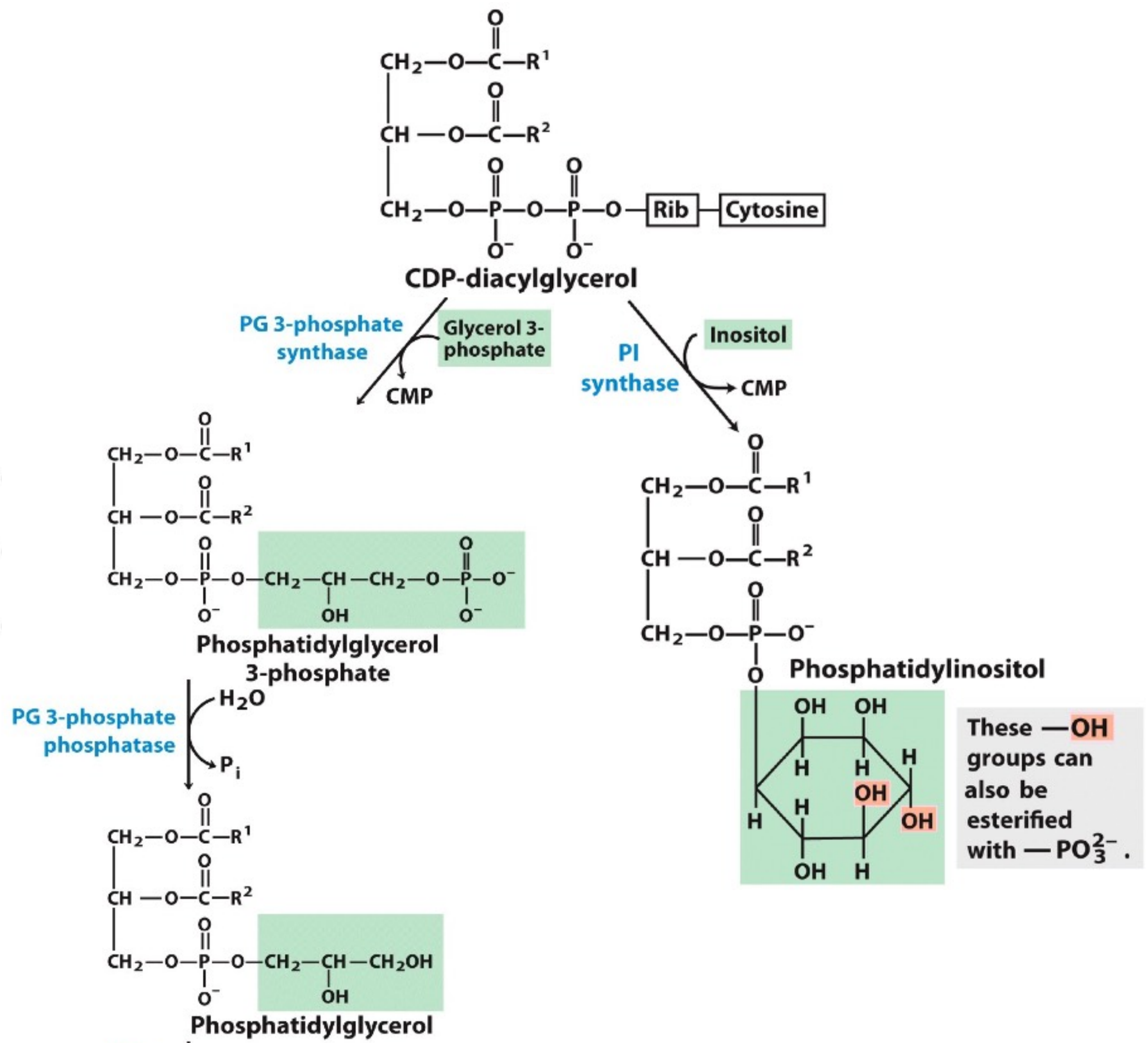
Two Strategies

- Either -OH is activated by attaching to CDP (cytidine diphosphate)
- The free -OH does nucleophilic attack
- Products are CMP and glycerophospholipid



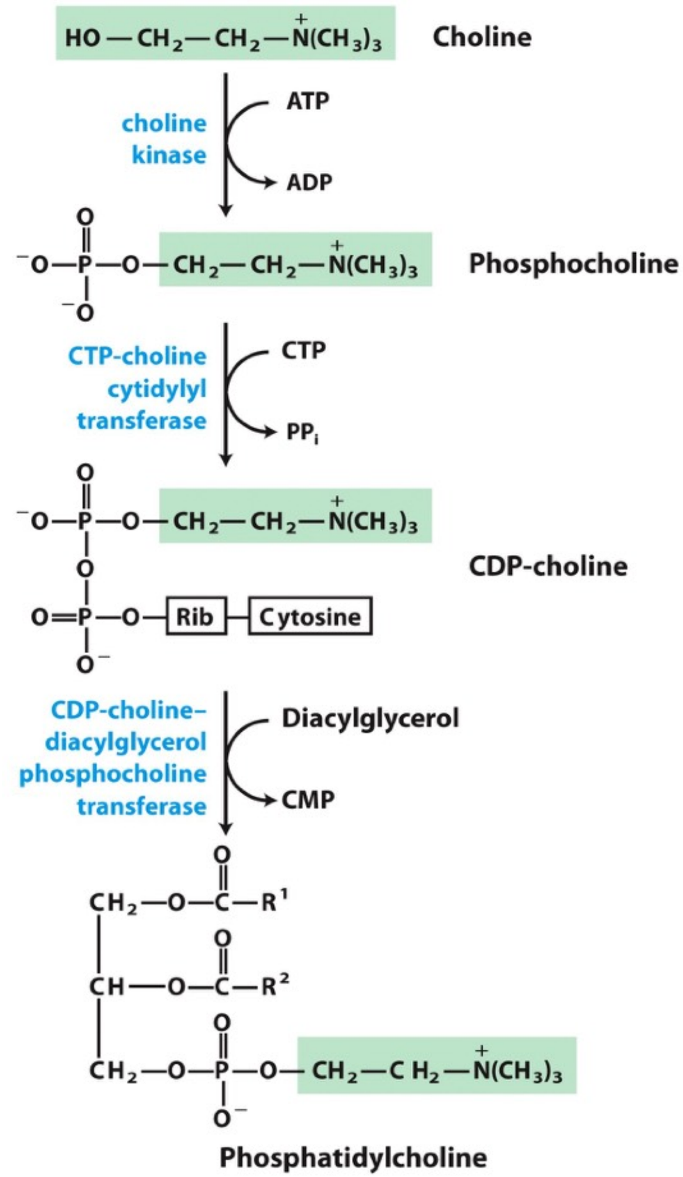
Strategy 1. CDP-Diacylglycerol

- Eukaryotes synthesize **anionic** phospholipids from CDP-diacylglycerol
- Nucleophilic attack by C-1 hydroxyl of glycerol 3-P yields phosphatidyl-glycerol 3-P
- Nucleophilic attack by C-1 hydroxyl of inositol yields phosphatidyl-inositol

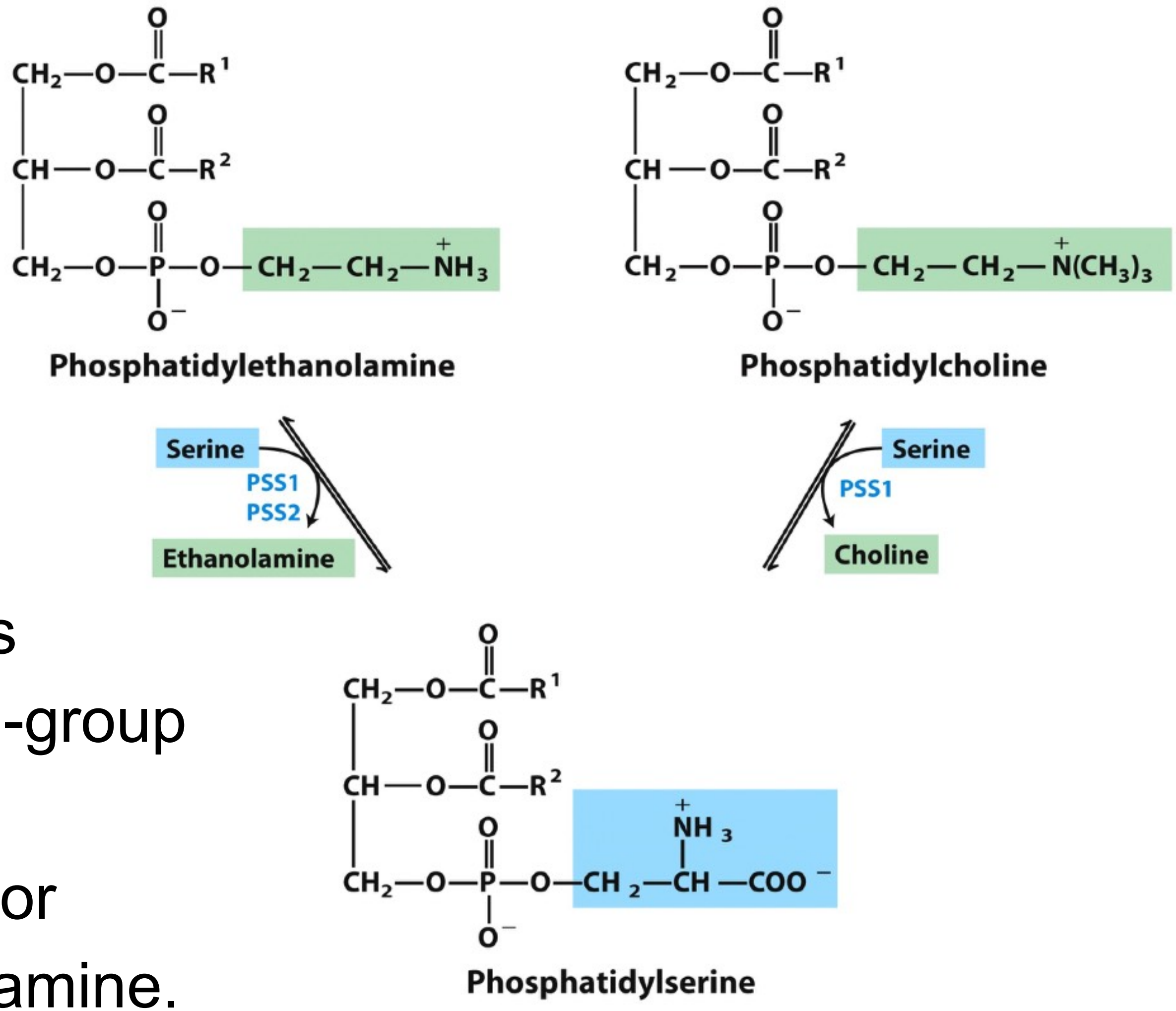


Strategy 2. CDP-Head Group

- Mammals synthesize phosphatidylcholine and phosphatidylethanolamine from CDP-head group
- Nucleophilic attack on CDP-choline by C-3 hydroxyl of diacylglycerol yields phosphatidylcholine
- Nucleophilic attack on CDP-ethanolamine by C-3 hydroxyl of diacylglycerol yields phosphatidylethanolamine

