Lipid Metabolism
Transport; Fatty Acid Degradation and Synthesis; Ketone Bodies

CHEM 420 – Principles of Biochemistry
Instructor – Anthony S. Serianni

Chapter 25: Voet/Voet, *Biochemistry*, 2011
Fall 2015

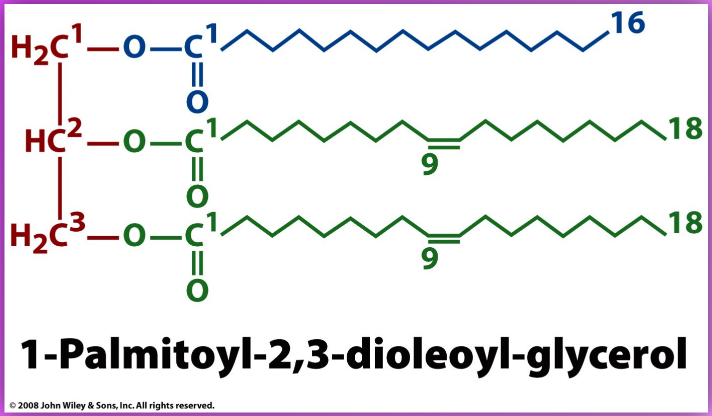
December 2 & 4

Energy content of food constituents

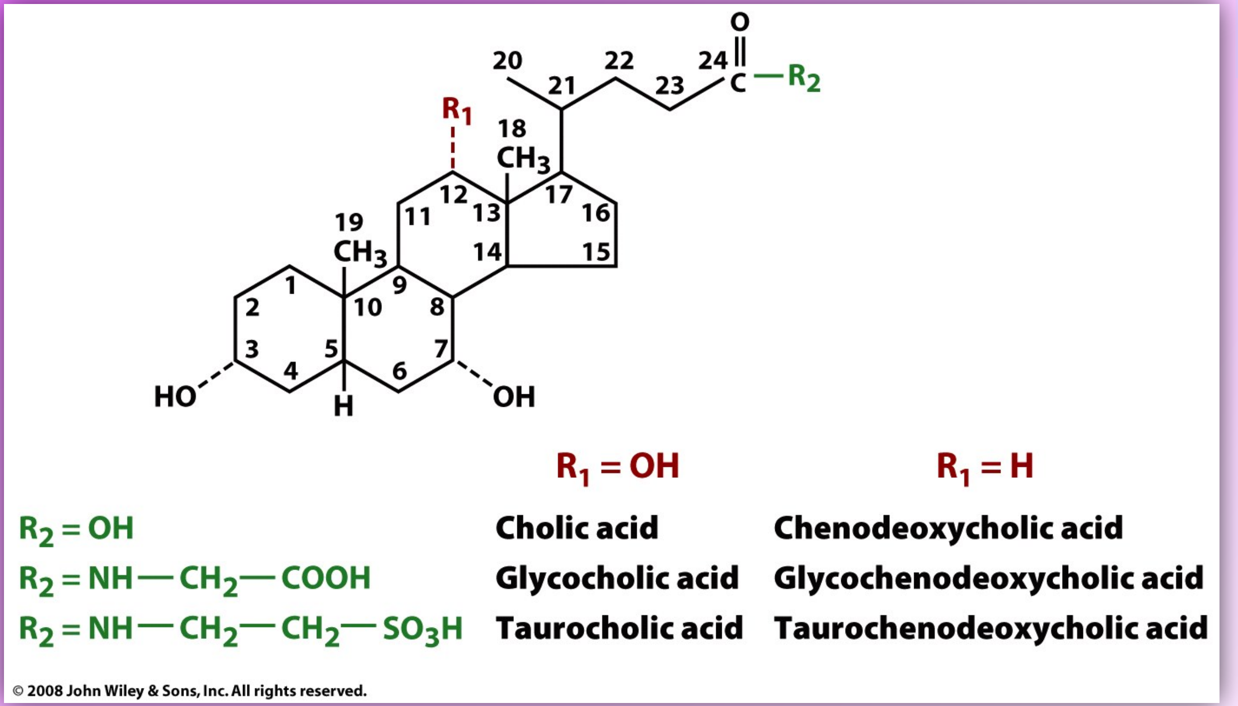
Constituent	$\Delta H (\text{kJ} \cdot \text{g}^{-1}$ dry weight)
Carbohydrate	16
Fat	37
Protein	17

Source: Newsholme, E.A. and Leech, A.R., *Biochemistry for the Medical Sciences*, p. 16, Wiley (1983).

Examples of lipids

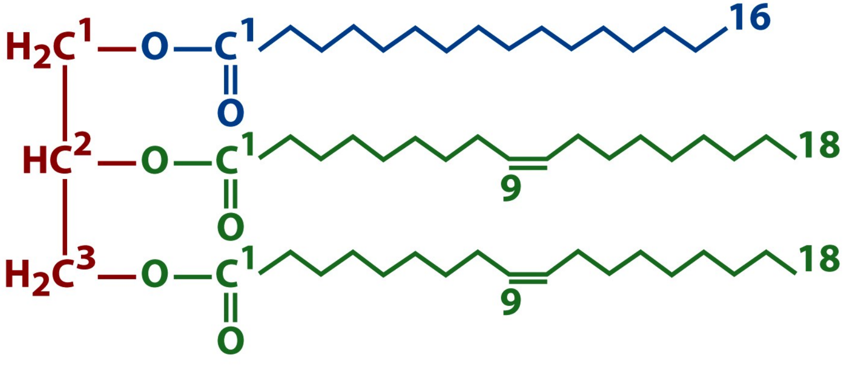


triacylglycerol



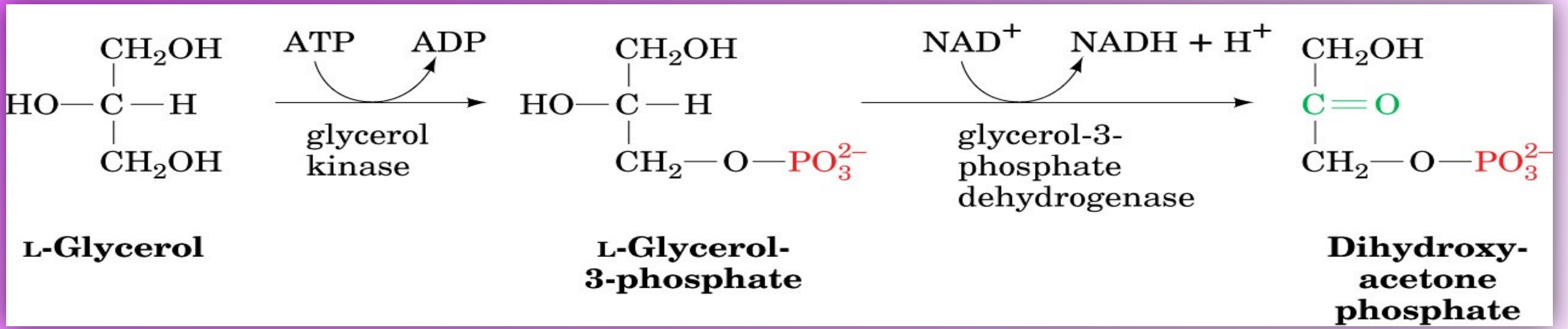
sterols

Dietary triacylglycerols are hydrolyzed before they are absorbed. Intestinal lipases are responsible for the hydrolysis of the fatty acid ester bonds in triacylglycerols, giving free fatty acids and glycerol as products.

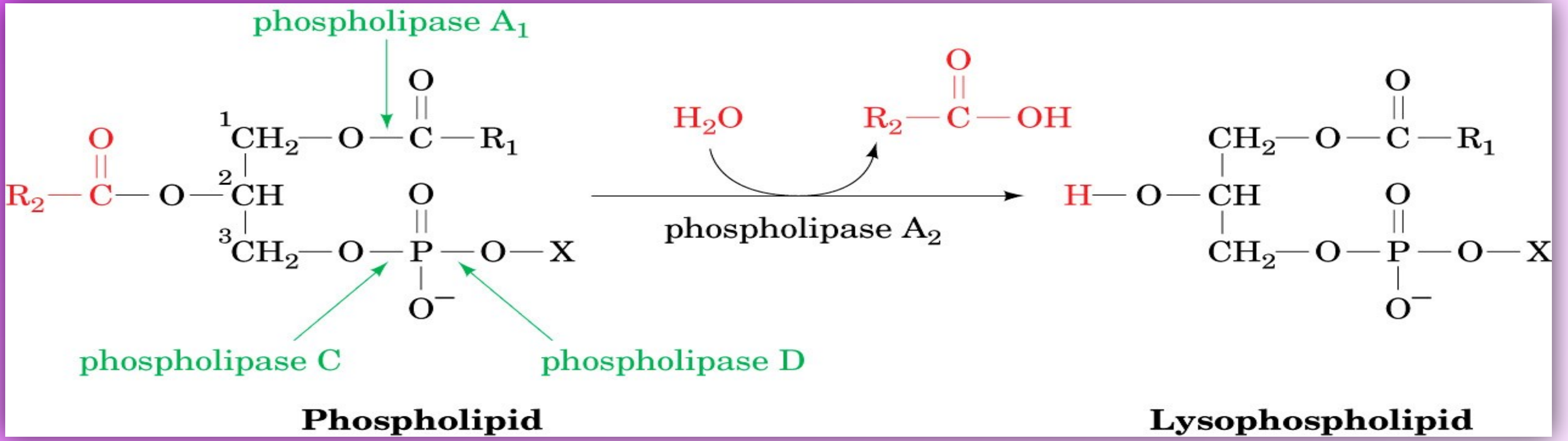


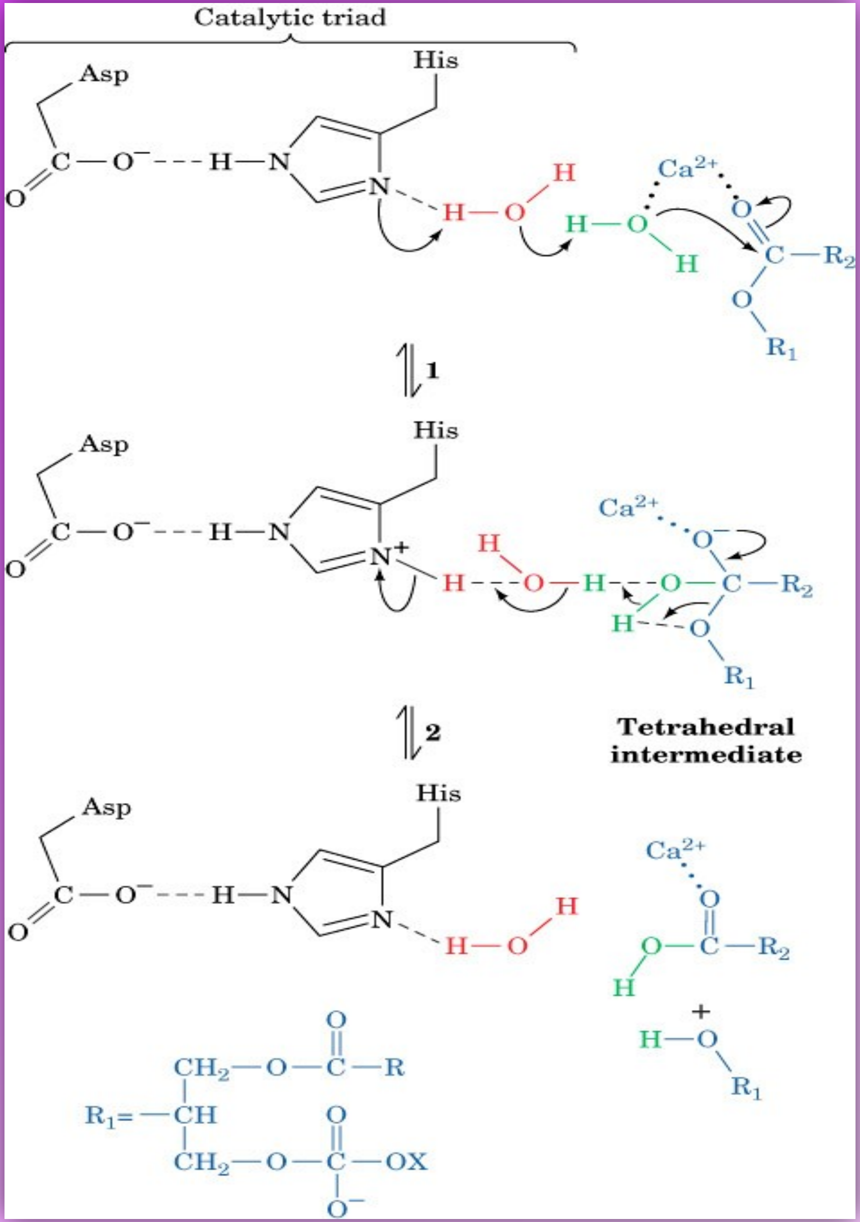
1-Palmitoyl-2,3-dioleoyl-glycerol

Conversion of glycerol to the glycolytic intermediate, dihydroxyacetone phosphate (DHAP)

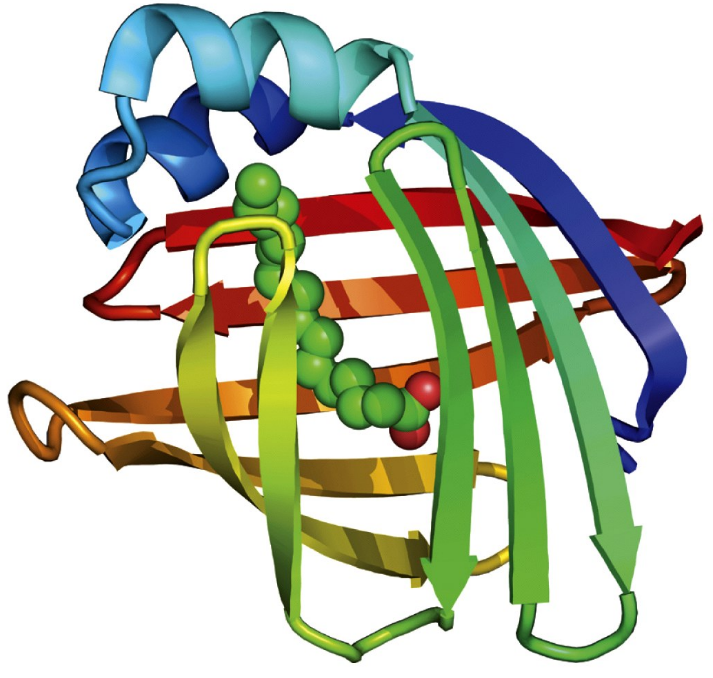


Catalytic action of phospholipase A_2





The catalytic mechanism of phospholipase A_2



Intestinal fatty acid-binding protein in complex with palmitate

Facilitates the absorption of lipids by cells lining the small intestine (intestinal mucosa)

Lipids are transported by the blood as lipoproteins. Lipoproteins are complexes of lipid and protein. They are globular micelle-like particles consisting of a non-polar core of triacylglycerols and cholesterol esters surrounded by an amphipathic coating of protein, phospholipid and cholesterol. There are five classes of lipoproteins.

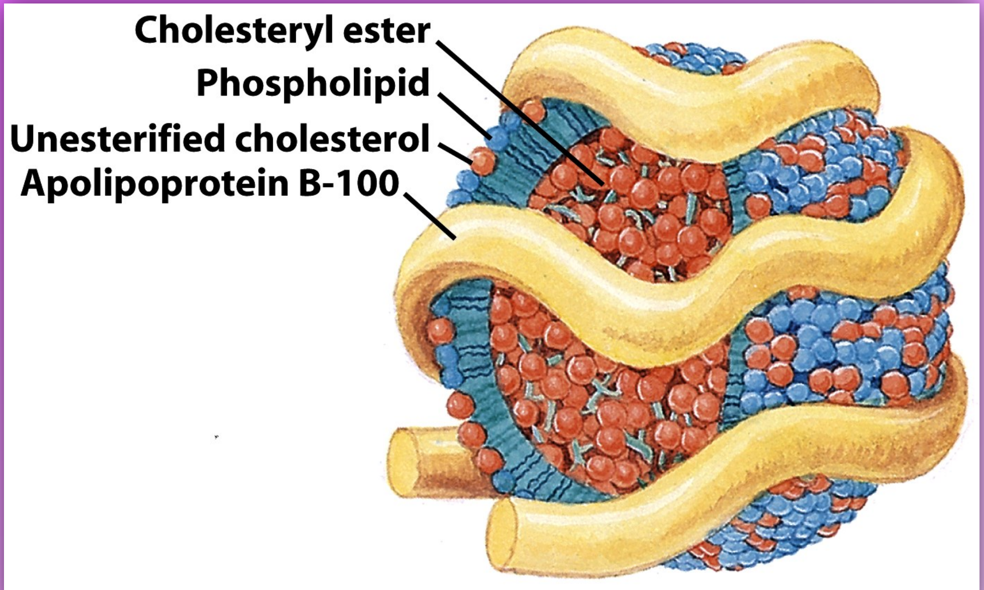


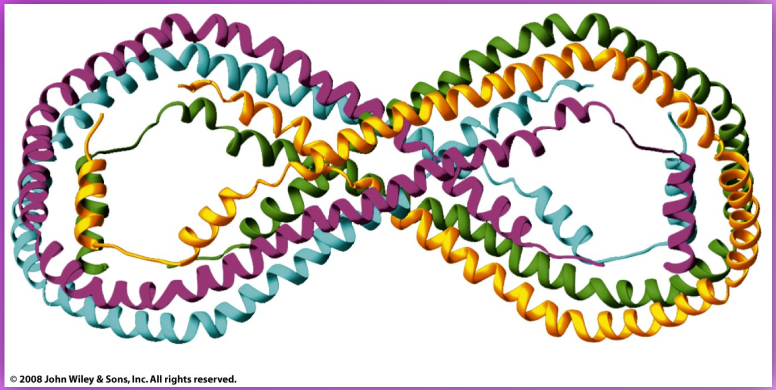
Diagram of low density lipoproteins (LDL), the major cholesterol carrier in the blood

Table 20-1 Characteristics of the Major Classes of Lipoproteins in Human Plasma

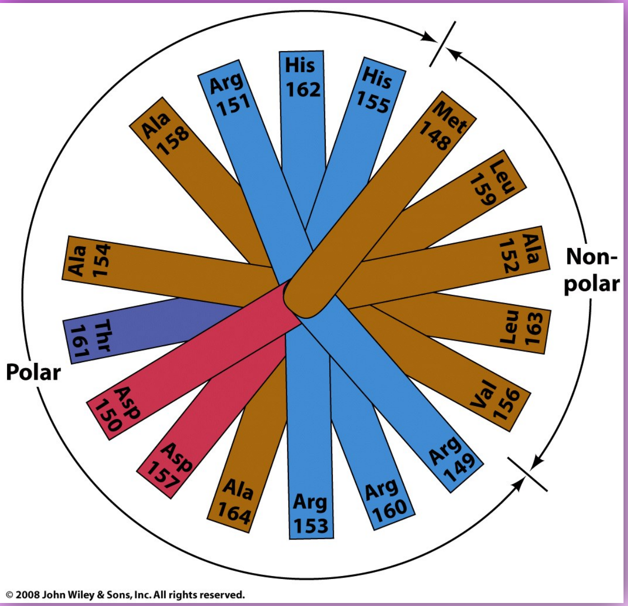
	Chylomicrons	VLDL	IDL	LDL	HDL
Density ($g \cdot cm^{-3}$)	<0.95	<1.006	1.006–1.019	1.019–1.063	1.063–1.210
Particle diameter (Å)	750–12,000	300–800	250–350	180–250	50–120
Particle mass (kD)	400,000	10,000–80,000	5000–10,000	2300	175–360
% Protein[a]	1.5–2.5	5–10	15–20	20–25	40–55
% Phospholipids[a]	7–9	15–20	22	15–20	20–35
% Free cholesterol[a]	1–3	5–10	8	7–10	3–4
% Triacylglycerols[b]	84–89	50–65	22	7–10	3–5
% Cholesteryl esters[b]	3–5	10–15	30	35–40	12
Major apolipoproteins	A-I, A-II, B-48, C-I, C-II, C-III, E	B-100, C-I, C-II, C-III, E	B-100, C-I, C-II, C-III, E	B-100	A-I, A-II, C-I, C-II, C-III, D, E

[a]Surface components
[b]Core lipids.