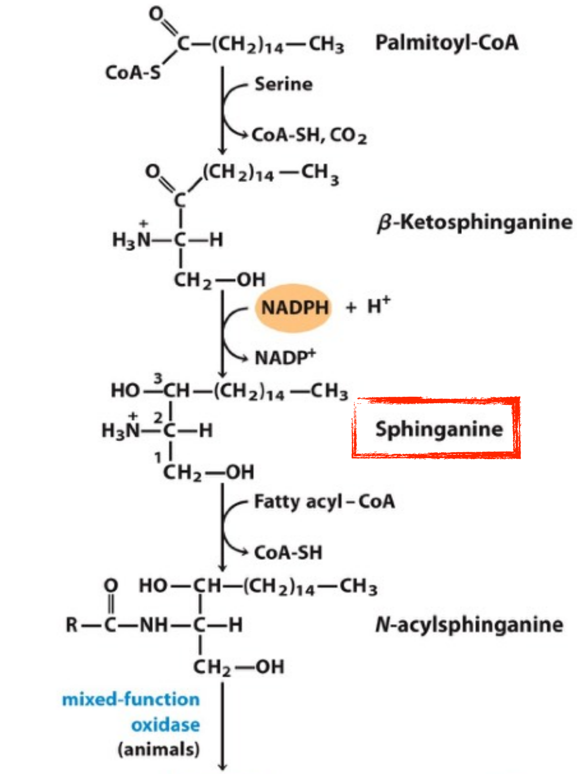


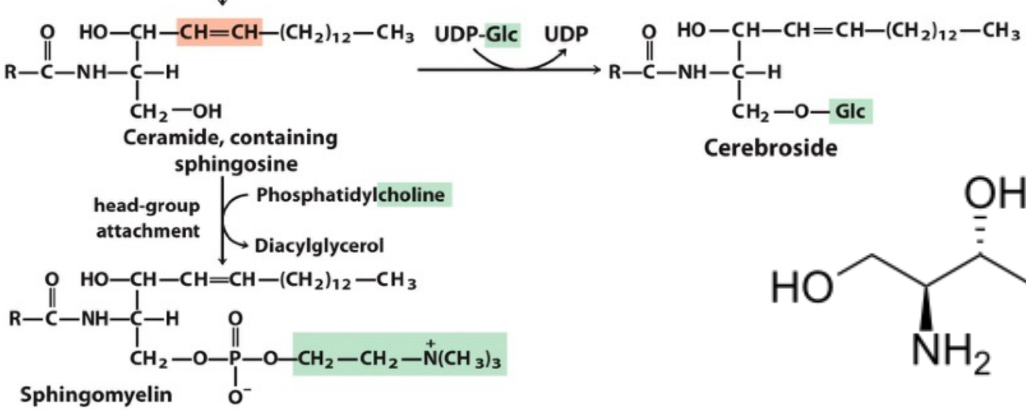
Synthesis of Phosphatidylserine



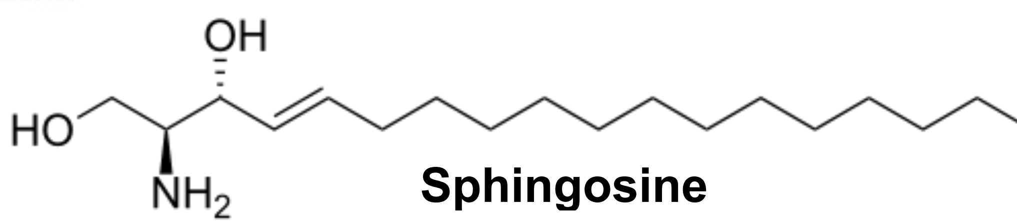
- In mammals, phosphatidylserine is synthesized by head-group exchange from phosphatidylcholine or phosphatidylethanolamine.

Synthesis of Sphingolipid





- Biosynthesis takes place in four stages.
  1. Synthesis of 18-carbon **sphinganine** from 16-carbon **palmitoyl-CoA** and **serine**
  2. Attachment of a fatty acid in amide linkage to yield N-acylsphinganine
  3. Desaturation to form N-acylsphingosine (also called ceramide)
  4. Attachment of a head group to produce a sphingolipid such as sphingomyelin or cerebroside



Sphingosine

Summary 21.3 Biosynthesis of P-lipids

- Diacylglycerols are principal precursors of glycerophospholipids
- In mammals, phosphatidylglycerol is formed by condensation of CDP-diacylglycerol with glycerol 3-P, followed by removal of P by phosphatase
- In biosynthesis of phosphatidylcholine and phosphatidylethanolamine in mammals, head-group alcohol is activated as CDP derivative, then condensed with diacylglycerol. Phosphatidylserine is derived from phosphatidylcholine or phosphatidylethanolamine

Week 15 Lipid Biosynthesis

21.1 Biosynthesis of Fatty Acids and Eicosanoids

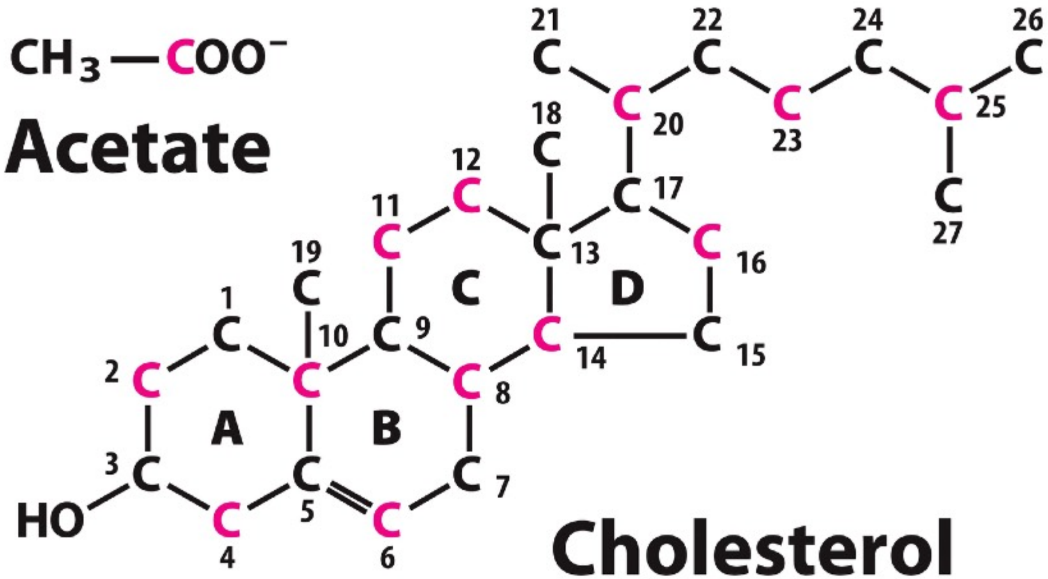
21.2 Biosynthesis of Triacylglycerols

21.3 Biosynthesis of Membrane Phospholipids

21.4 Cholesterol, Steroids, and Isoprenoids

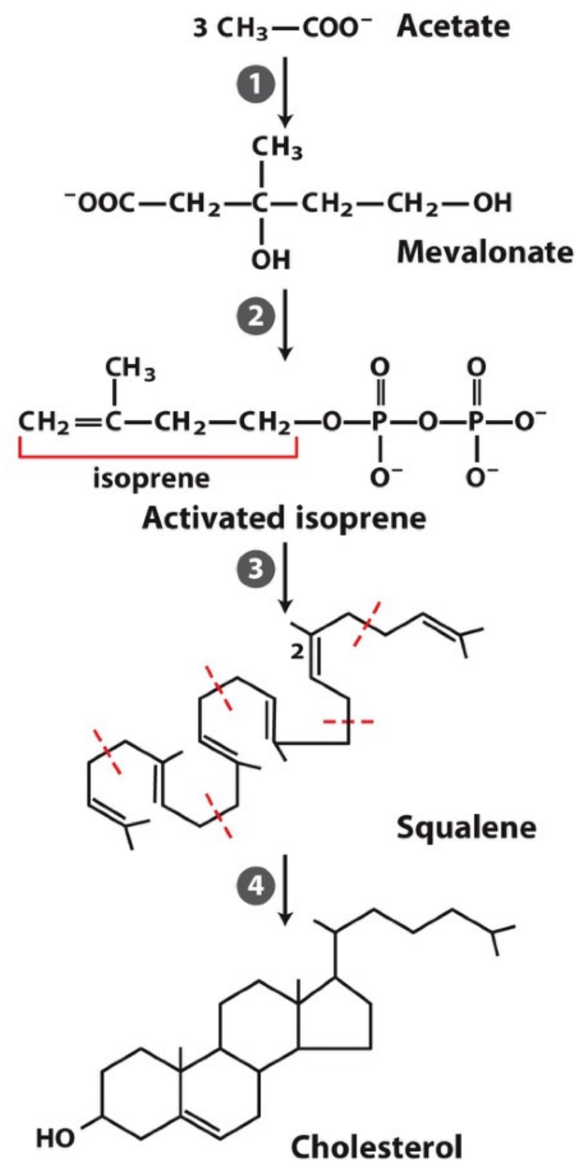
Cholesterol is A 27-Carbon Compound

- Cholesterol is **notorious** because of strong correlation between high [cholesterol] and human cardiovascular diseases.
- Cholesterol is an **essential** component of cellular membrane, and a precursor of steroid hormones and bile acids.
- Cholesterol is essential but **not required in diet**. Mammalian cells can synthesize it from simple precursors (acetyl-CoA).



Four-Stage Synthesis of Cholesterol

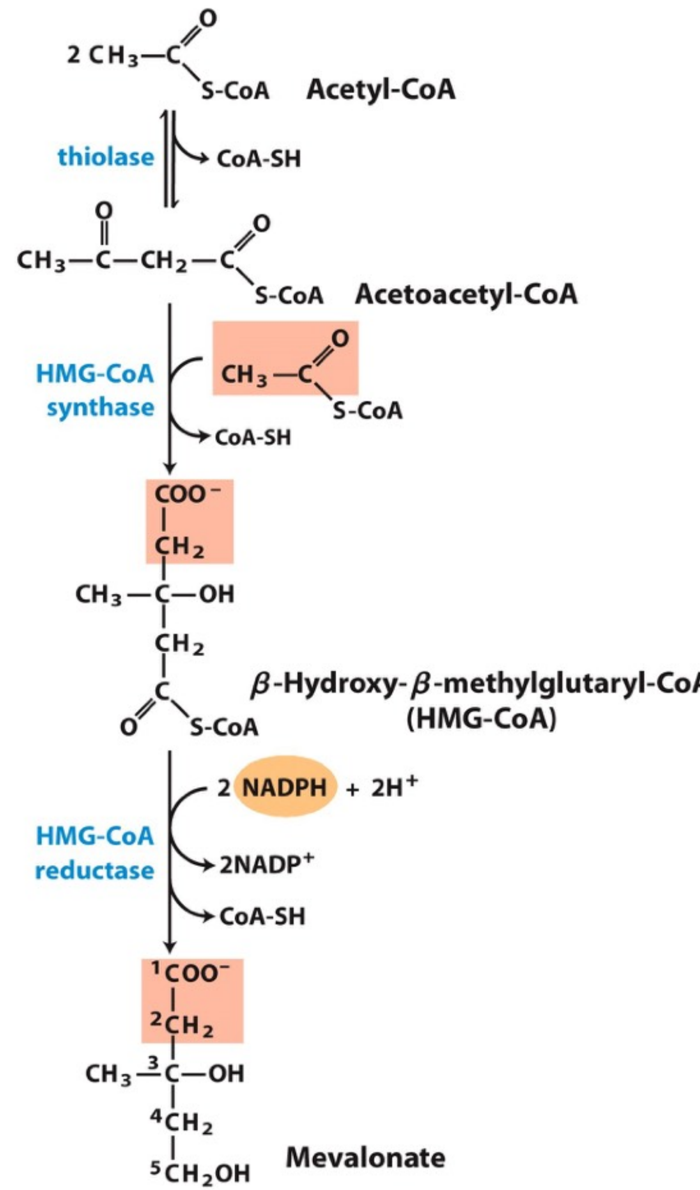
- Cholesterol is made from acetyl-CoA. Synthesis takes place in **four stages** (37 steps)
  1. Condensation of three acetate units to form a six-carbon intermediate, mevalonate
  2. Conversion of mevalonate to activated five-carbon isoprene units
  3. Polymerization of six isoprene units to form **30-carbon linear squalene**
  4. Cyclization of squalene to form four rings of steroid nucleus, with further changes to produce cholesterol



Stage 1. Formation of Mevalonate

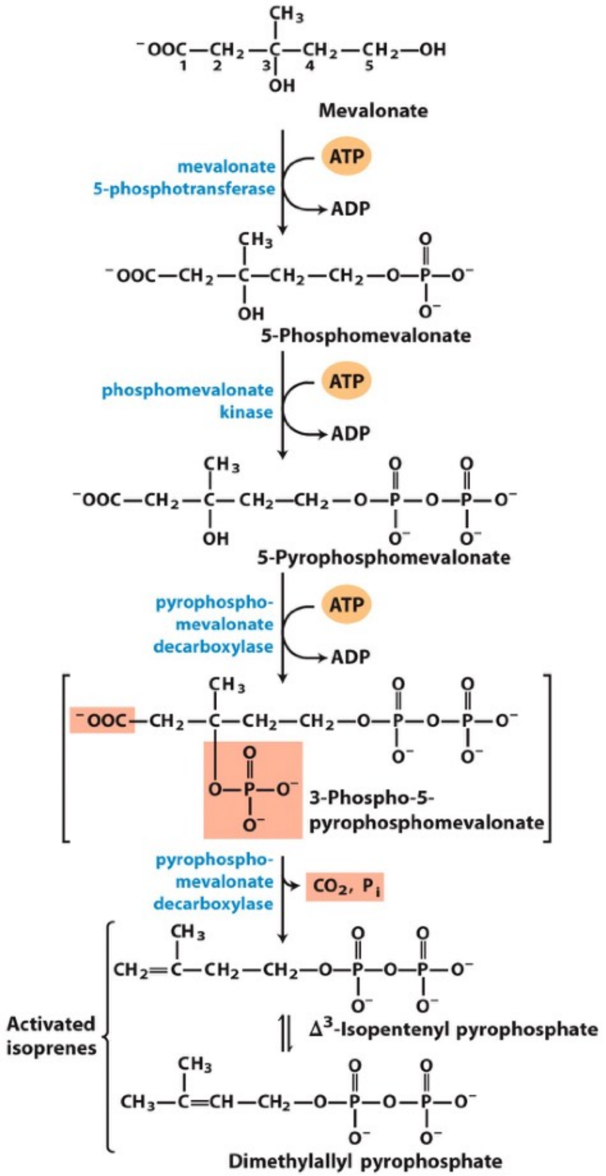
1. Two molecules of acetyl-CoA condense to form acetoacetyl-CoA
   - Catalyzed by transferase (or thiolase)
2. Acetoacetyl-CoA condenses with acetyl-CoA to yield HMG-CoA
   - Catalyzed by synthase
3. HMG-CoA is reduced to mevalonate
   - Consumes two molecules of **NADPH**
   - Catalyzed by **HMG-CoA reductase**
   - Major point of regulation

- Compare first two reactions with ketone body formation
  - Cholesterol biosynthesis in cytosol
  - Ketone body formation in mitochondria



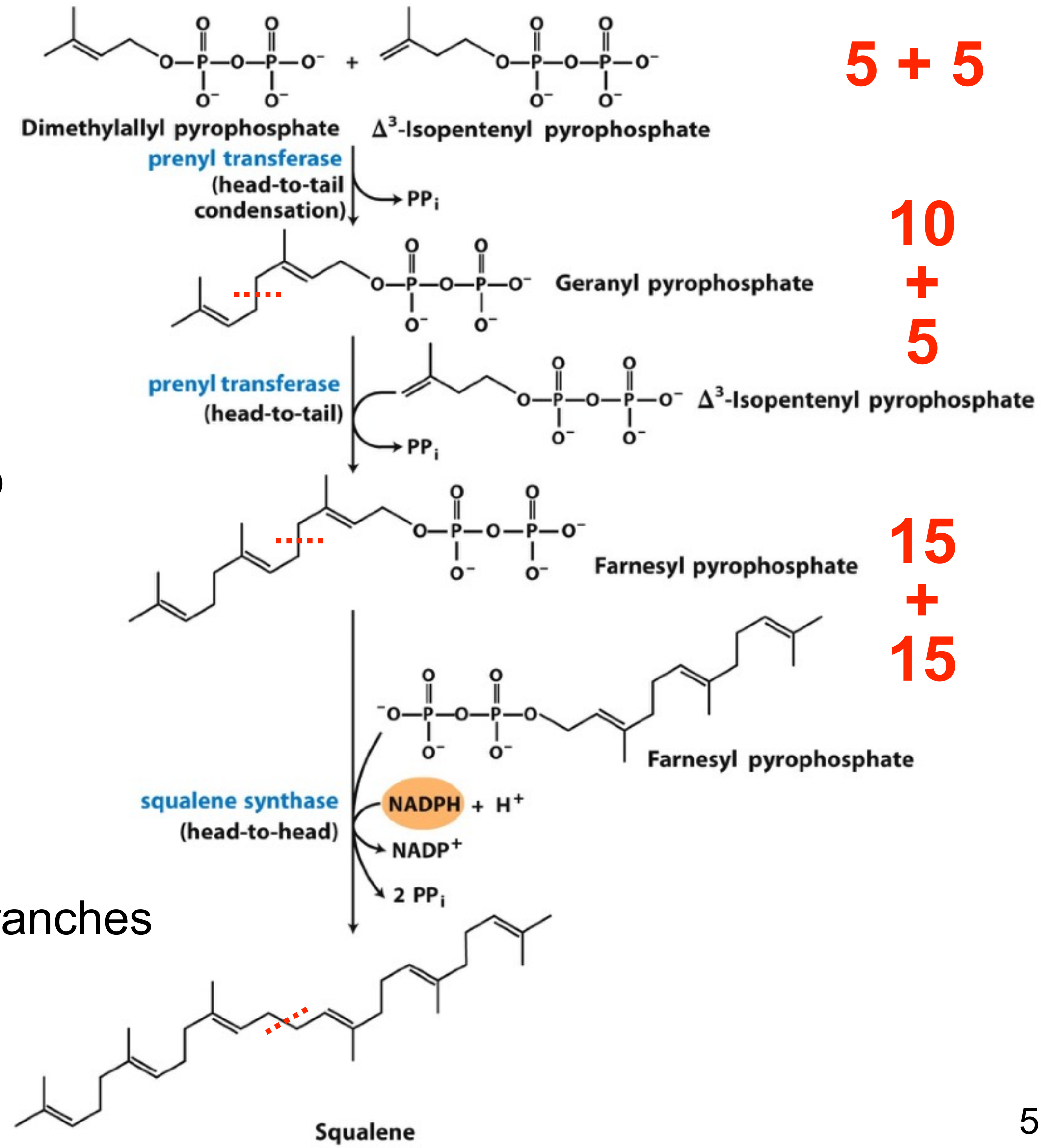
Stage 2. Formation of Activated Isoprenes

1. Mevalonate is phosphorylated
   - Catalyzed by transferase
   - Consumes **ATP**
2. 5-P-mevalonate is phosphorylated
   - Catalyzed by kinase
   - Consumes **ATP**
3. 5-PP-mevalonate is decarboxylated and phosphorylated
   - Catalyzed by decarboxylase
   - Consumes **ATP**
   - Releases CO_2 and P_i
4. Isopentenyl group is isomerized to dimethylallyl group
   - Catalyzed by isomerase
   - Forms two activated isoprenes



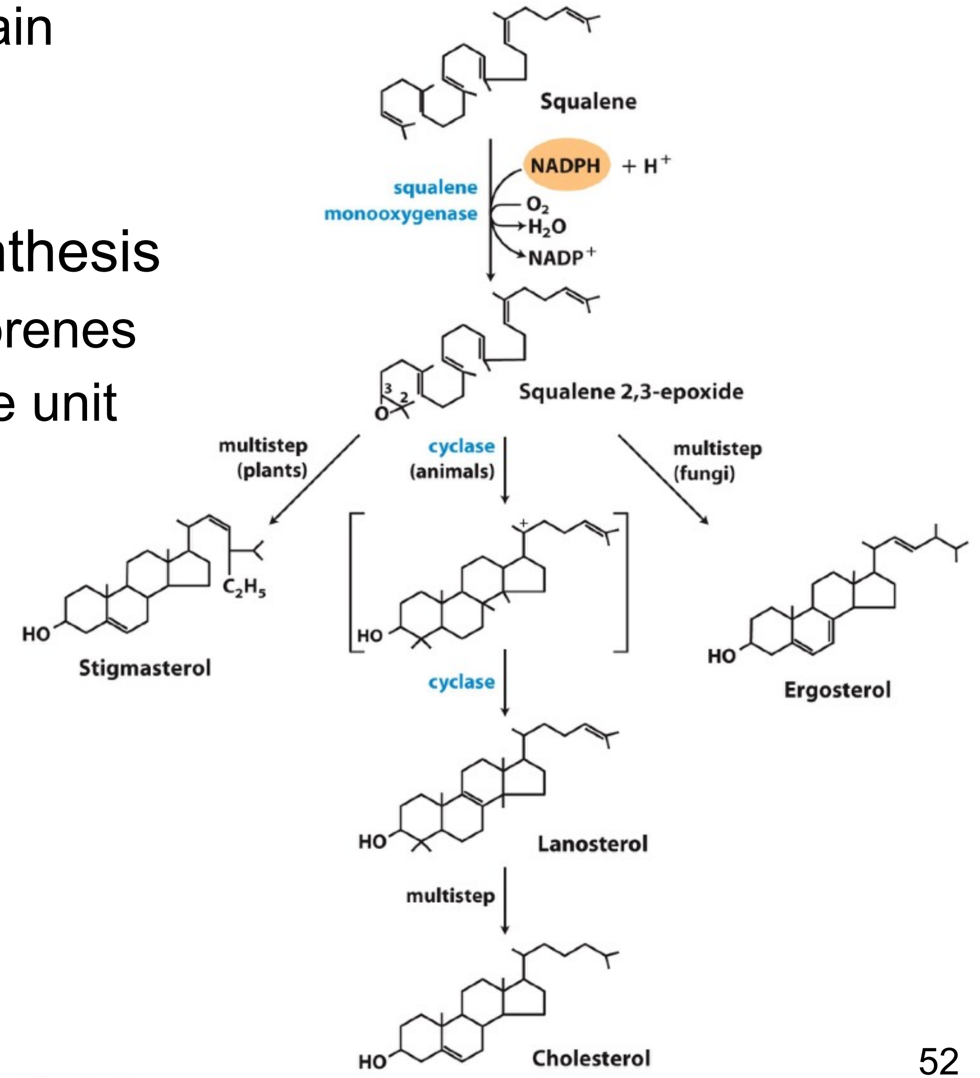
Stage 3. Formation of Squalene

1. Head-to-tail condensation
   - Catalyzed by transferase
   - Forms a 10-C geranyl group
   - Releases PP_i
2. Head-to-tail condensation
   - Catalyzed by transferase
   - Forms a 15-C farnesyl group
   - Releases PP_i
3. Head-to-head condensation
   - Catalyzed by synthase
   - Forms a 30-C squalene
     - 24 carbons in main chain
     - 6 carbons as methyl group branches
   - Consumes **NADPH**
   - Releases 2 PP_i