Apolipoproteins coat lipoprotein surfaces.



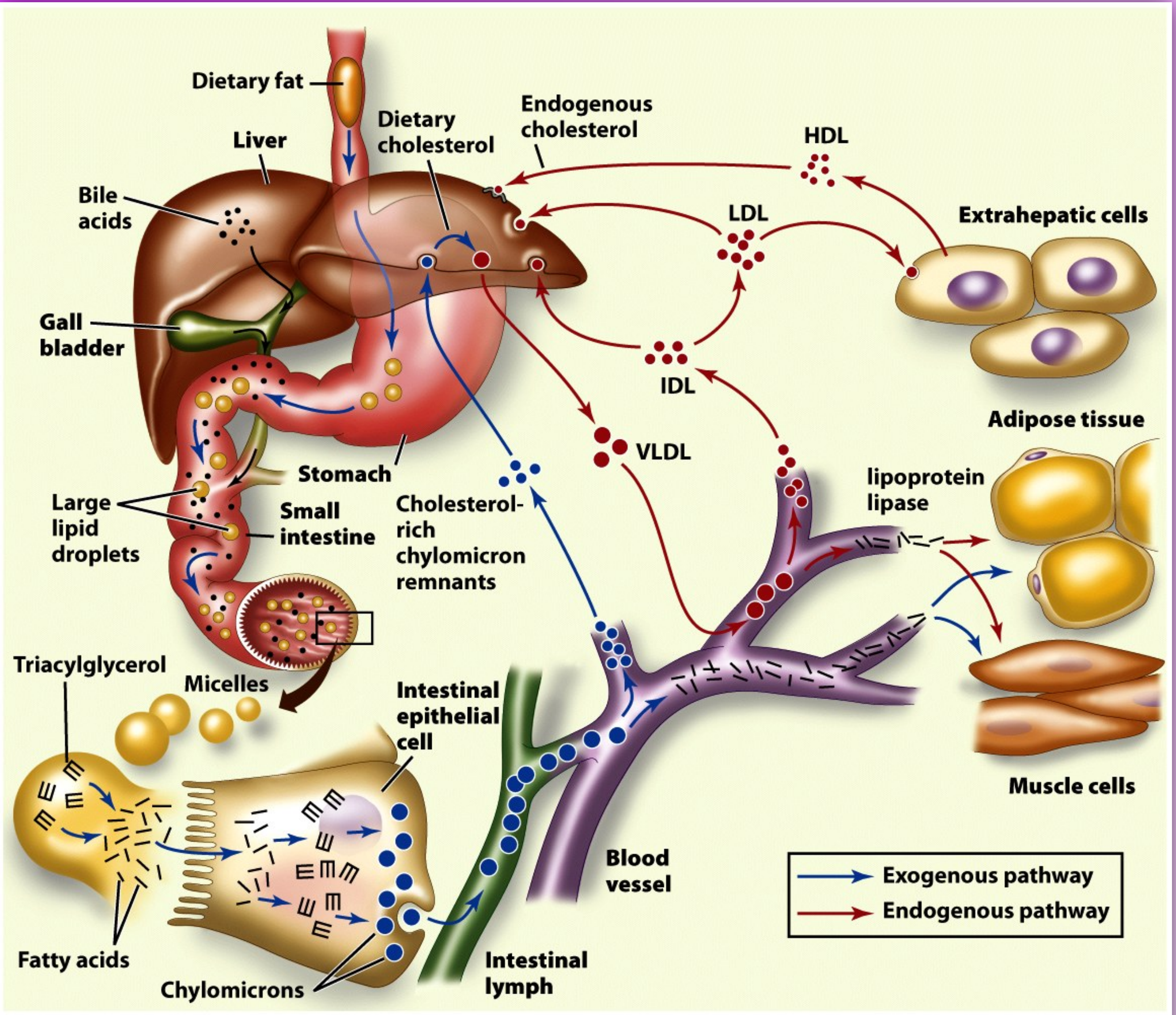
Structure of human apolipoprotein A-I (apoA-I, homotetramer)



Helical wheel projection of the amphipathic α helix constituting residues 148 to 164 of apoA-I

Intestinal mucosal cells convert <u>dietary</u> fatty acids to triacylglycerols and package them into lipoproteins called **chylomicrons**. Chylomicrons are released into the intestinal lymph and from there are transported to large veins. The blood then delivers chylomicrons throughout the body.

VLDLs, IDLs and LDLs are synthesized by the *liver* to transport *endogenous* triacylglycerols from liver to tissues. HDLs transport lipids from the tissues back to the liver.



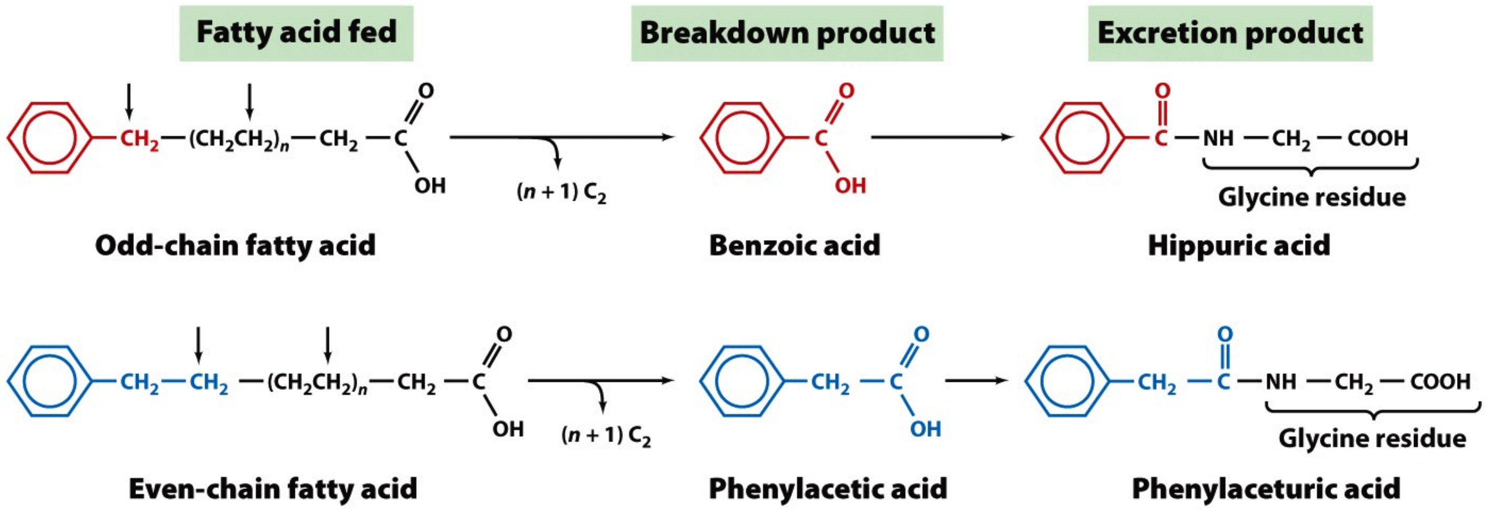
Plasma triacylglycerol and cholesterol transport in humans

Triacylglycerols stored in adipocytes are mobilized by the action of hormone-sensitive lipase. The free fatty acids are released into the bloodstream, where they bind to albumin.

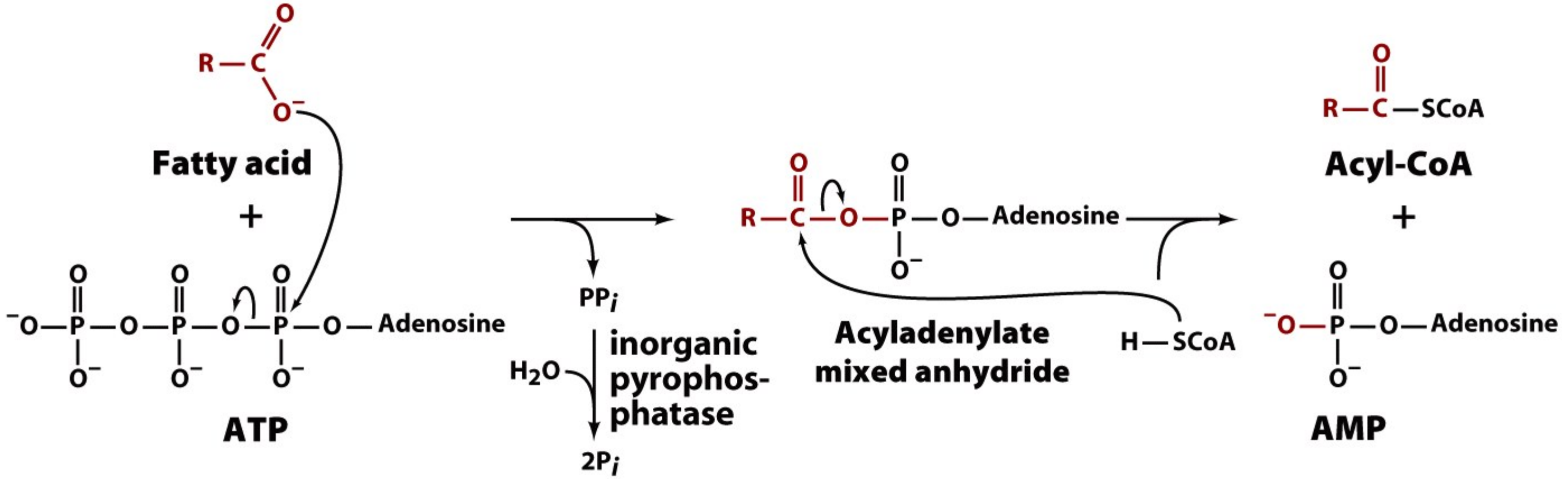
X-Ray structure of human serum albumin in complex with 7 molecules of palmitic acid

Degradation of fatty acids

Classic experiment (Knoop) showing that fatty acids are metabolically oxidized at their β-carbon atom

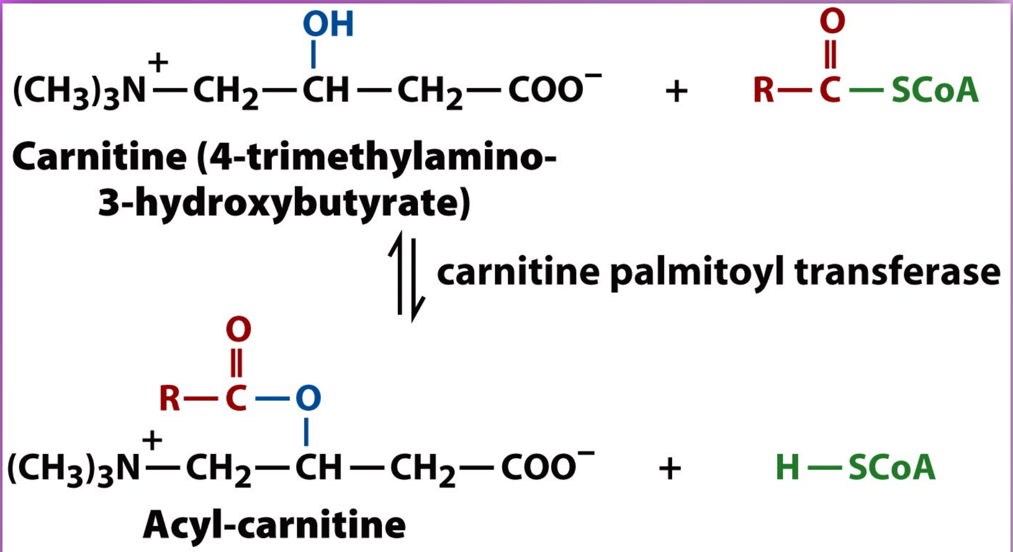


Biological activation of a fatty acid: Fatty acyl CoAs synthesized by acyl-CoA synthetases (thiokinases)