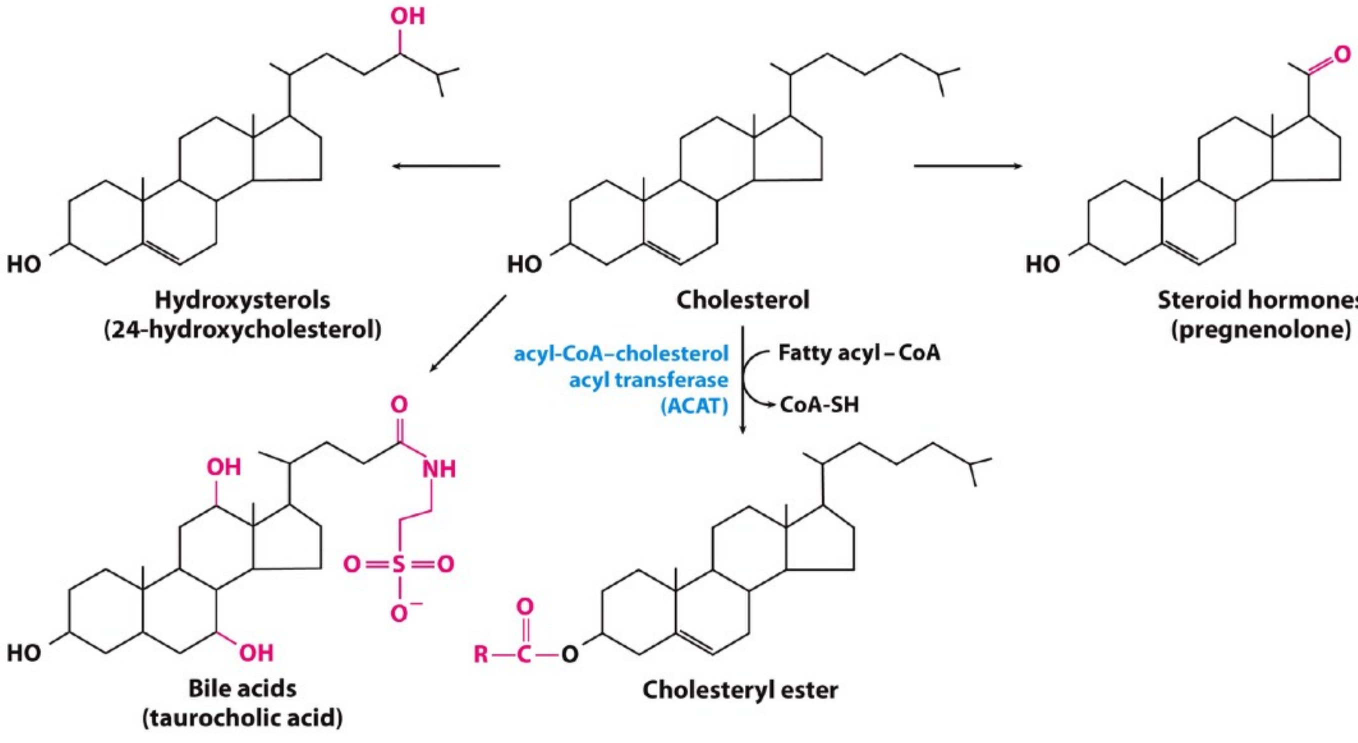
Stage 4. Conversion to Four-Ring

- Squalene **monooxygenase**
  - One oxygen atom to squalene chain
  - The other oxygen atom to H_2O
  - NADPH provides reducing power
- Energy cost of cholesterol biosynthesis
  - Only in formation of activated isoprenes
  - Three ATP molecules per isoprene unit
  - A total cost of 18 ATP molecules



Fates of Cholesterol

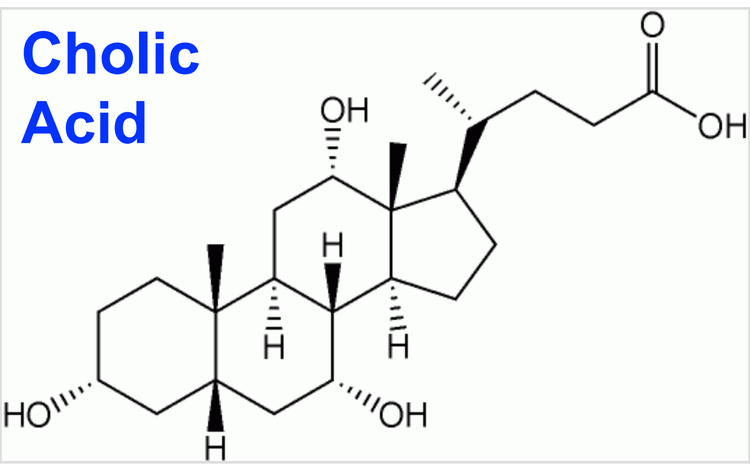
- Most cholesterol synthesis takes place in liver
- Most is exported in one of three forms
  - Bile acids. Biliary cholesterol. Cholesteryl esters
  - A small fraction of cholesterol is incorporated into hepatocyte membrane
- In other tissues, cholesterol is converted to steroid hormones

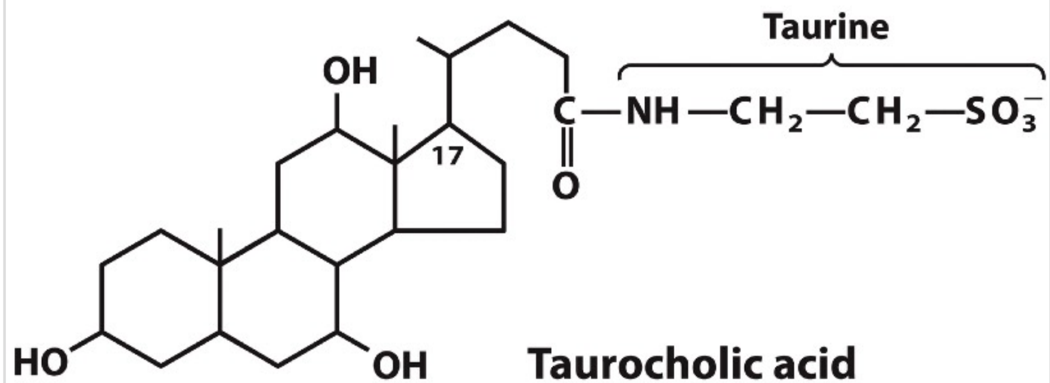


Bile Acids Assist in Fat Digestion

- Bile is stored in gallbladder and excreted into small intestine
- Bile acids aid in digestion of fat-containing meals
  - More hydrophilic cholesterol derivates
  - Serve as emulsifier to convert large fat particles to tiny micelles
  - Greatly increase surface where digestive lipases can act

Cholic Acid

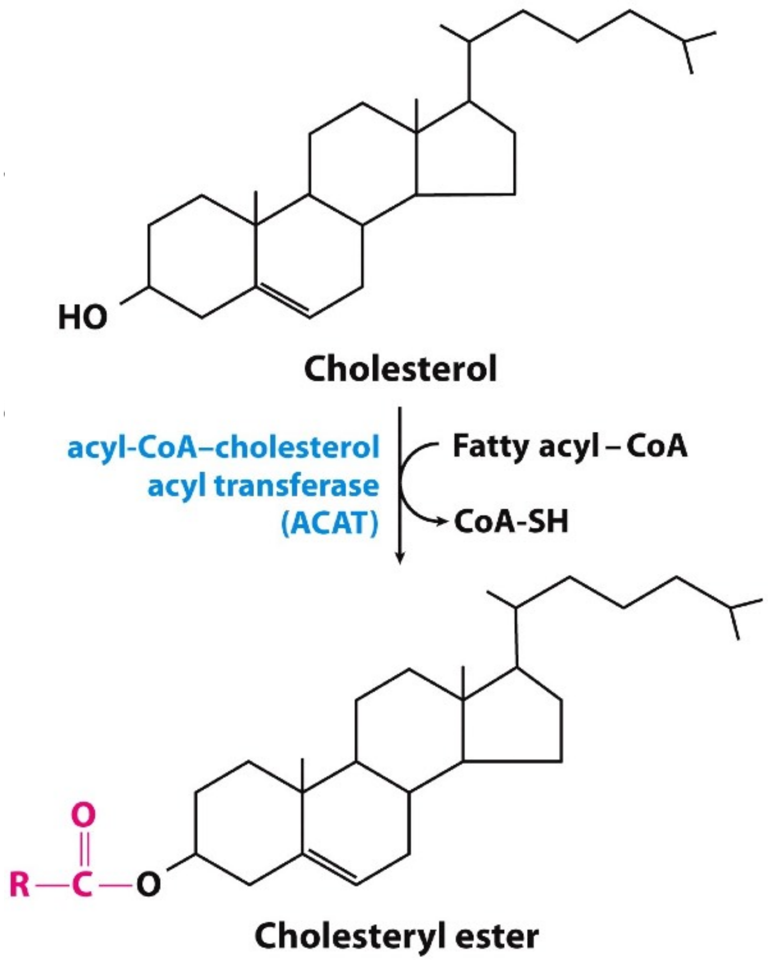




Taurocholic acid
(a bile acid)

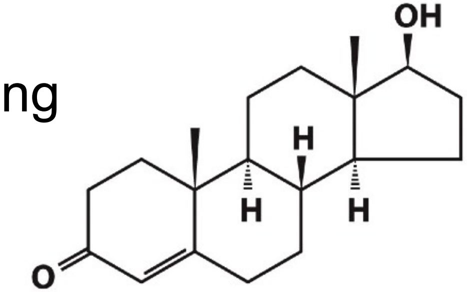
Cholesteryl Esters Are More Hydrophobic

- Cholesterol reacts with fatty acyl-CoA to form cholesteryl ester
  - Catalyzed by acyl-CoA-cholesterol acyl transferase (ACAT)
  - Transfer of a fatty acid from coenzyme A to cholesterol
- More hydrophobic
  - Unable to enter membrane
  - Transported in secreted lipoprotein particles to other tissues
  - Stored in liver in lipid droplets

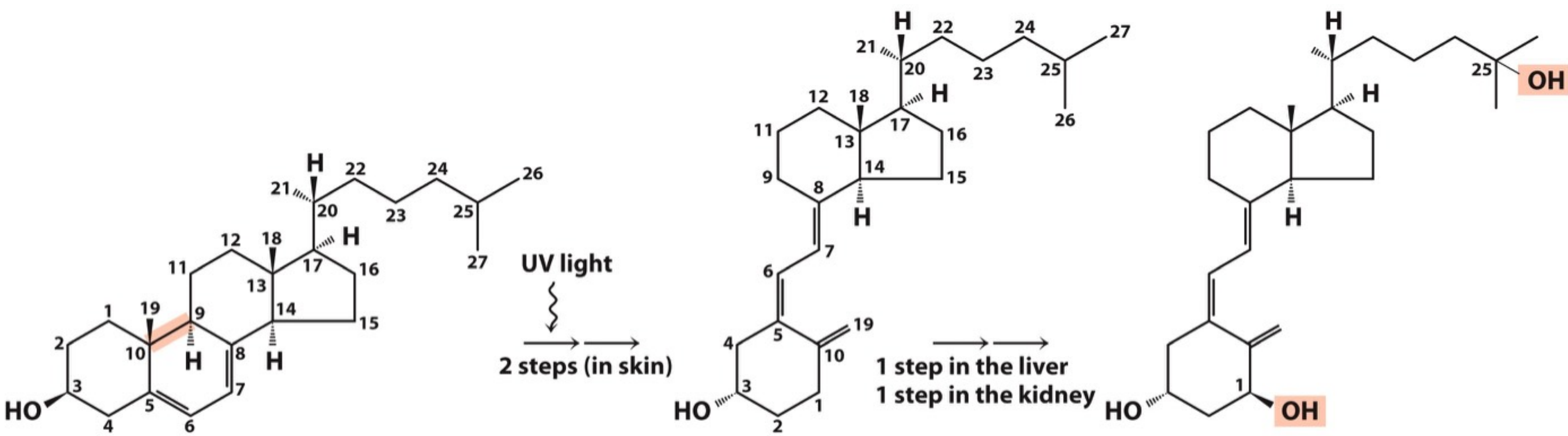


Steroid Hormones

- Steroid hormones carry messages between tissues
  - Oxidized derivatives of sterols
  - Have sterol nucleus but lack alkyl chain attached to D ring
  - Move through **bloodstream** to target tissues
- Vitamin D_3 is formed from 7-dehydrocholesterol
  - Its metabolic product regulates calcium uptake in intestine
  - Deficiency of vitamin D_3 leads to disease rickets



Testosterone



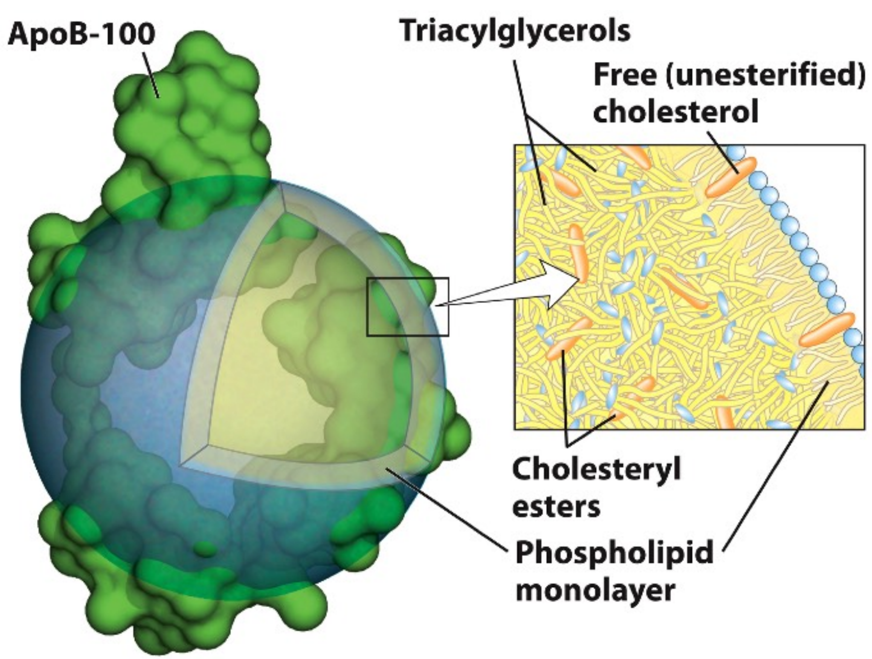
7-Dehydrocholesterol

Cholecalciferol (vitamin D_3)

1α,25-Dihydroxyvitamin D_3 (calcitriol)

Cholesterol is Carried on Lipoproteins

- Cholesterol is insoluble in water, but must be moved from tissue of origin to tissues in which it is stored or consumed
- Carried in blood as **lipoproteins**
  - Macromolecular complex of carrier proteins and lipids
  - Phospholipids, cholesterol, cholesteryl esters, and triacylglycerols
  - Hydrophobic lipids in the core and hydrophilic side chains at the surface



Four Major Classes of Lipoproteins

- Named based on density in centrifuge
- Large enough to see in electron microscopy
  - Chylomicrons. Largest and least dense
  - Very low-density lipoproteins (VLDL)
  - Low-density lipoproteins (LDL)
  - High-density lipoproteins (HDL) Smallest and most dense

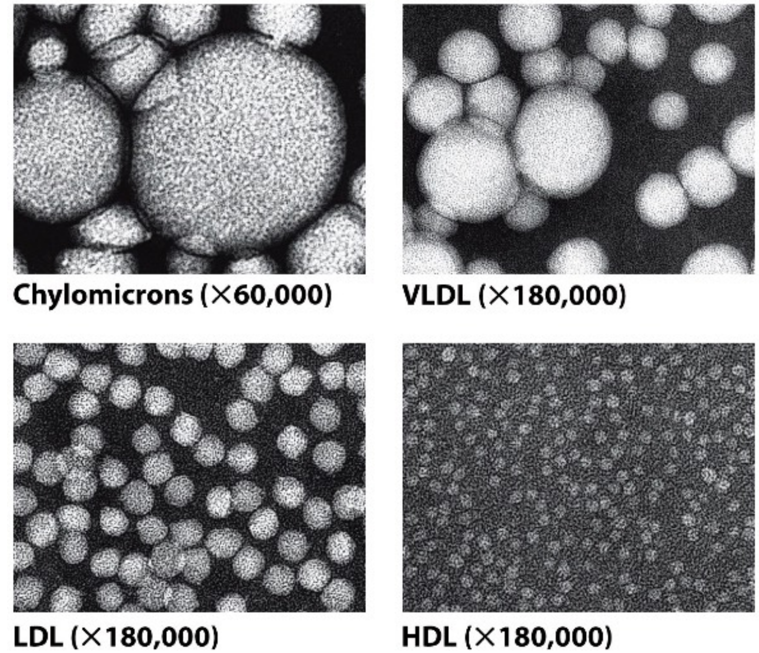
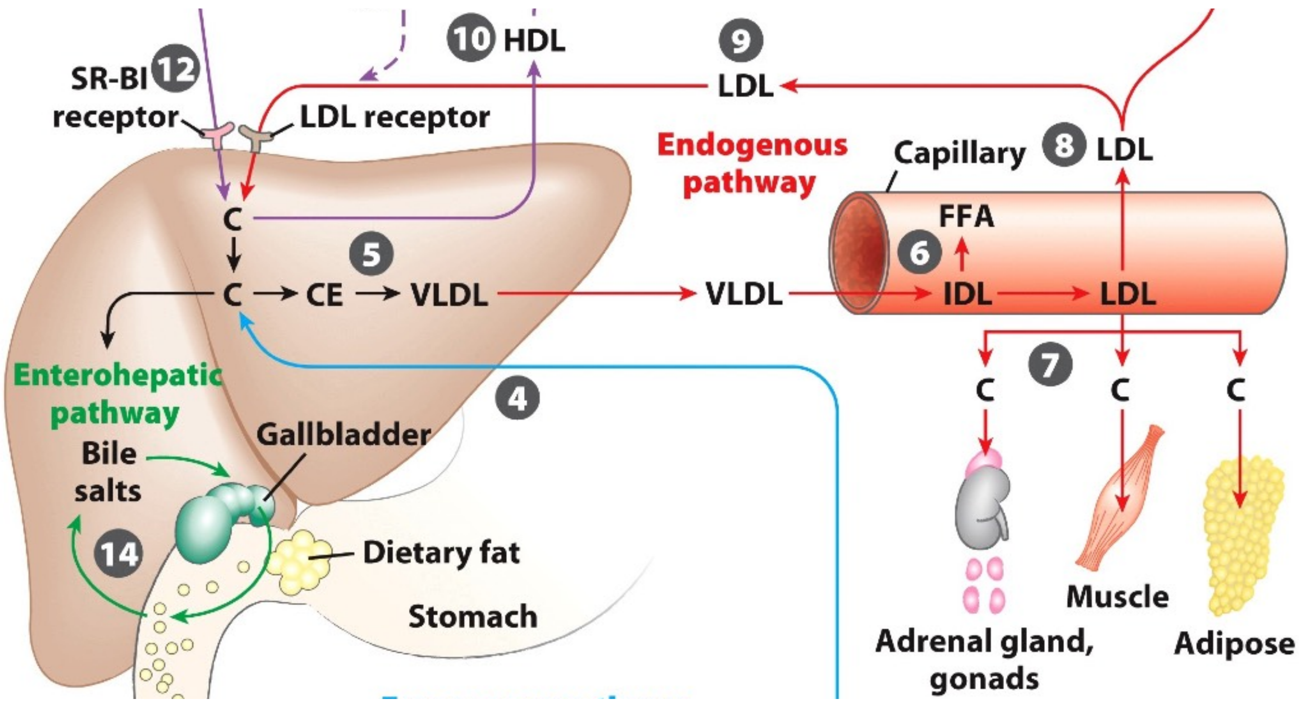


TABLE 21–1 Major Classes of Human Plasma Lipoproteins: Some Properties

		Composition (wt %)				
Lipoprotein	Density (g/mL)	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