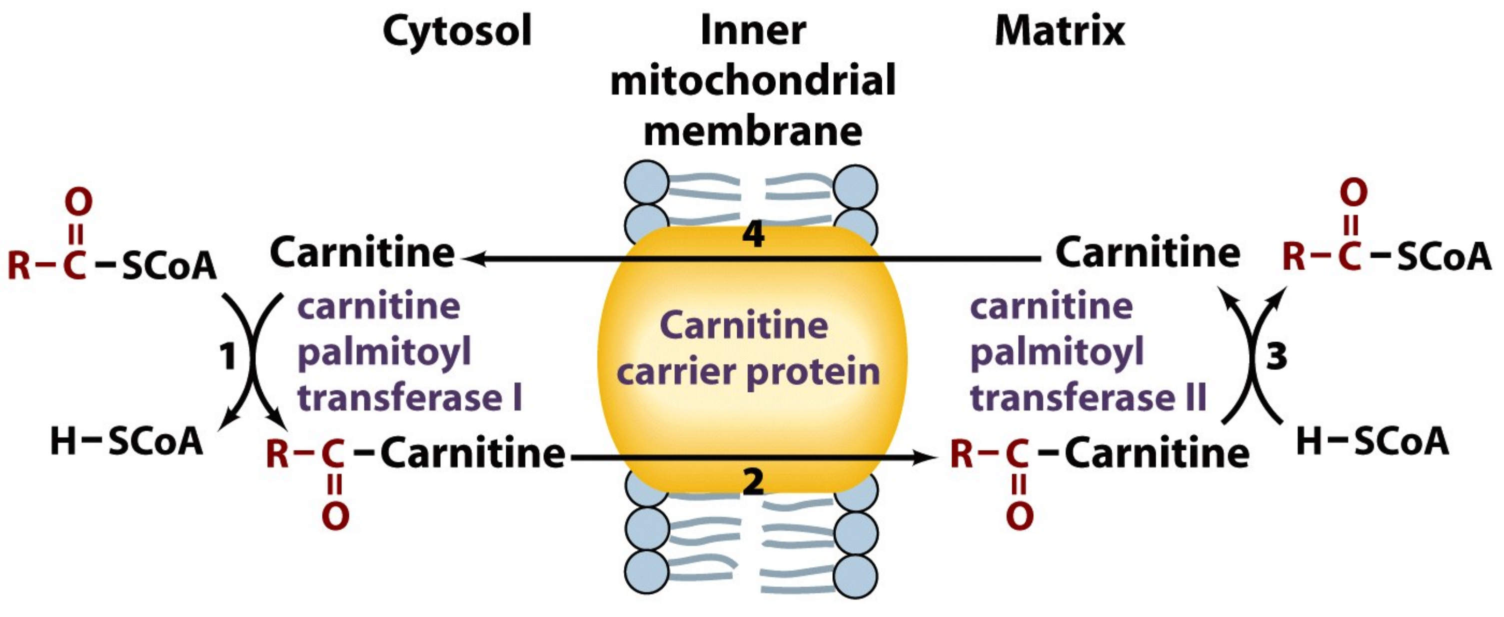


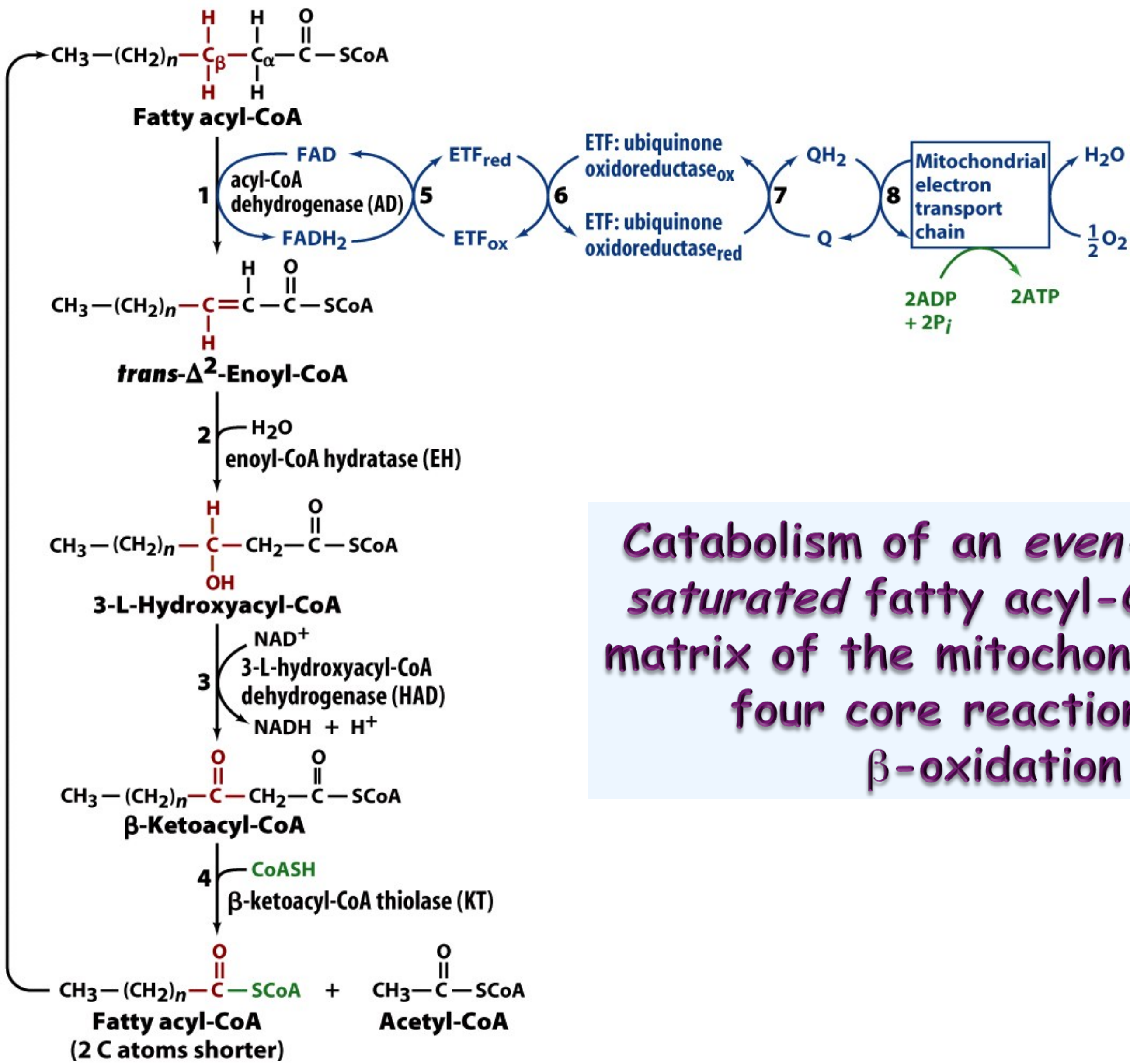
Reaction occurs in the ER or outer mitochondrial membrane

Transport of fatty acyl groups into mitochondria: conversion of a fatty acyl CoA to a fatty acyl carnitine derivative

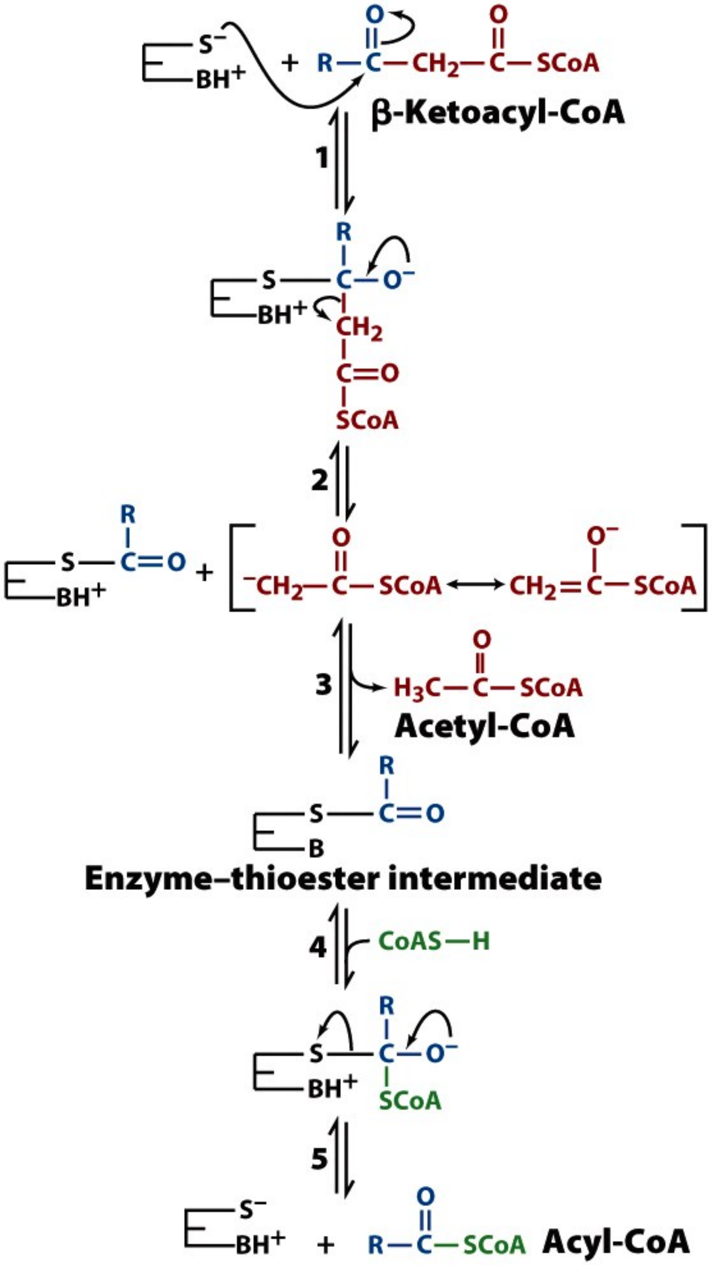


Transport of fatty acids into the mitochondrion





Catabolism of an *even-numbered saturated* fatty acyl-CoA in the matrix of the mitochondrion: the four core reactions of β-oxidation



Mechanism of action of β-ketoacyl-CoA thiolase

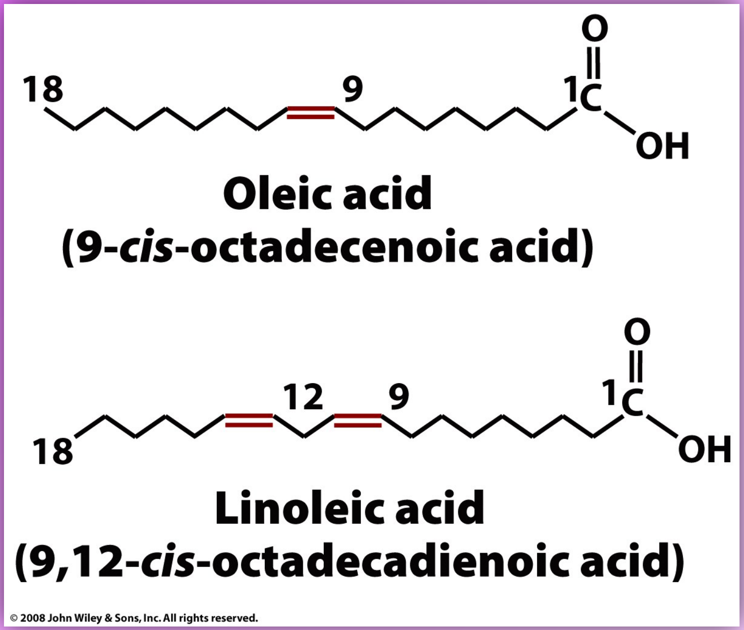
Fatty acid oxidation is exergonic.

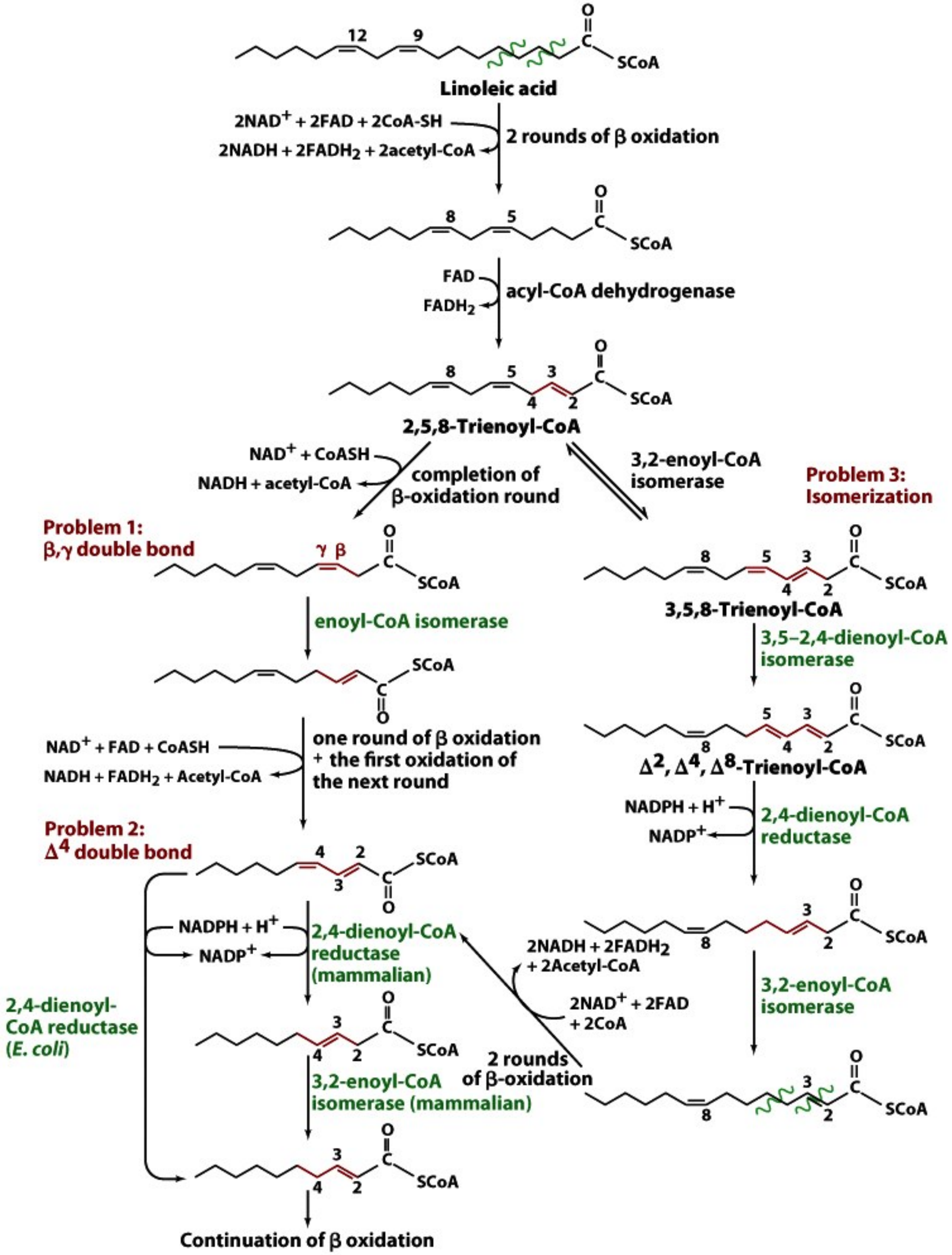
Example: C_{16} fatty acid (palmitic acid): involves seven rounds of β-oxidation, yielding 7 $FADH_2$, 7 NADH, and 8 acetyl CoAs. Oxidation of the 8 acetyl CoAs yields 8 GTP, 24 NADH, and 8 $FADH_2$. Ox/Phos of the 31 NADH gives 77.5 ATP, and 22.5 ATP are generated from the 15 $FADH_2$.

2 ATP equivalents are subtracted for fatty acyl-CoA formation.

Thus, the complete oxidation of palmitic acid gives a net yield of 106 ATP.

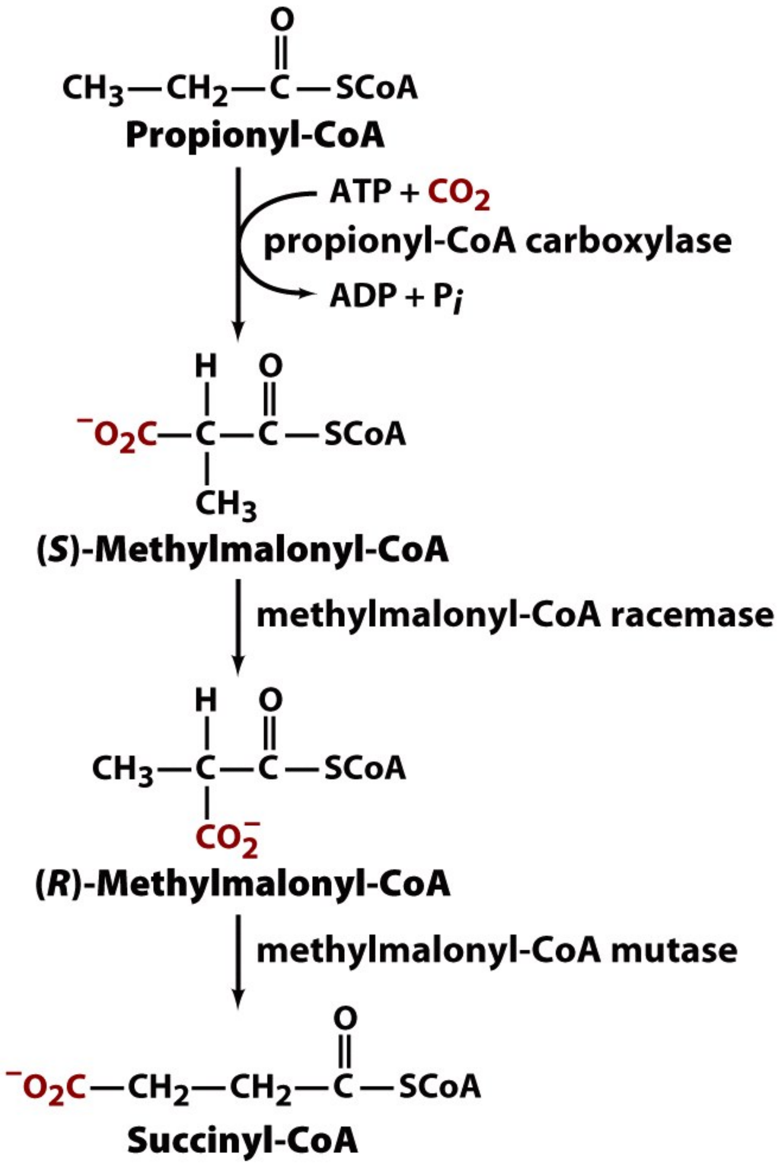
Additional degradative enzymes are needed to oxidize unsaturated fatty acids



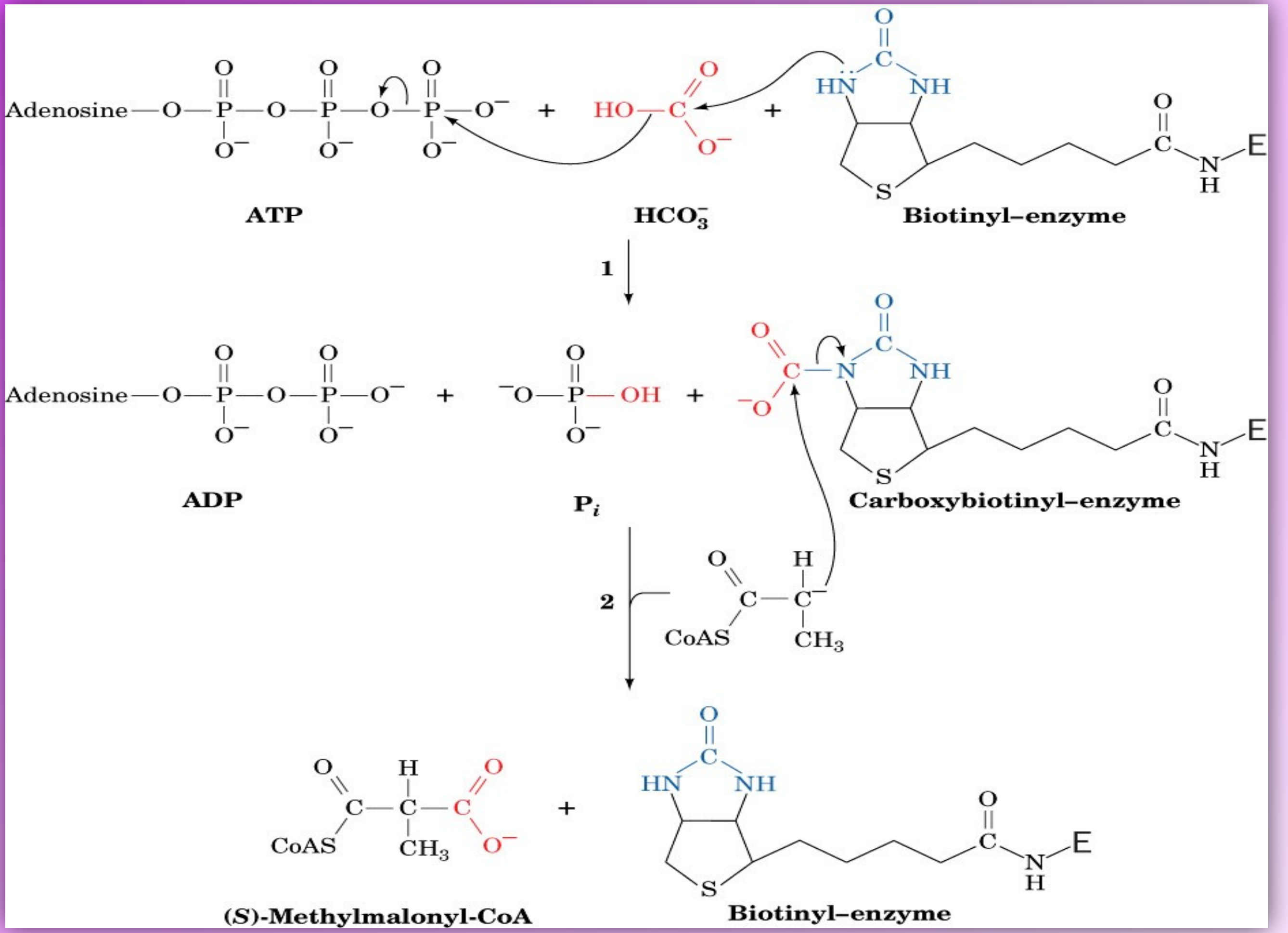


Biological oxidation of linoleic acid

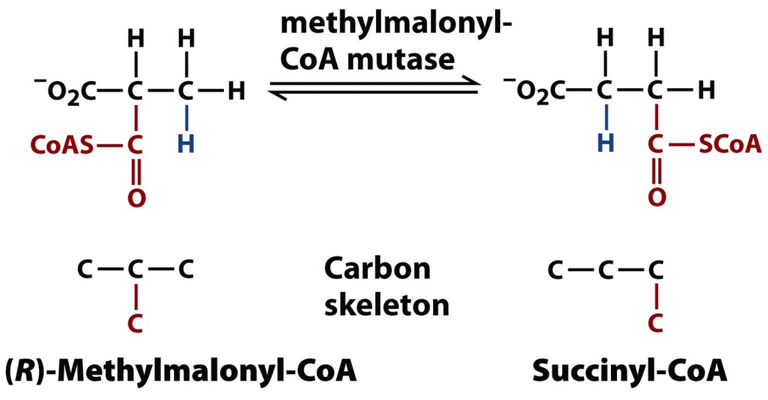
Oxidation of odd-carbon saturated fatty acids