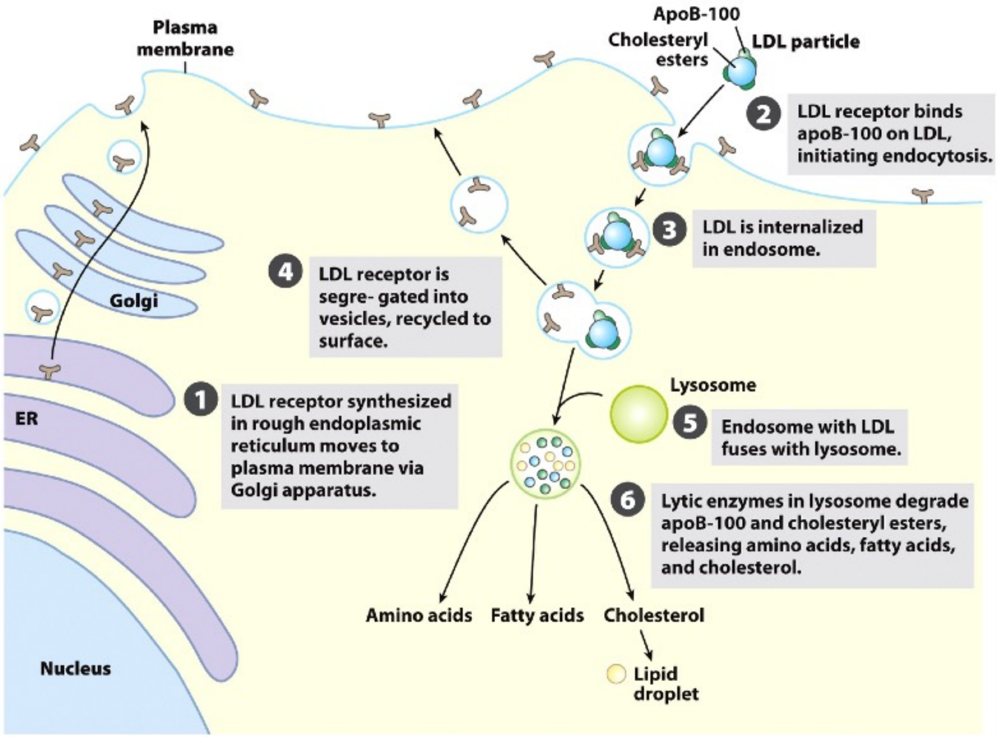
LDL Carries Cholesterol to Adipose Tissue

- LDL carries cholesterol to extrahepatic tissues such as adipose tissue
- Membrane receptors mediate uptake of cholesterol
- LDL not taken up returns to liver
  - Incorporated to membranes
  - Converted to bile acids
  - Re-esterified by ACAT



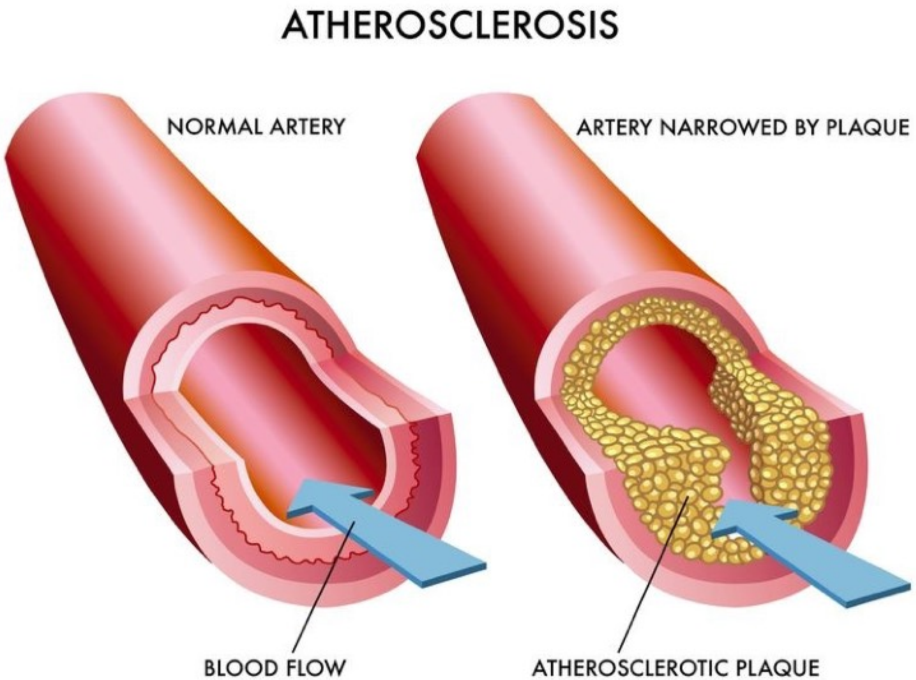
Cholesterol Enter Cells by Endocytosis

1. LDL receptor synthesized and transported to membrane
2. Binding of LDL to LDL receptor initiates endocytosis
3. LDL and LDL receptor form an endosome
4. LDL receptor returns to cell surface
5. Endosome fuses with lysosome
6. Enzymatic hydrolysis releases cholesterol and fatty acids

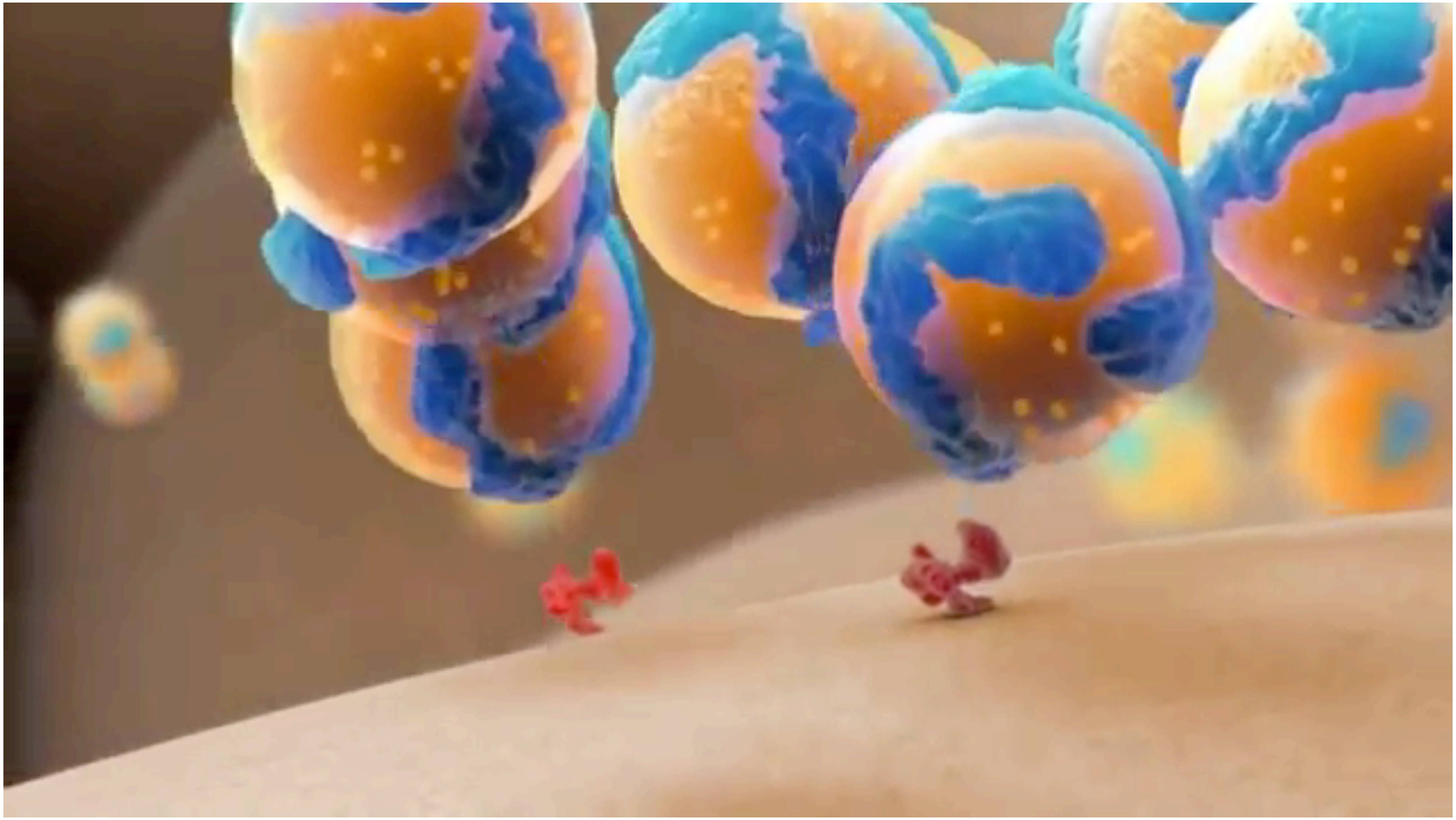


Familial Hypercholesterolemia (FH)

- Have mutations in LDL receptor
- Prevent normal uptake of LDL by liver and other tissues
- Result in high blood levels of LDL and cholesterol
  - A greatly increased probability of **atherosclerosis**
  - A cardiovascular disease in which blood vessels are occluded by cholesterol-rich plaques

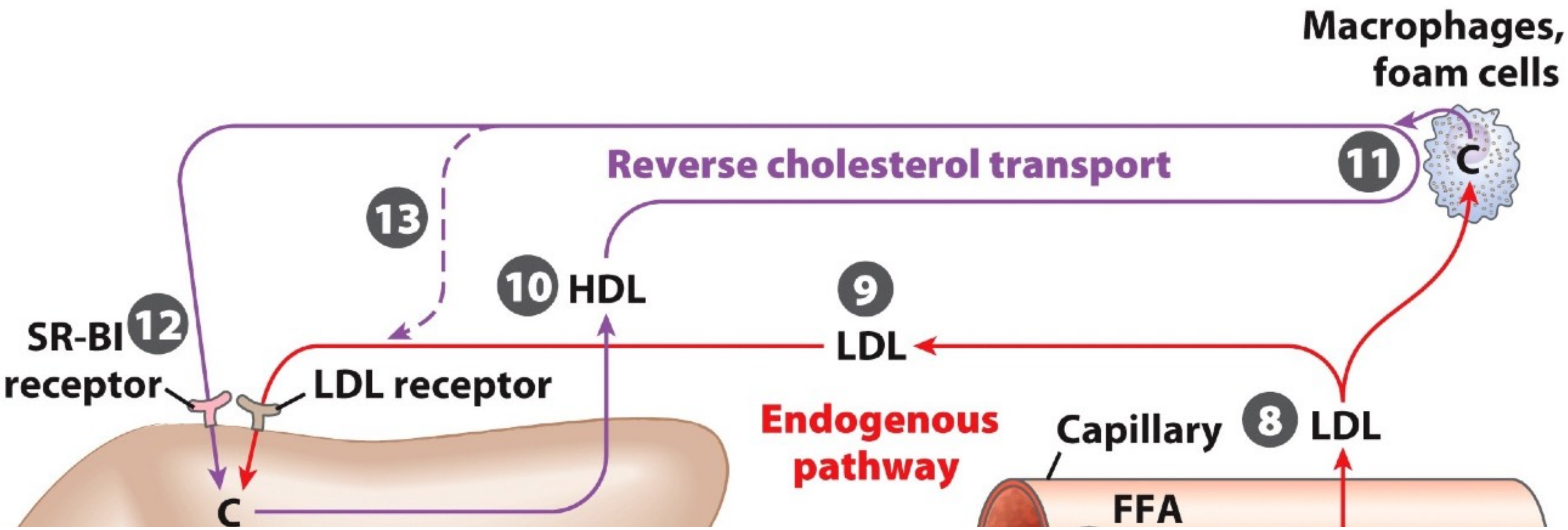


Familial Hypercholesterolemia (FH)



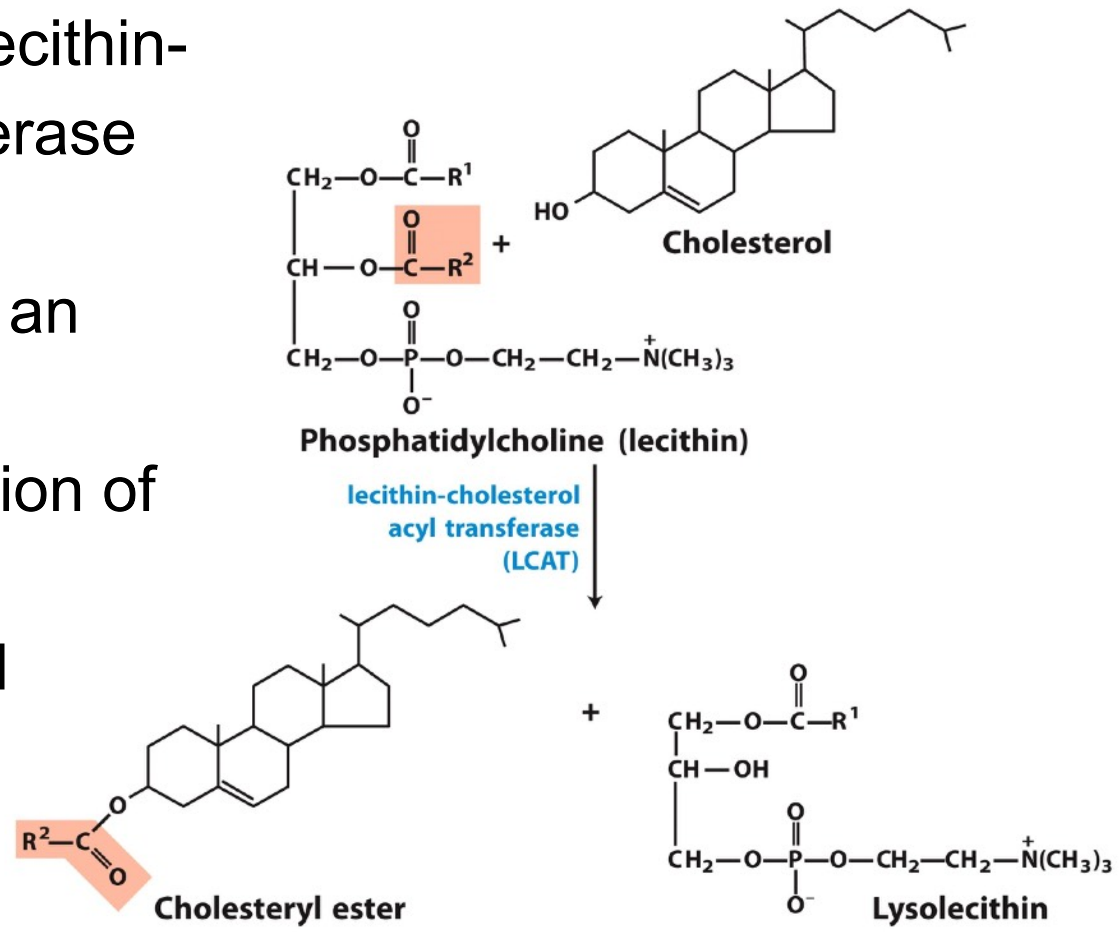
Reverse Cholesterol Transport by HDL

10. HDL are protein-rich and contain little cholesterol
11. HDL picks up cholesterol from blood and from cholesterol-rich extrahepatic cells such as macrophages and foam cells
12. HDL returns to liver and unloads cholesterol
    - Much cholesterol is converted to bile salts in liver and stored in gallbladder
13. Some cholesteryl esters in HDL are transferred to LDL



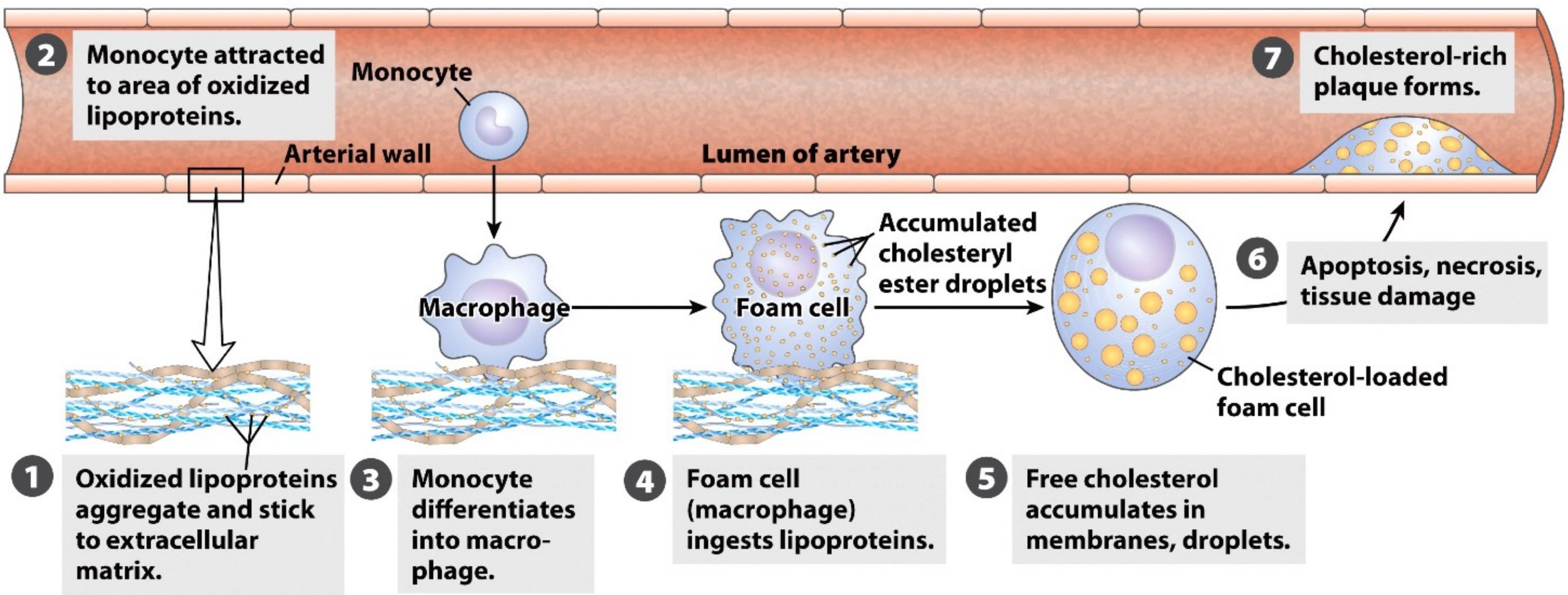
Transferase Enzyme on HDL Surface

- HDL contain enzyme lecithin-cholesterol acyl transferase (LCAT)
- Phosphatidylcholine is an example of lecithin
- LCAT catalyzes formation of cholesteryl esters from lecithin and cholesterol



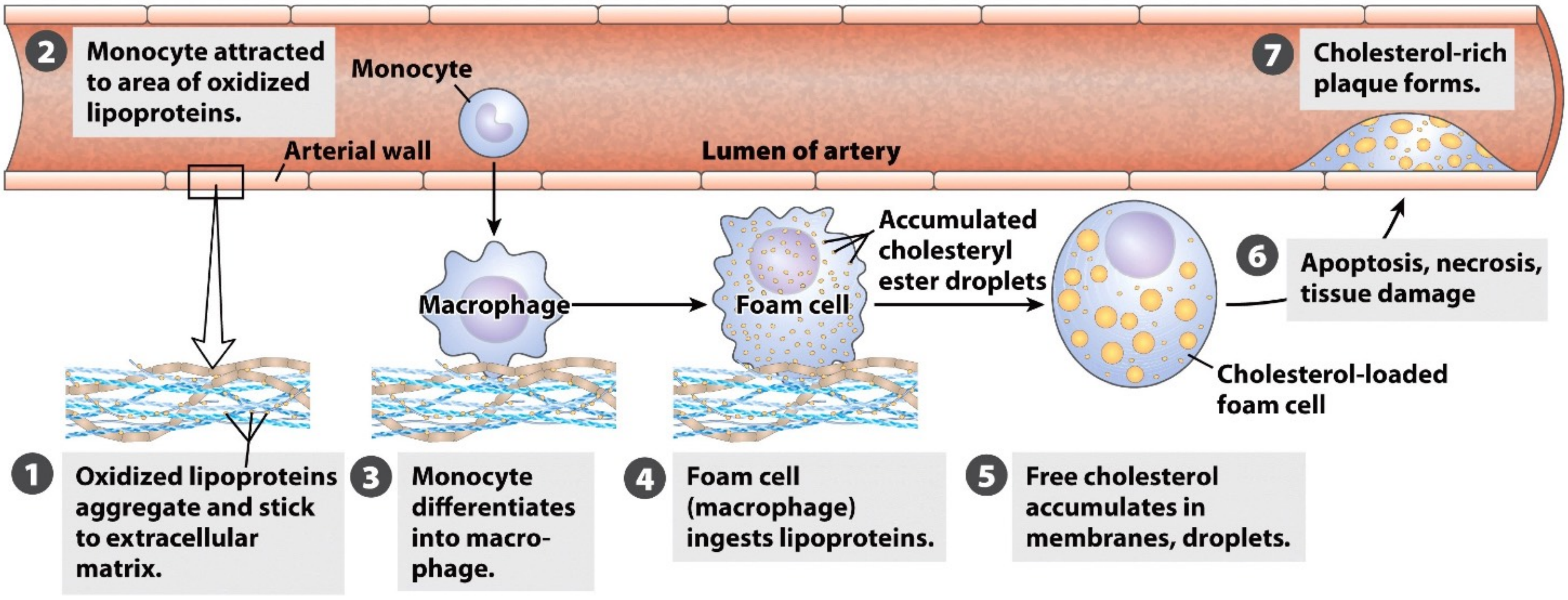
Atherosclerosis Linked to LDL Levels

- Pathological accumulation of cholesterol obstructs blood vessels
  - Synthesized + Dietary > Required [membrane + bile + steroid]
- Linked to high [LDL]. Negative correlation with HDL
  - LDL often called “bad cholesterol”, and HDL often called “good cholesterol”