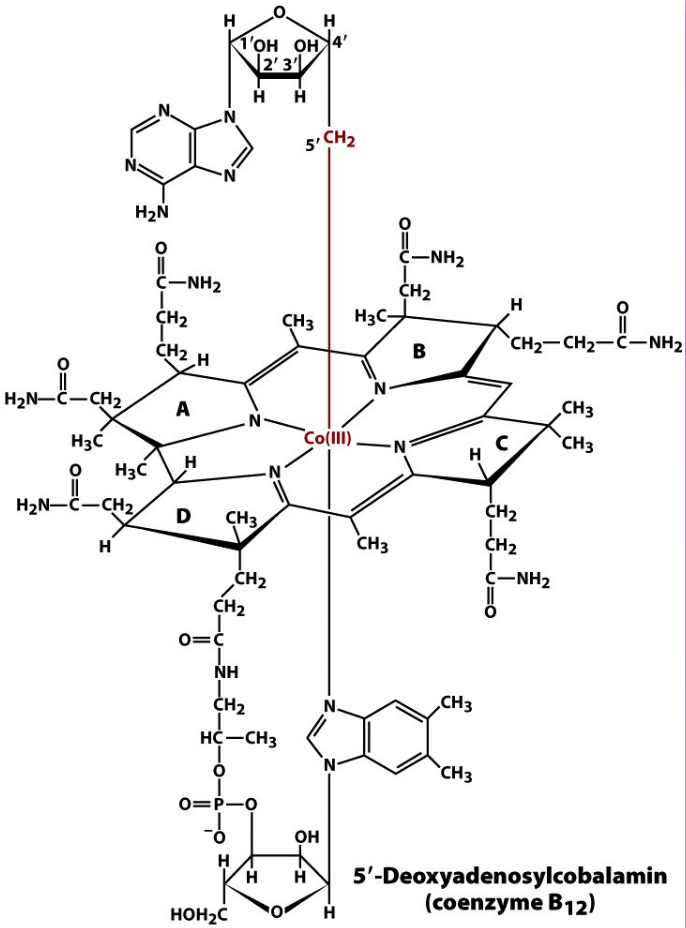


The propionyl-CoA carboxylase reaction

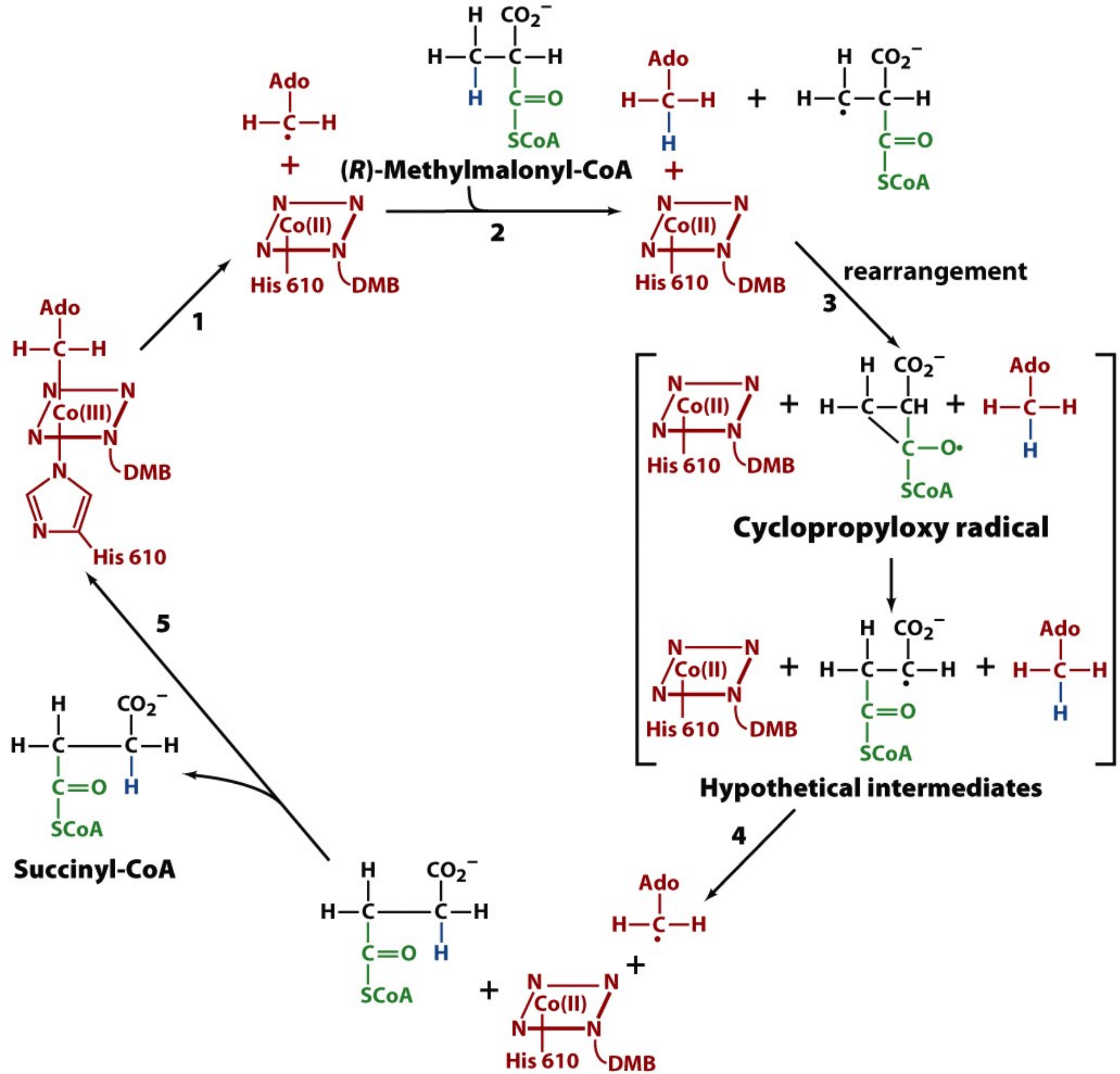


Conversion of (*R*)-methylmalonyl-CoA to succinyl-CoA: Methylmalonyl-CoA mutase

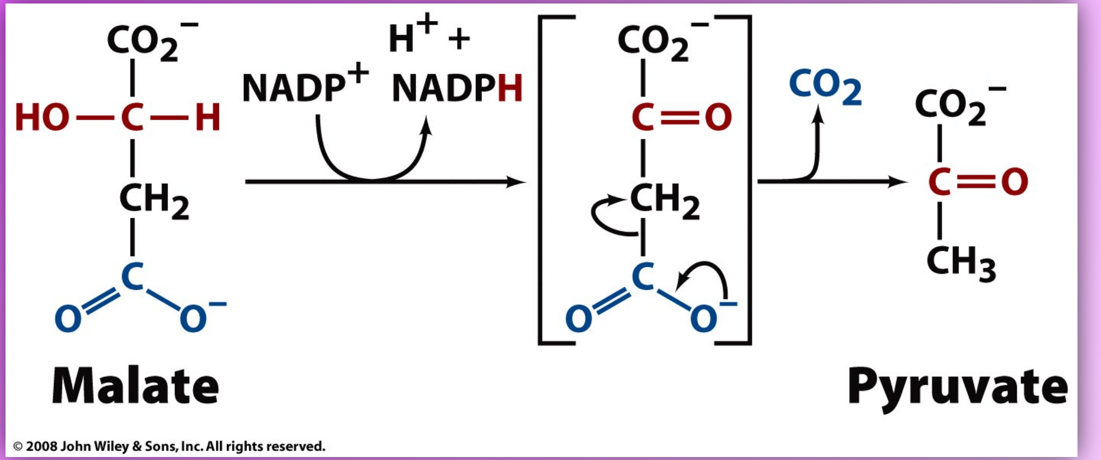




Mechanism of methylmalonyl CoA mutase

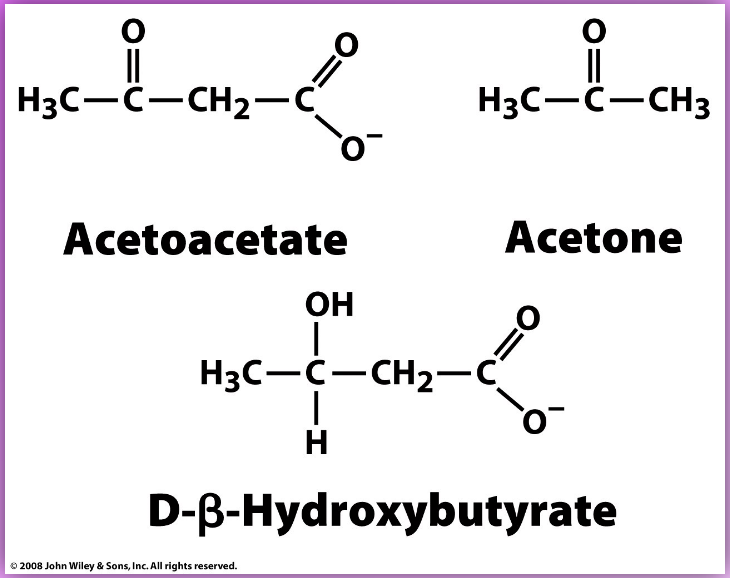


Reaction catalyzed by malic enzyme



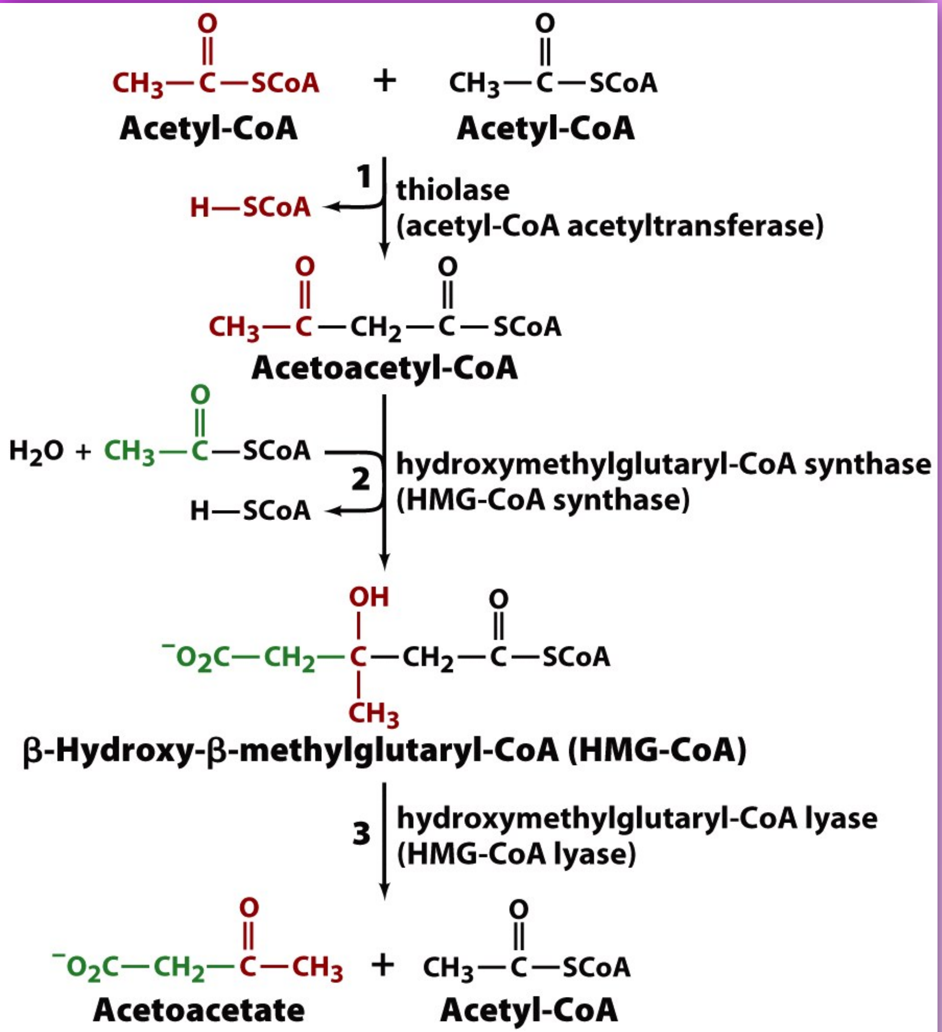
In order for succinyl CoA to undergo *net* oxidation by the TCA cycle, it must first be converted to pyruvate and thence to acetyl CoA.

Ketone bodies are produced by the liver as a means of distributing acetyl CoA to other tissues in the body. Ketone body formation is commonly associated with starvation conditions, where glycogen stores in the body have been depleted, and fats become the major fuel source. Under these conditions, brain cells convert to ketone bodies as their fuel source (normally, only glucose is used by these cells).



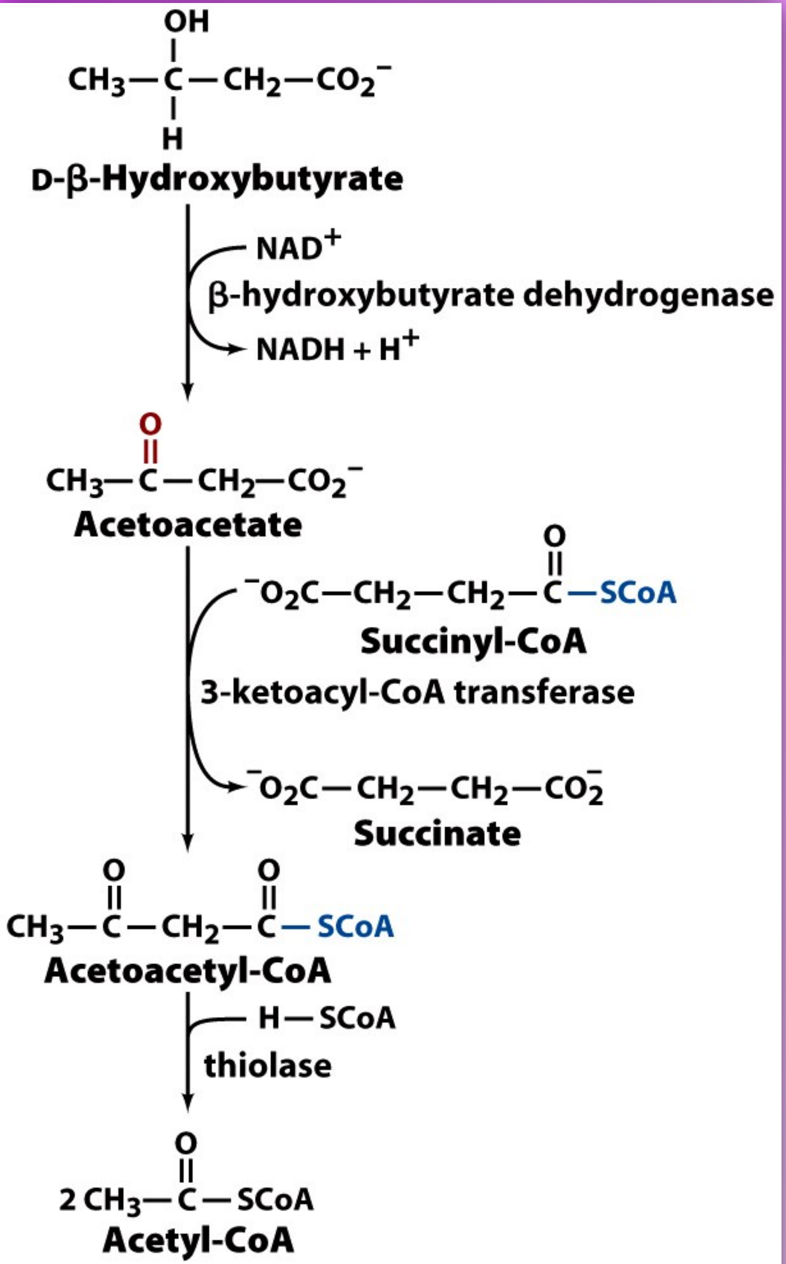
Examples of ketone bodies

The reactions of ketogenesis



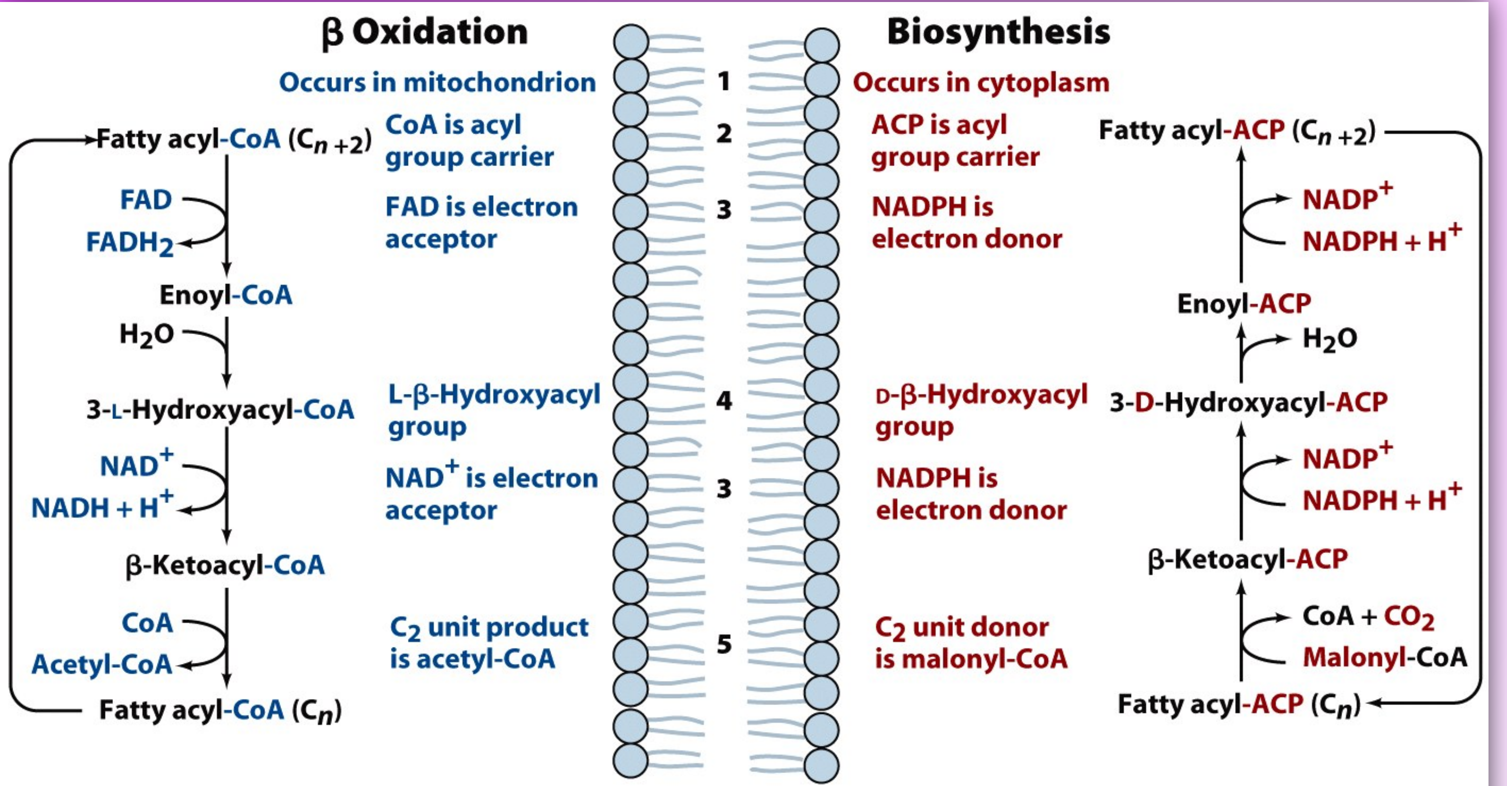
Acetoacetate can be reduced by NAD^+-linked β-hydroxybutyrate dehydrogenase to give D-β-hydroxybutyrate.

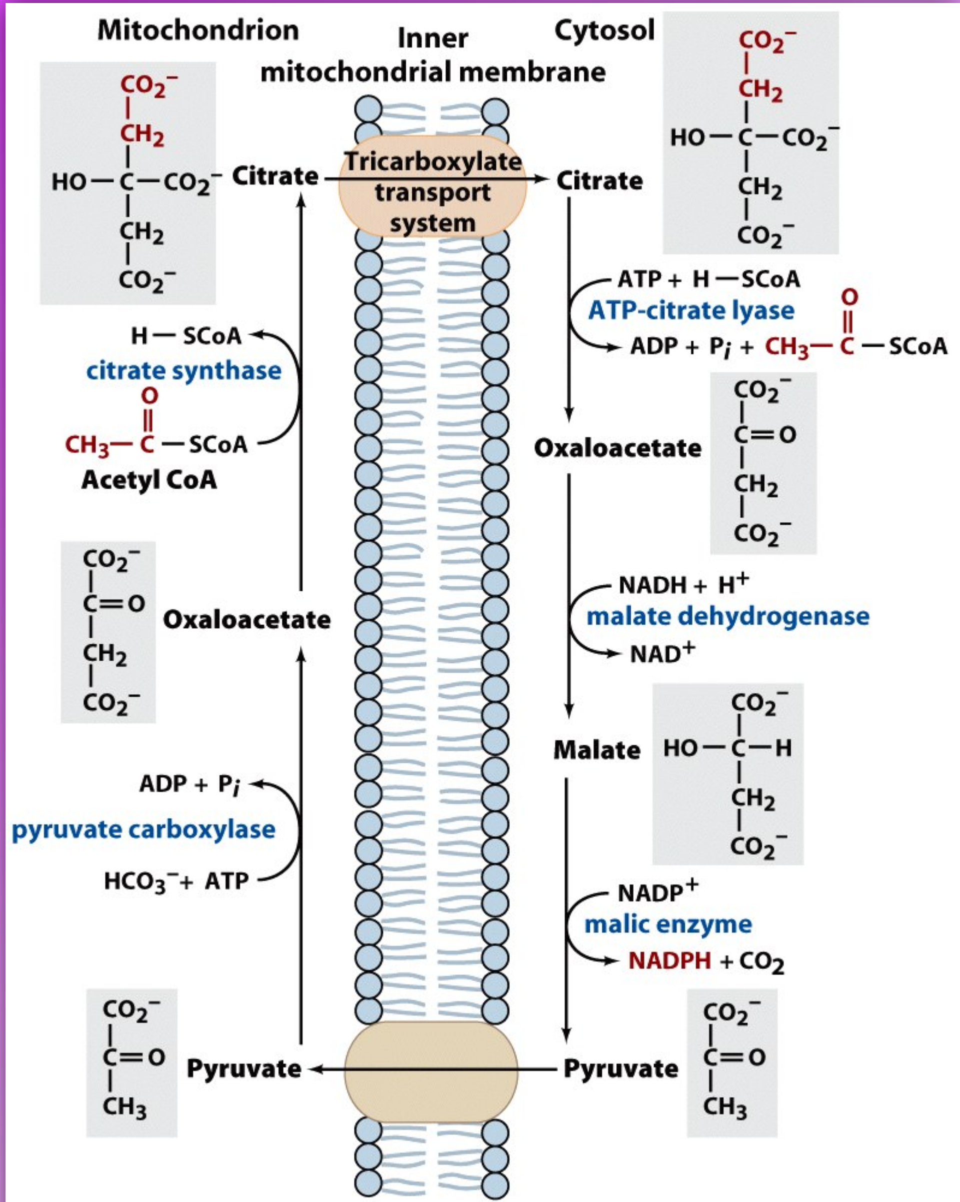
Acetone is produced *in vivo* from acetoacetate by non-enzymic decarboxylation.



Metabolic conversion of ketone bodies to acetyl CoA in the peripheral tissues

Comparison of fatty acid β-oxidation and biosynthesis





Transport of mitochondrial acetyl CoA into the cytosol for fatty acid synthesis: The tricarboxylic acid transport system

Fatty acid metabolism: Biosynthesis

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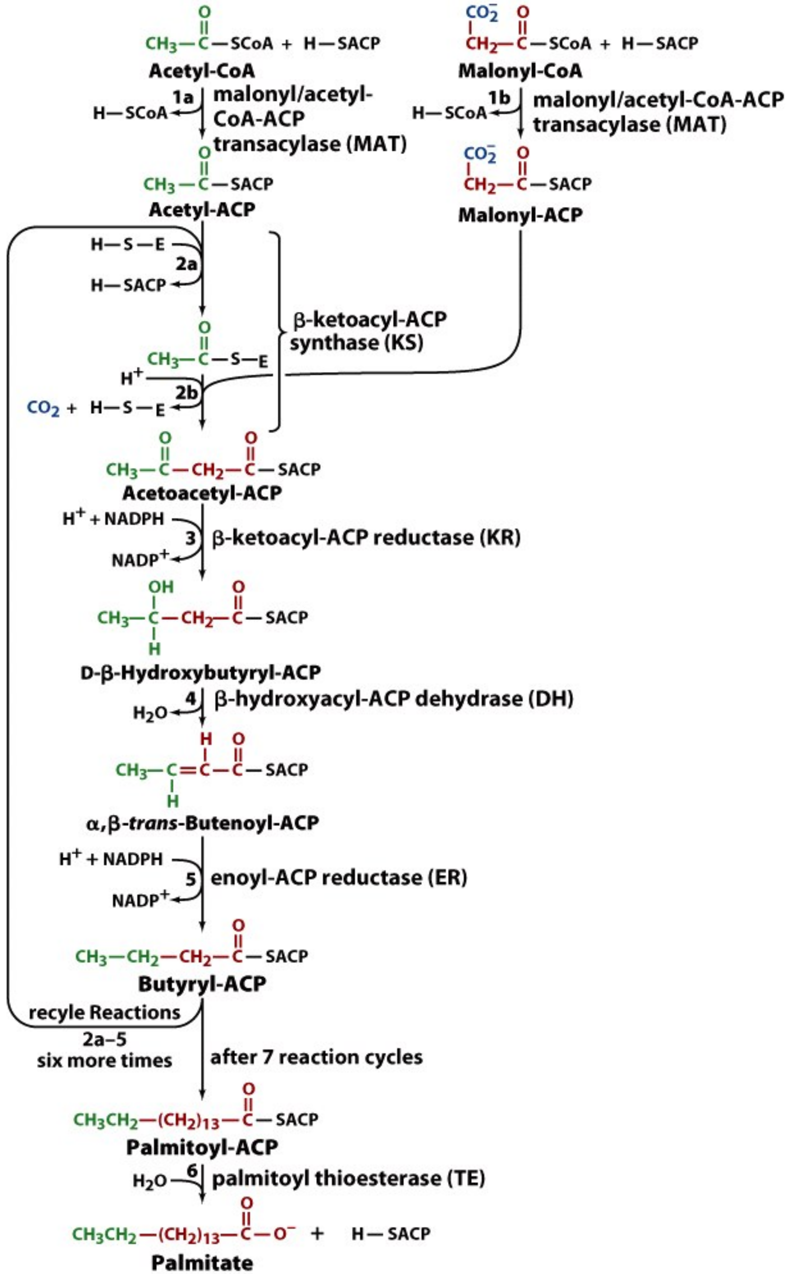
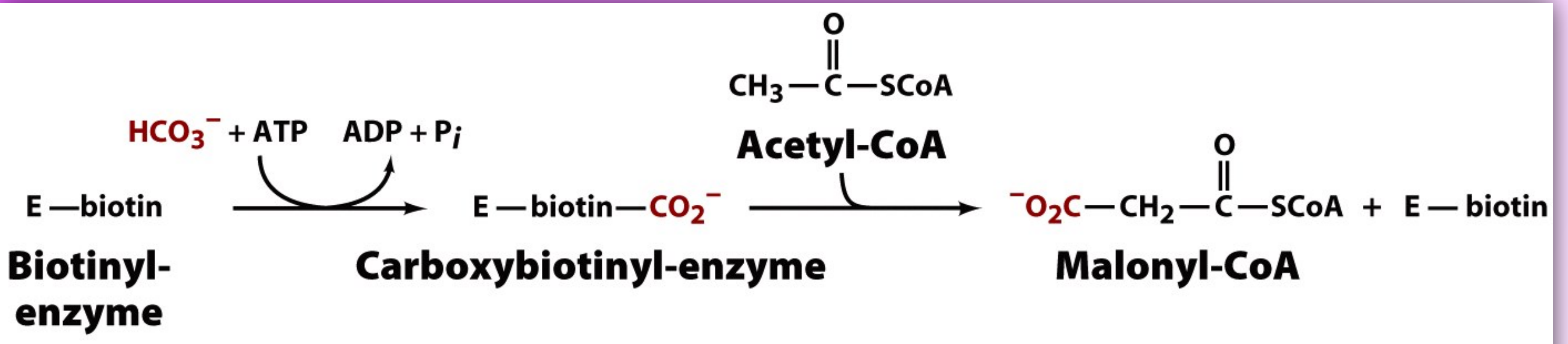
Chapter X: Voet/Voet, *Biochemistry*, 2011
Spring 2015



Summary of the reactions in the biosynthesis of the C_{16} saturated fatty acid, palmitic acid

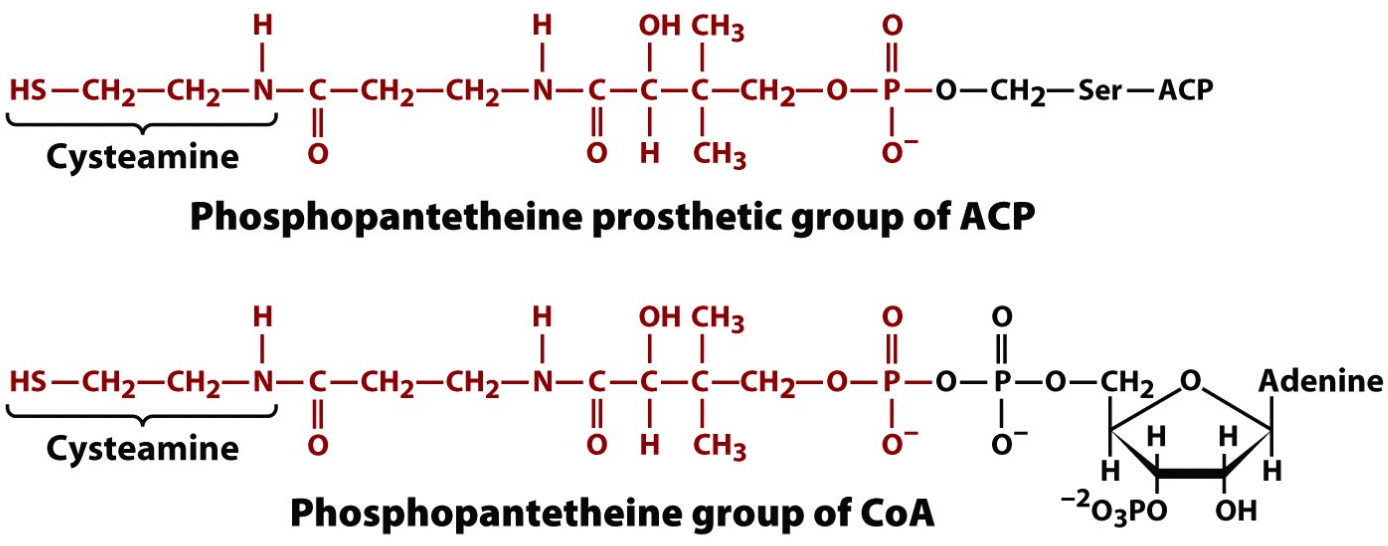
Synthesis of malonyl CoA: acetyl CoA carboxylase catalyzes the first committed step of fatty acid biosynthesis and one of its rate-controling steps.



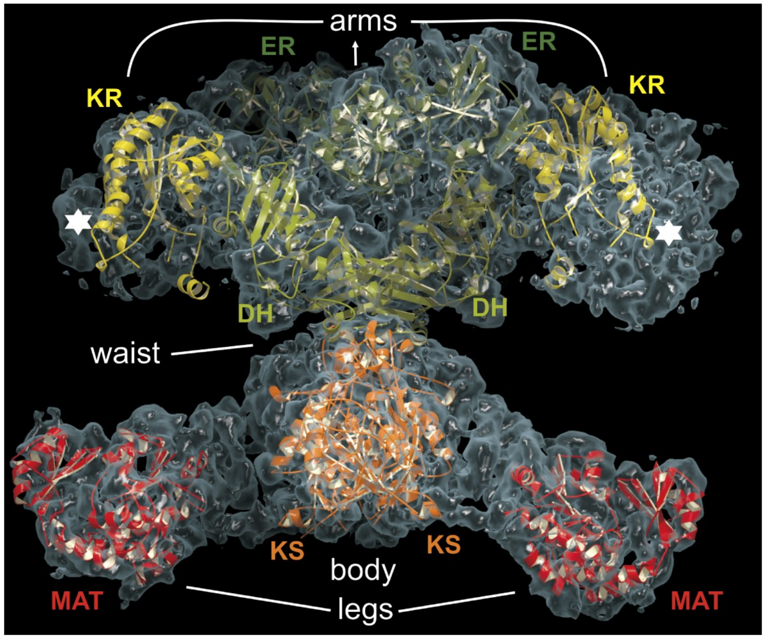
The mammalian enzyme is subject to allosteric and hormonal control.

Fatty acid synthase: in animals, a cytosolic multifunctional enzyme consisting of two identical polypeptide chains; catalyzes the seven enzymatic reactions of FA biosynthesis

The growing fatty acid is anchored to *acyl-carrier protein* (ACP), which, like CoA, contains a phosphopantetheine group that forms a thioester with an acyl group.