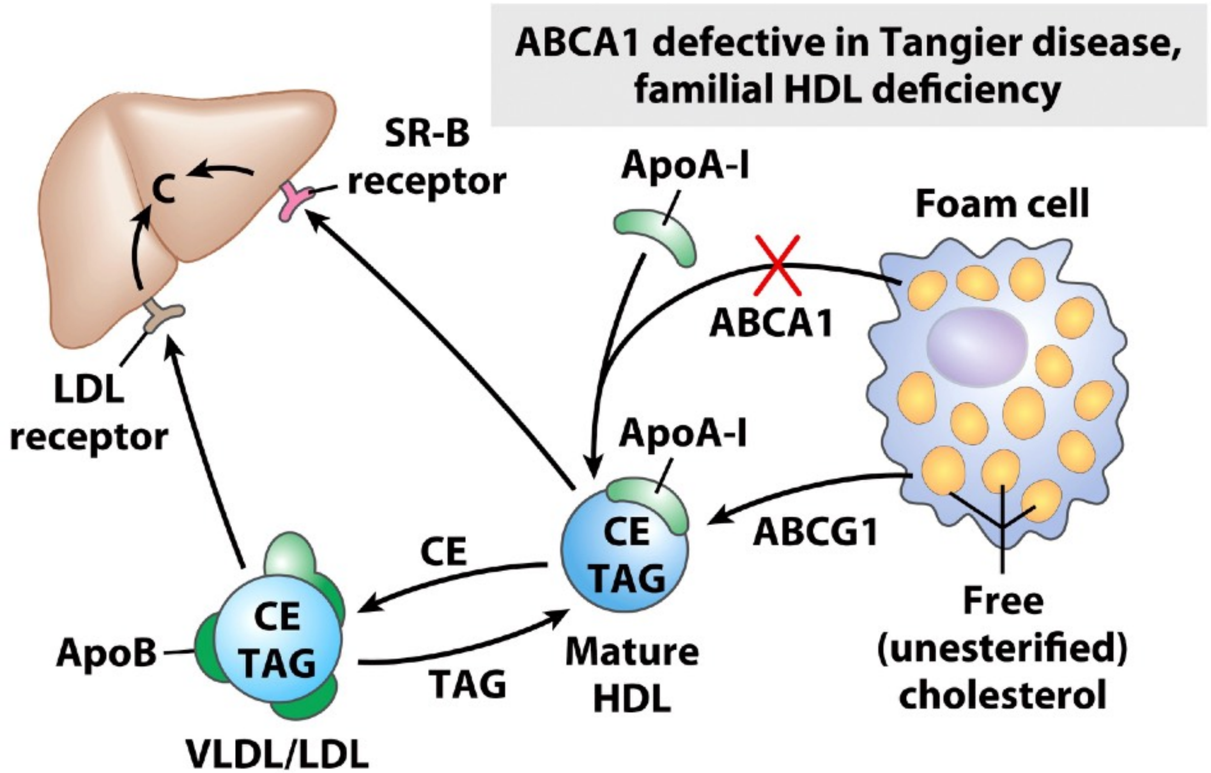
How LDL Causes Atherosclerosis

- Plaque formation is initiated when LDL accumulates
- Immune cells are attracted. Monocyte -> macrophage -> foam cell
- Foam cells undergo apoptosis. Artery becomes progressively occluded as plaques gradually become larger



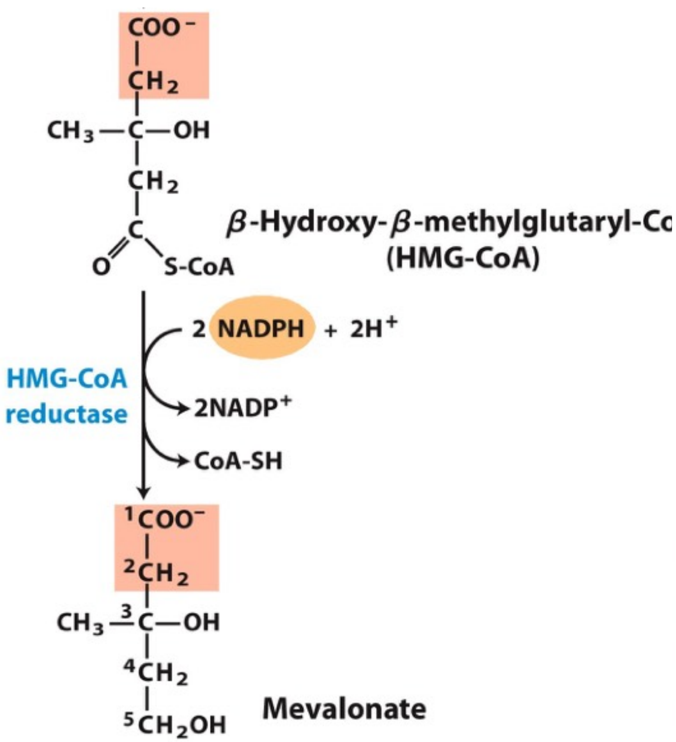
HDL Counters Plaque Formation

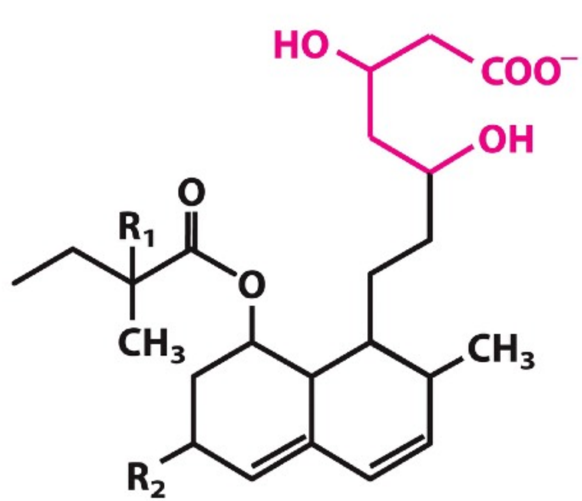
- HDL picks up cholesterol stored in extrahepatic tissues (including foam cells) and carries it back to liver
- Two transporters (ABCA1 and ABCG1) move cholesterol from inside the cell to outer surface of membrane

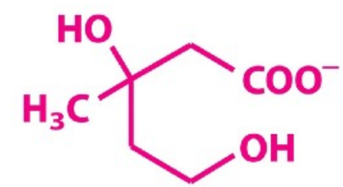


Treat FH Patients with Statins

- Patients have defective LDL receptor
- Cholesterol synthesis continues despite excessive cholesterol in blood
- Statins resemble mevalonate and inhibit HMG-CoA reductase





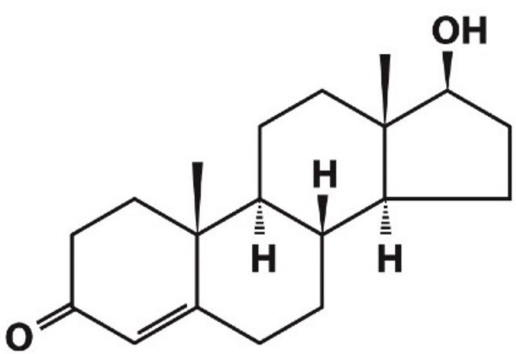


Mevalonate

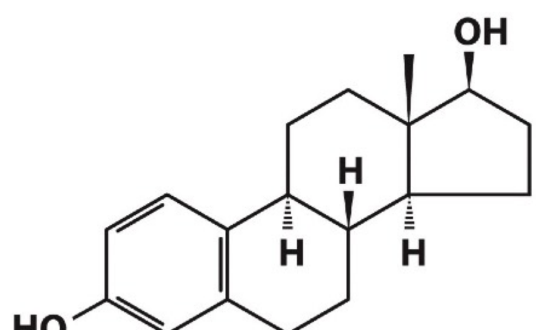
$R_1 = H$	$R_2 = H$	Compactin
$R_1 = CH_3$	$R_2 = CH_3$	Simvastatin (Zocor)
$R_1 = H$	$R_2 = OH$	Pravastatin (Pravachol)
$R_1 = H$	$R_2 = CH_3$	Lovastatin (Mevacor)

Steroid Hormones Made From Cholesterol

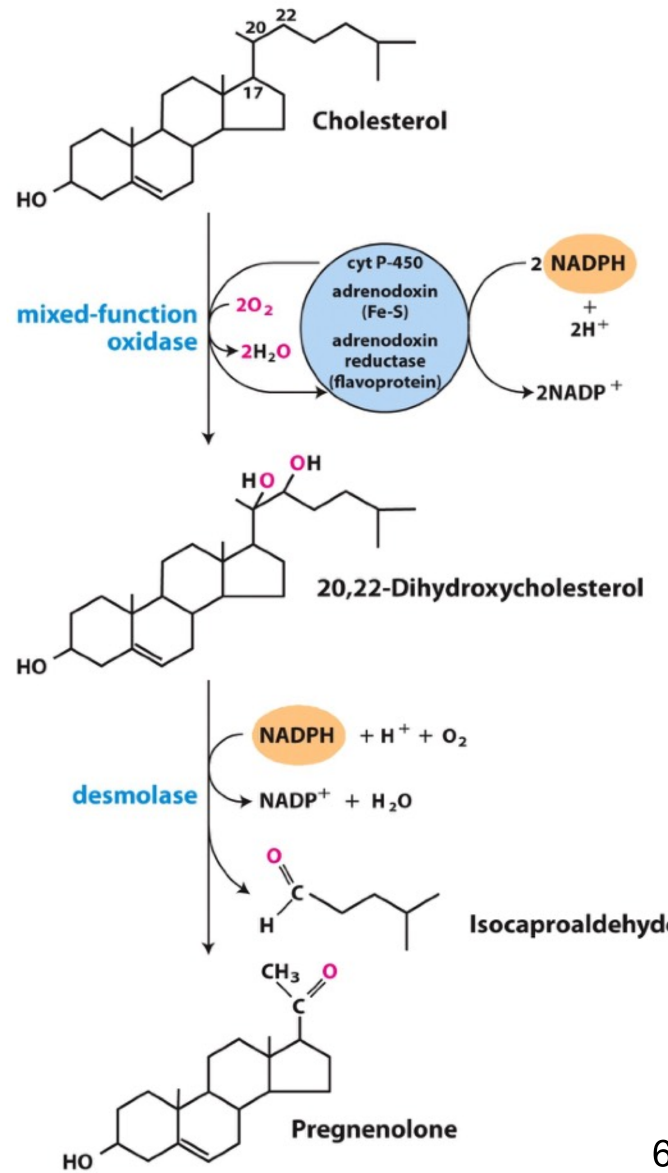
- Humans derive all their steroid hormones from cholesterol
- Steroid hormones are effective at very low concentrations, and are synthesized in small quantities
- Synthesis requires removal of some or all of carbons in side chain on C-17



Testosterone



β-Estradiol



Summary 21.4 Cholesterol

- Cholesterol is formed from acetyl-CoA in a complex series of reactions, through mevalonate, activated isoprenes, noncyclic squalene, and steroid ring system
- Cholesterol is carried in blood as lipoproteins. LDL, rich in cholesterol, is taken up by receptor-mediated endocytosis. HDL removes cholesterol from peripheral tissues and carries it to liver
- Dietary conditions or genetic defects may lead to atherosclerosis. In reverse cholesterol transport, HDL protects against atherosclerosis

Example Question

If malonyl-CoA is synthesized from $^{14}CO_2$ and unlabeled acetyl-CoA, and the labeled malonate is then used for fatty acid synthesis, the final product (fatty acid) will have radioactive carbon in:

A) every C.
B) every even-numbered C-atom.
C) every odd-numbered C-atom.
D) no part of the molecule.
E) only the omega-carbon atom (farthest carbon from C-1).

Example Question

Explain why patients with a genetic defect called familial hypercholesterolemia have an elevated blood serum cholesterol level.