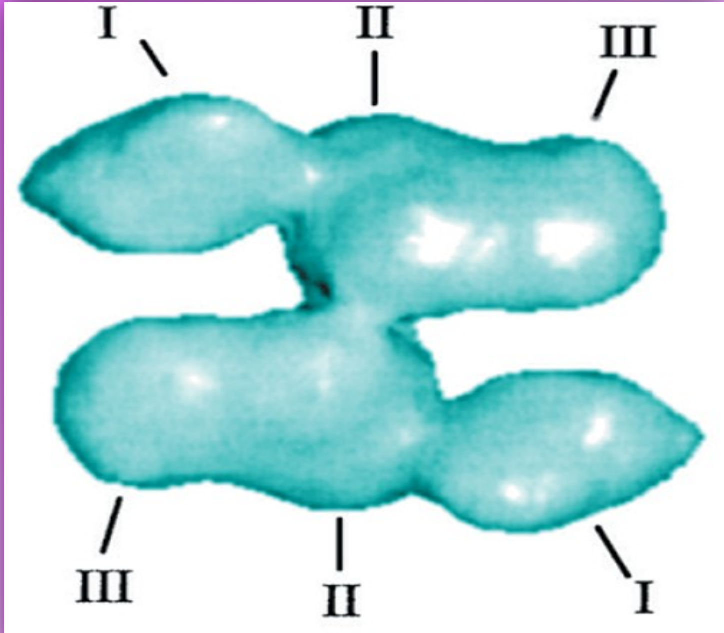
Mammalian FA synthase: Order of enzymatic activities along the polypeptide chain of a monomer: KS = β-ketoacyl-ACP synthase; MAT = malonyl/acetyl-CoA-ACP transacylase; DH = β-hydroxyacyl-ACP dehydratase; ER = enoyl-ACP reductase; KR = β-ketoacyl-ACP reductase; TE = palmitoyl thioesterase



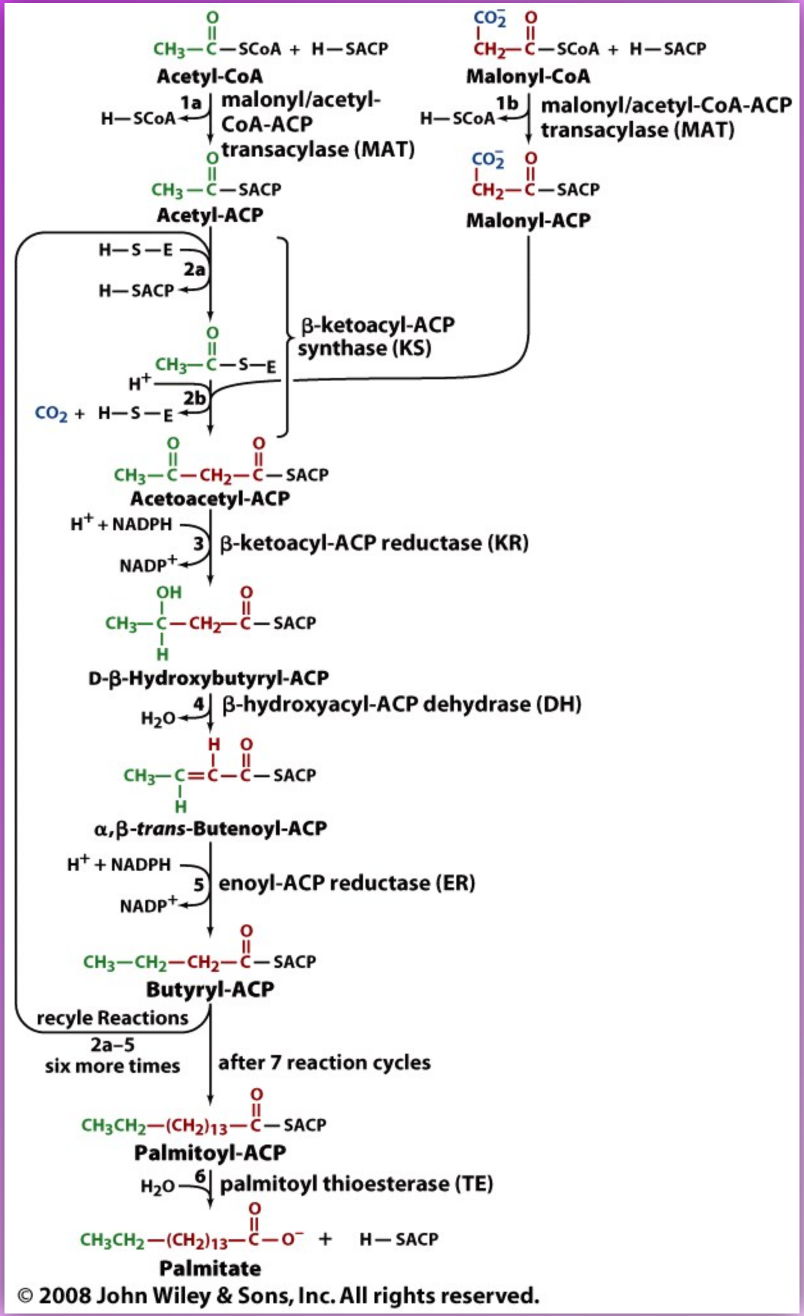
Courtesy of Nenad Ban and Tim Maier, Swiss Federal Institute of Technology

X-ray structure of porcine FA synthase

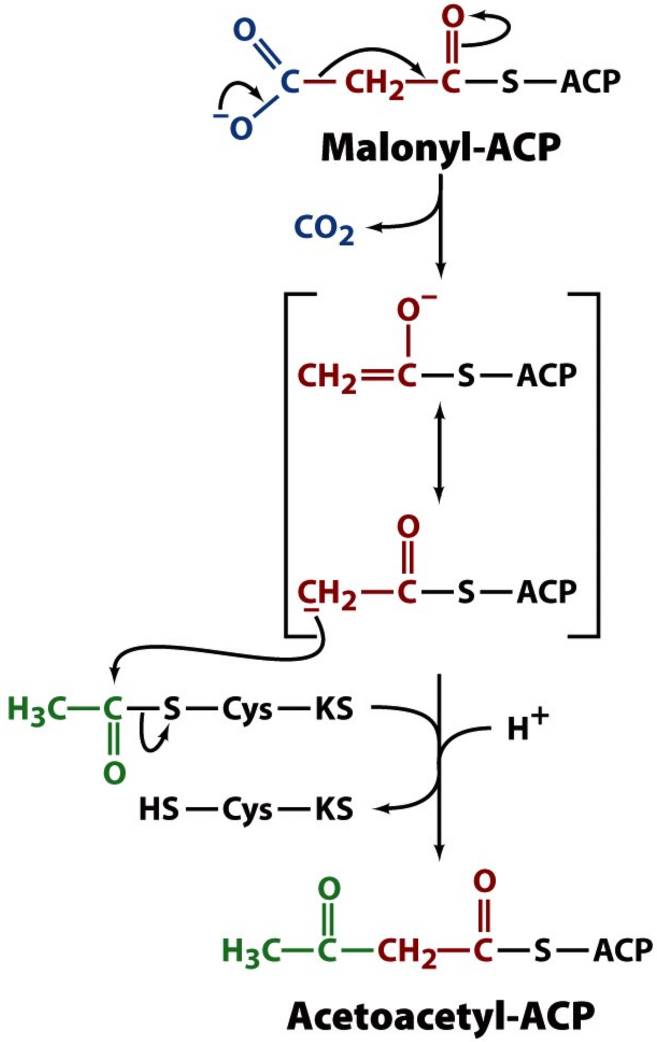
EM-based image of the human FAS dimer as viewed along its 2-fold axis



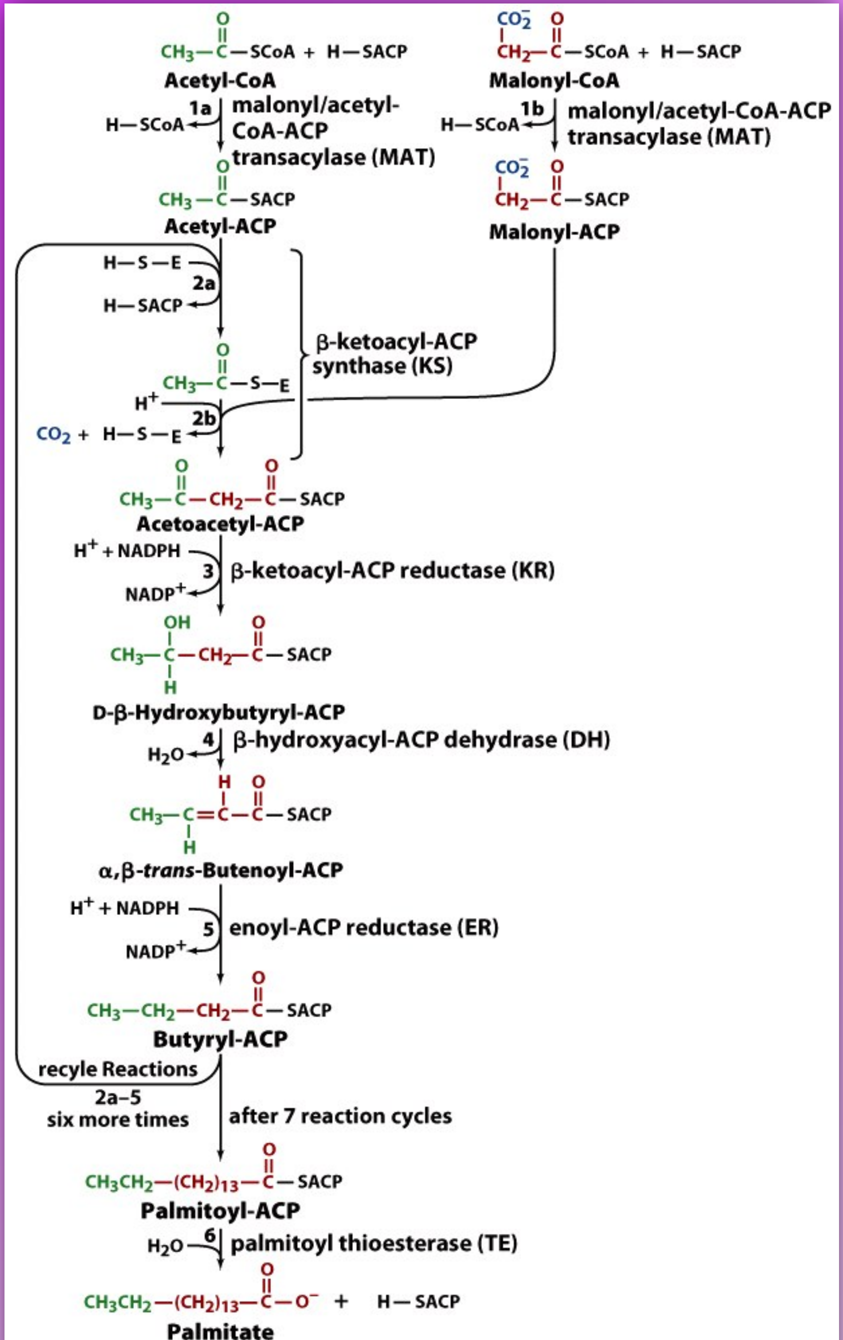
Courtesy of Salih Wakil and Wah Chiu, Baylor College of Medicine



Summary of the reactions in the biosynthesis of the C_{16} saturated fatty acid, palmitic acid



The mechanism of carbon-carbon bond formation in fatty acid biosynthesis; decarboxylation of a β-keto thioester



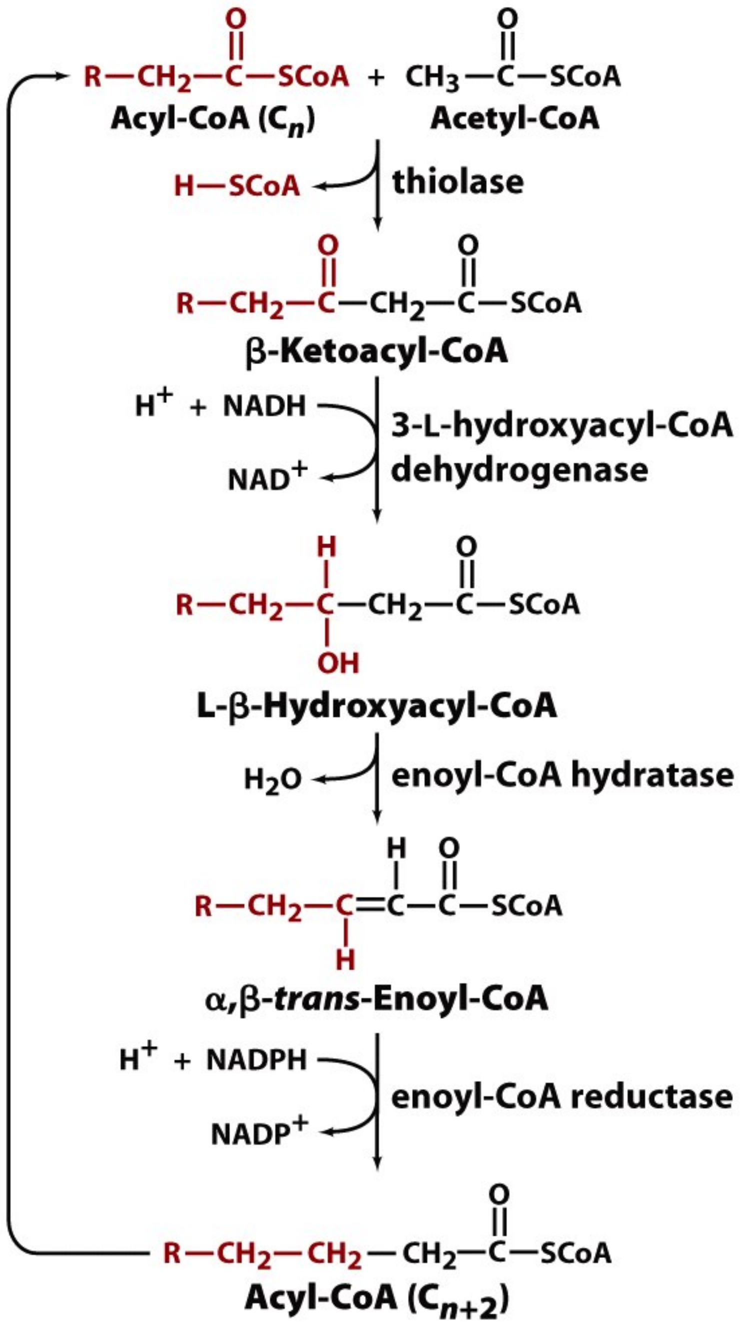
The fatty acid synthase reaction cycle

Note that fatty acid biosynthesis occurs from the methyl terminus to the carboxyl terminus (opposite to the direction of β-oxidation)

Palmitic acid (C_{16}, saturated) is the major fatty acid produced by cytosolic fatty acid synthase. This product is elongated by elongases which are present in mitochondria and the ER.

Mitochondrial elongation: occurs by successive addition and reduction of acetyl units in a reversal of β-oxidation

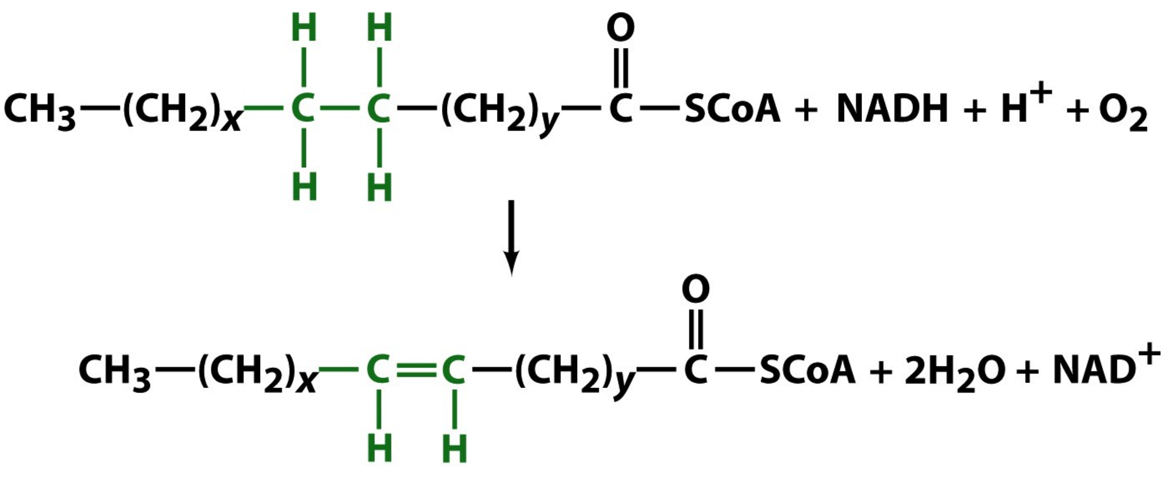
ER elongation: occurs by successive condensations of malonyl CoA with acyl CoA (similar to the FA synthase route)



Mitochondrial fatty acid elongation

This process is the reverse of β-oxidation except for the final reaction which employs NADPH rather than $FADH_2$.

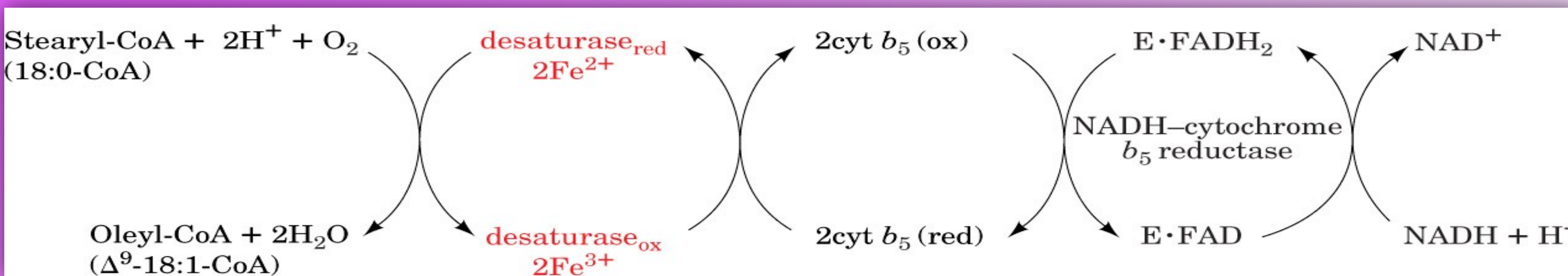
Unsaturated fatty acids are produced by terminal desaturases. In mammalian systems, there are four terminal desaturases of broad chain-length specificities designated Δ^9-, Δ^6-, Δ^5-, and Δ^4-fatty acyl-CoA desaturases.



General reaction catalyzed by terminal desaturases

X is at least five and $(CH_2)_x$ can contain one or more double bonds; the $(CH_2)_y$ portion of the substrate is always saturated.

The electron-transfer reactions mediated by the Δ^9-fatty acyl-CoA desaturase complex



Palmitate biosynthesis

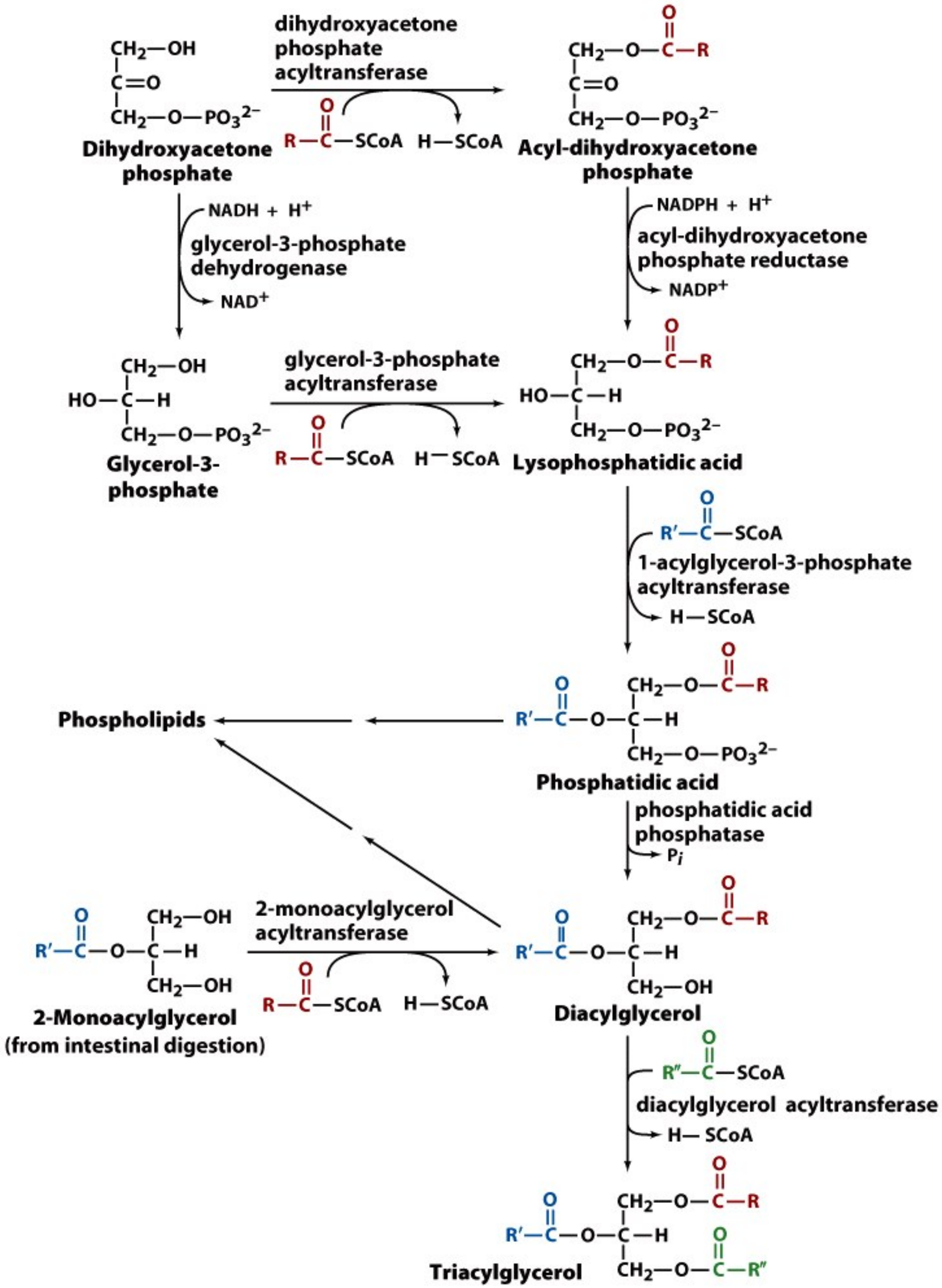
Reactants: 1 acetyl CoA + 7 malonyl CoA + 14 NADPH + 7 H^+

Products: 1 palmitate + 7 CO_2 + 14 $NADP^+$ + 8 CoA + 6 H_2O

To generate 7 malonyl CoA: 7 acetyl CoA + 7 CO_2 + 7 ATP give 7 malonyl CoA + 7 ADP + 7 P_i + 7 H^+

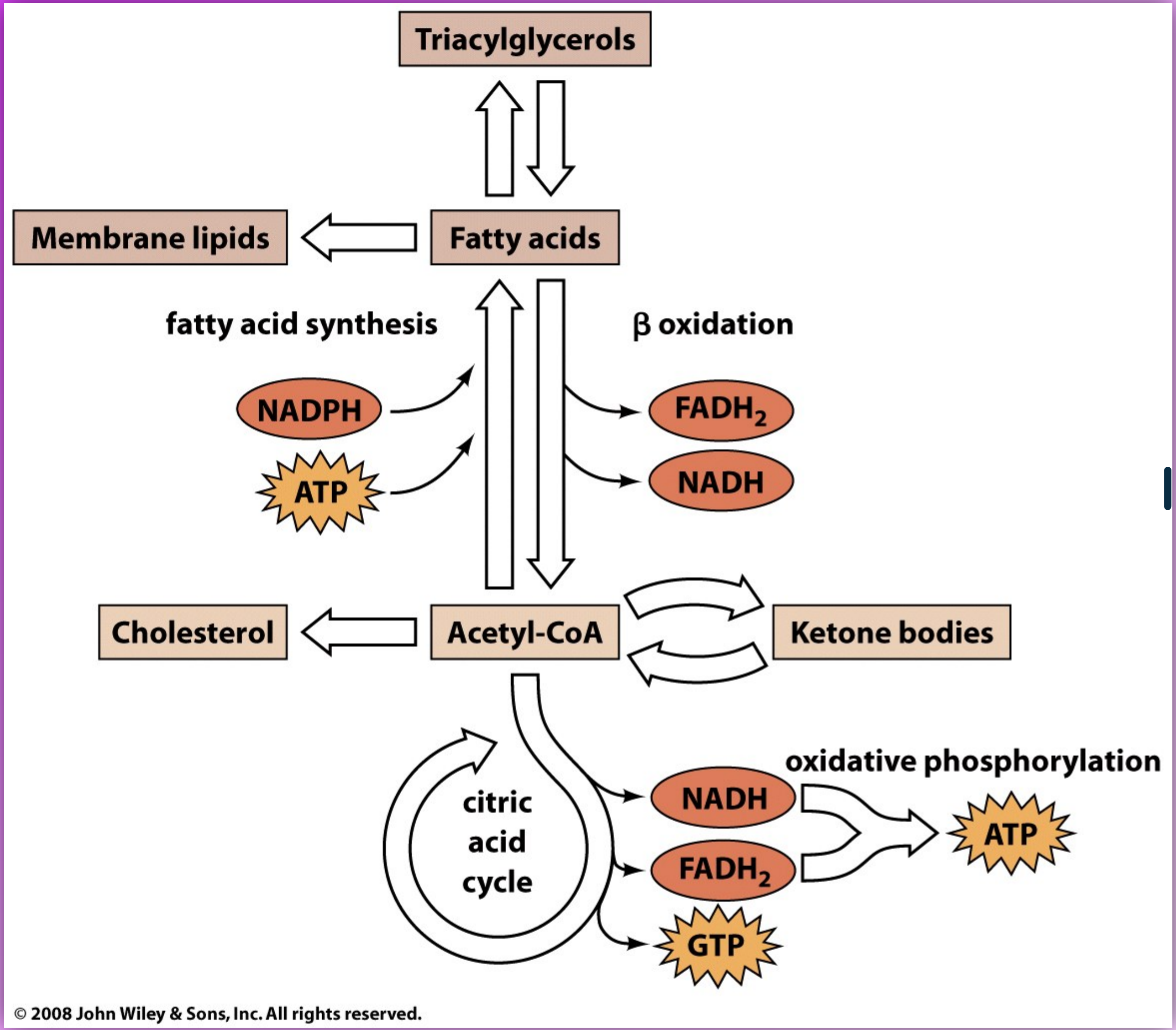
Overall:

8 acetyl CoA + 14 NADPH + 7 ATP gives 1 palmitate + 14 $NADP^+$ + 8 CoA + 6 H_2O + 7 ADP + 7 P_i



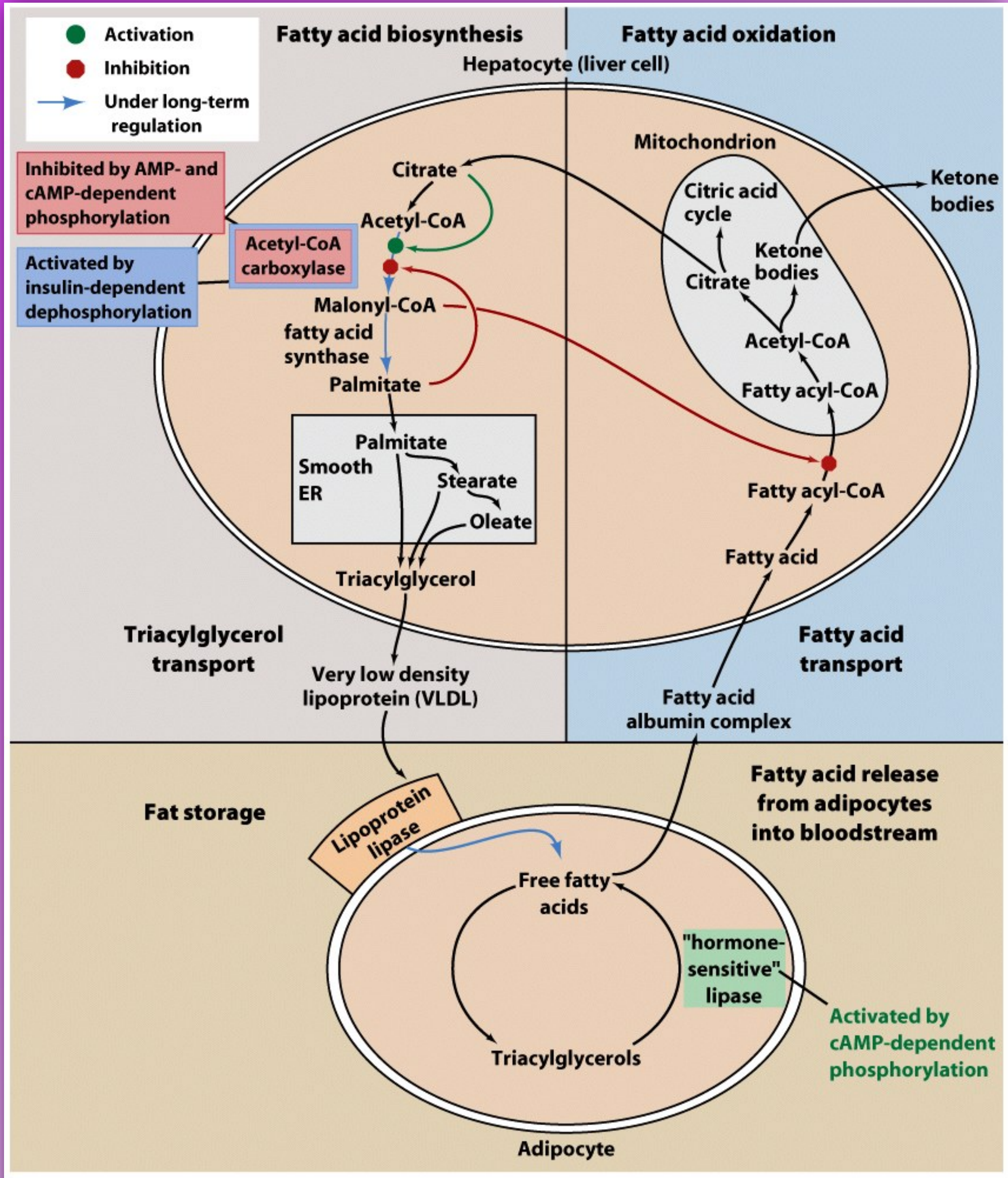
Enzyme reactions that convert fatty acids to triacylglycerols

These reactions occur in mitochondria, the ER, or peroxisomes.



Summary of lipid metabolism

Sites of regulation of fatty acid metabolism

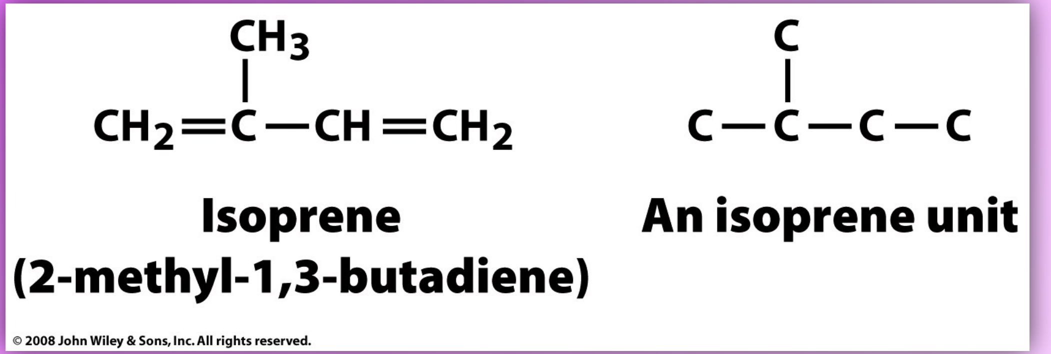


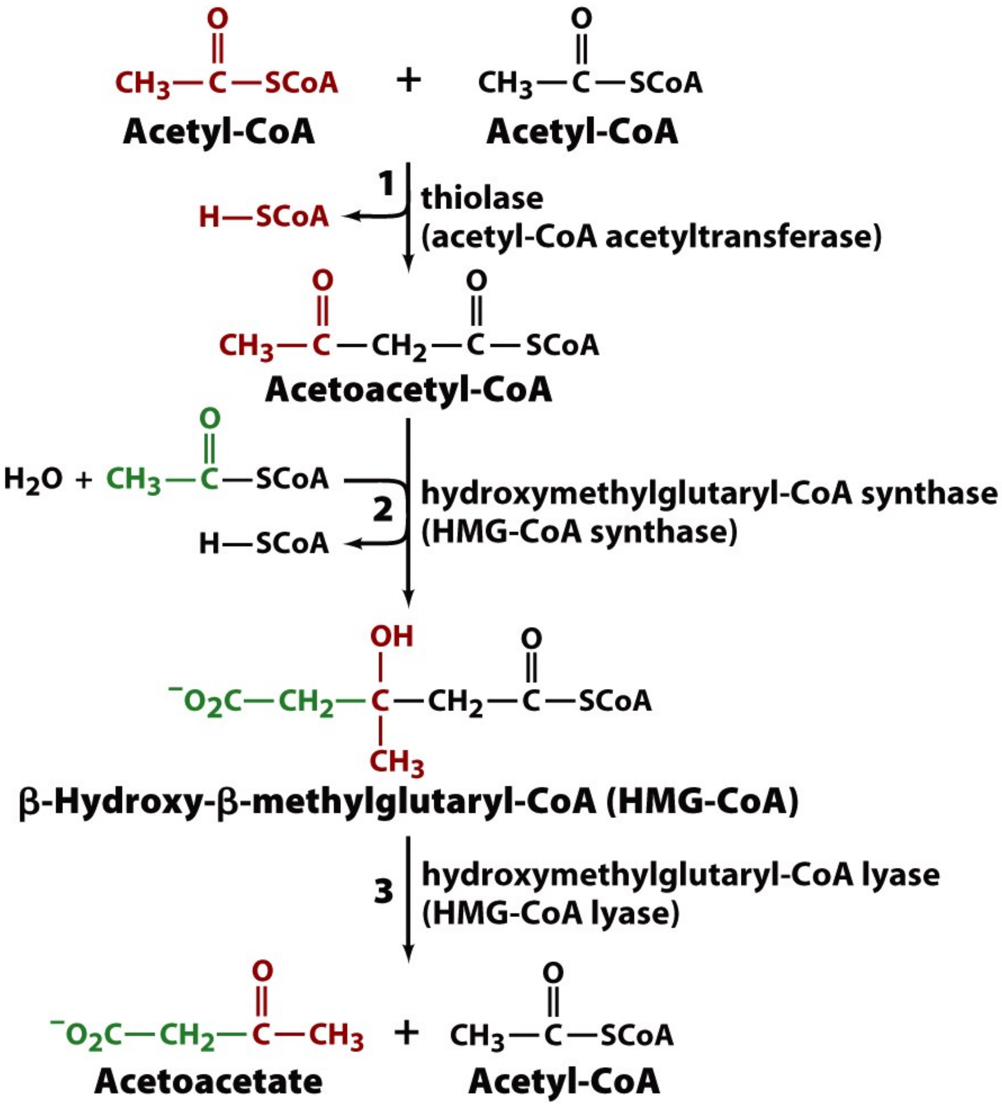
Long term regulation (hours/days) involves altering the amount of enzyme present, either through changes in the rates of protein synthesis and/or breakdown.

Biosynthesis of other lipids

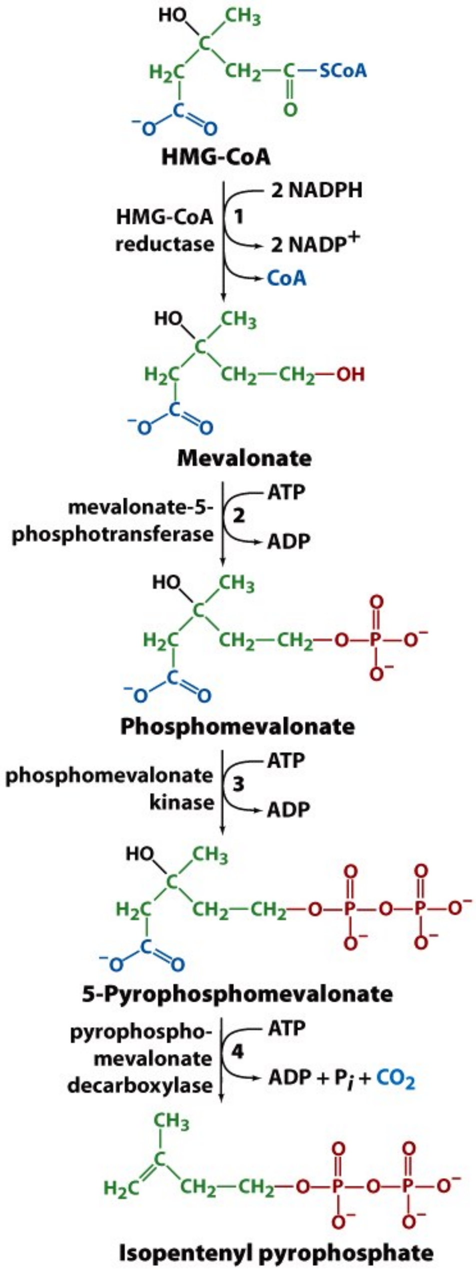
Cholesterol and prostaglandins

Cholesterol is built from acetyl CoA which is converted to isoprene units

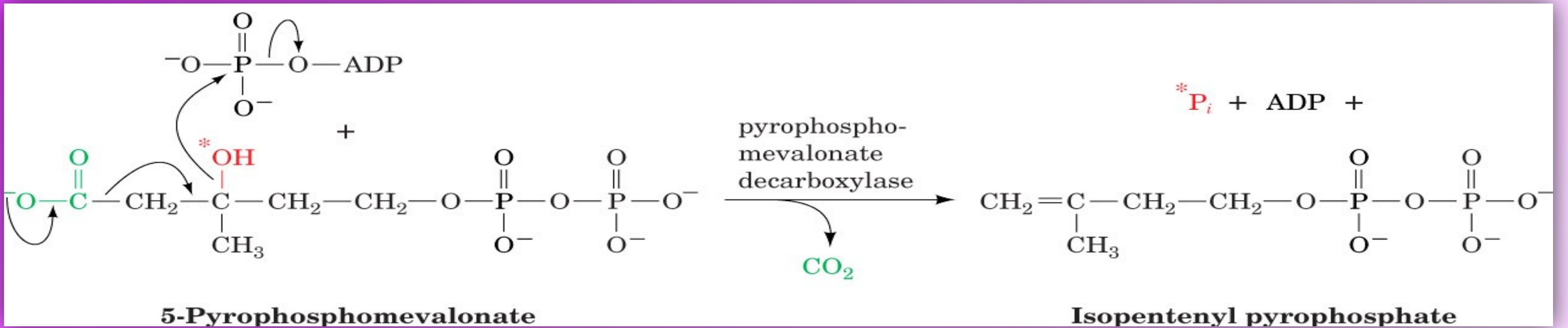


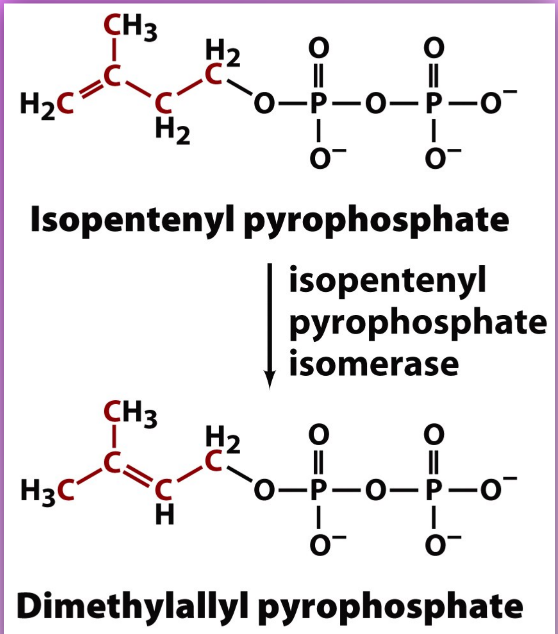


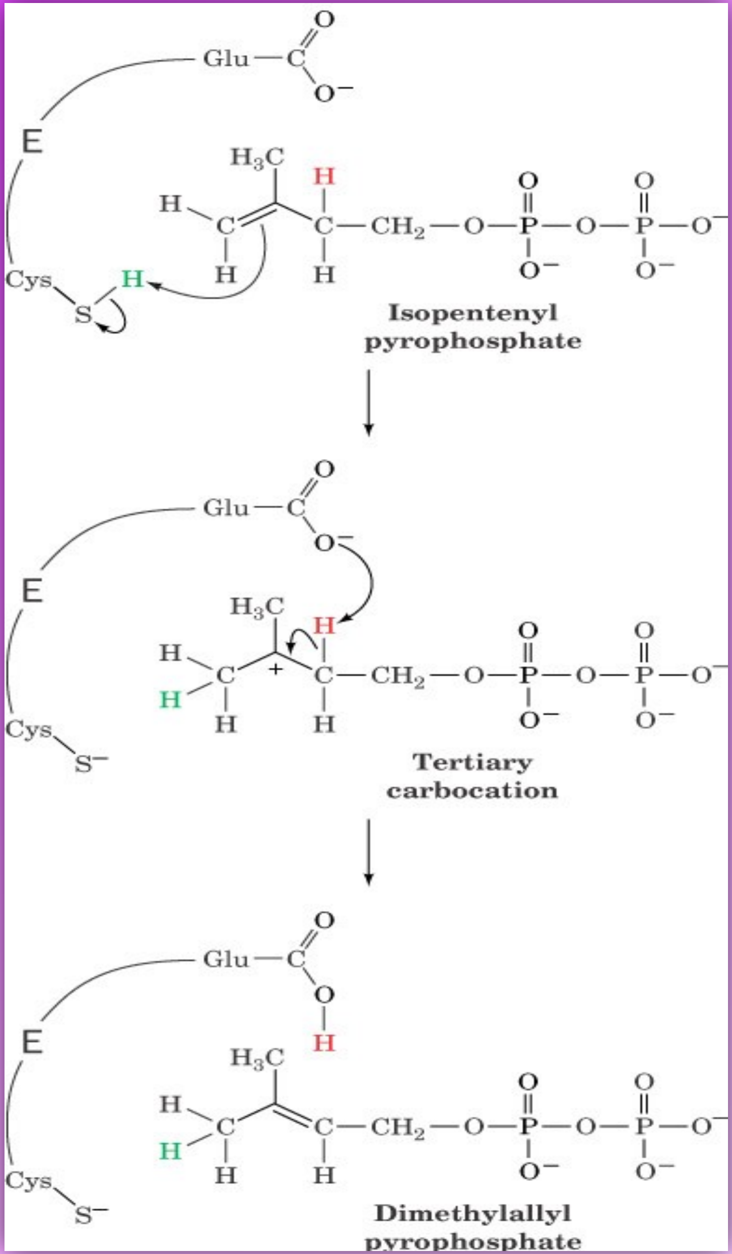
HMG-CoA is a key cholesterol precursor; it is an intermediate in ketone body formation.



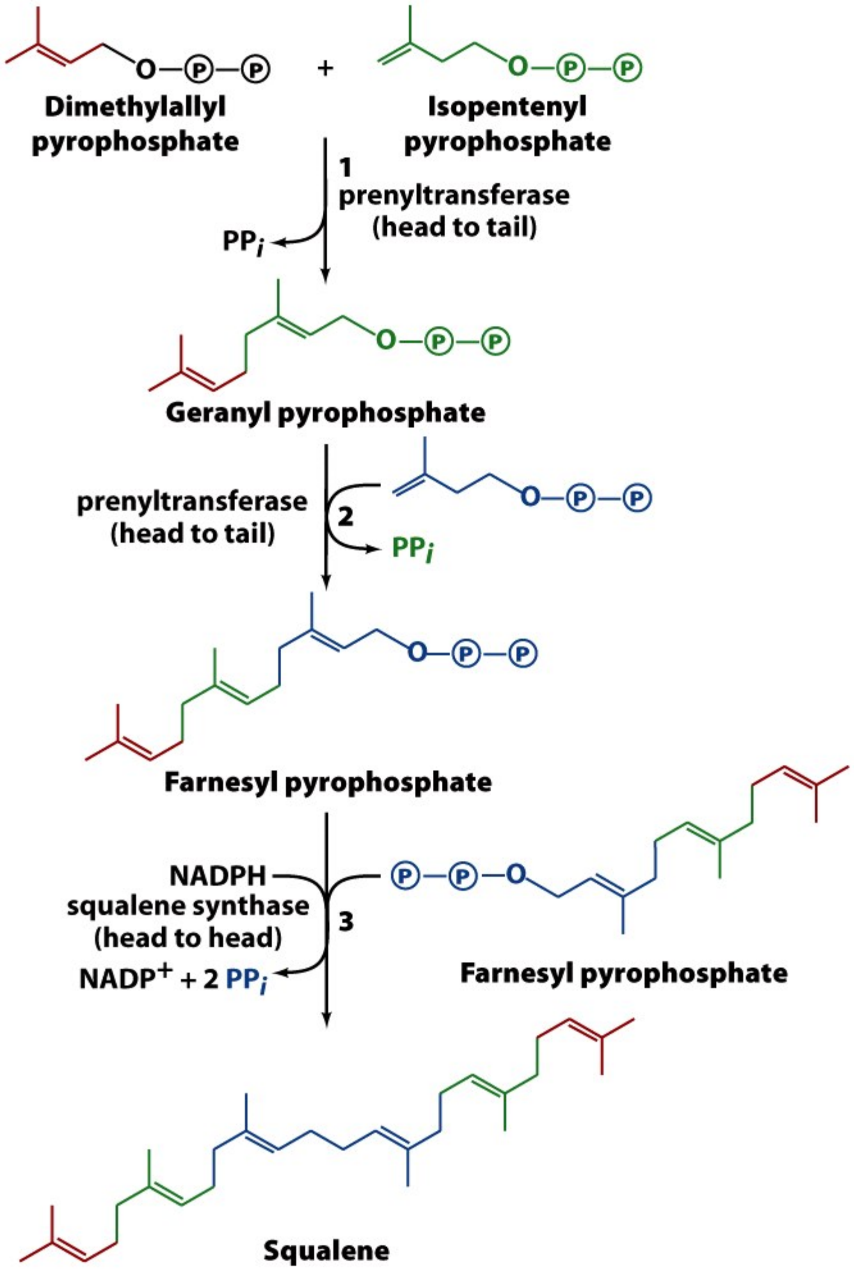
Formation of isopentenyl pyrophosphate from HMG-CoA


pyrophospho-
mevalonate
decarboxylase
ADP
*OH
CO_2
*P_i + ADP +
5-Pyrophosphomevalonate
Isopentenyl pyrophosphate

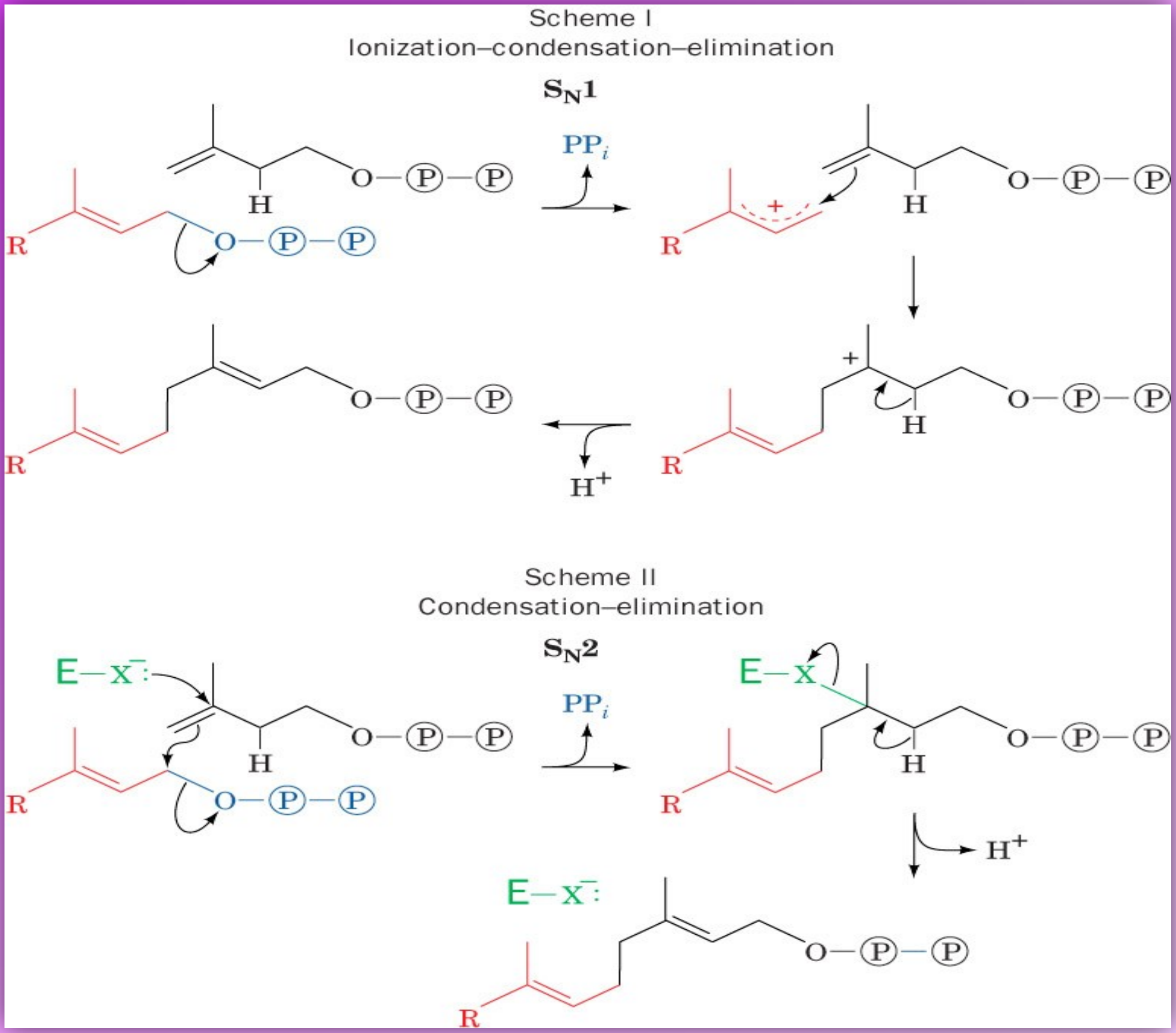

Isopentenyl pyrophosphate
isopentenyl
pyrophosphate
isomerase
Dimethylallyl pyrophosphate



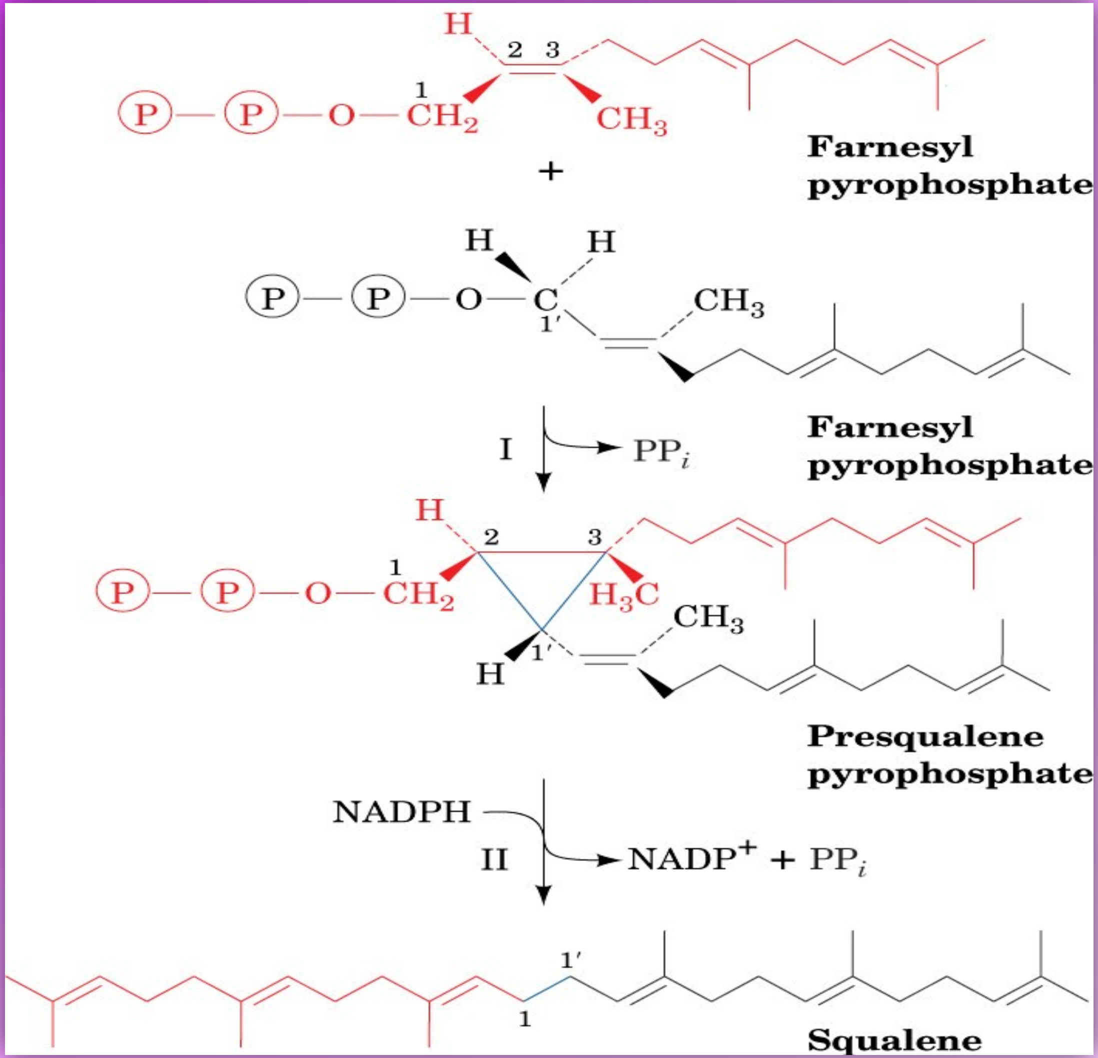
Mechanism of isopentenyl pyrophosphate isomerase



Formation of squalene from isopentenyl pyrophosphate and dimethylallyl pyrophosphate

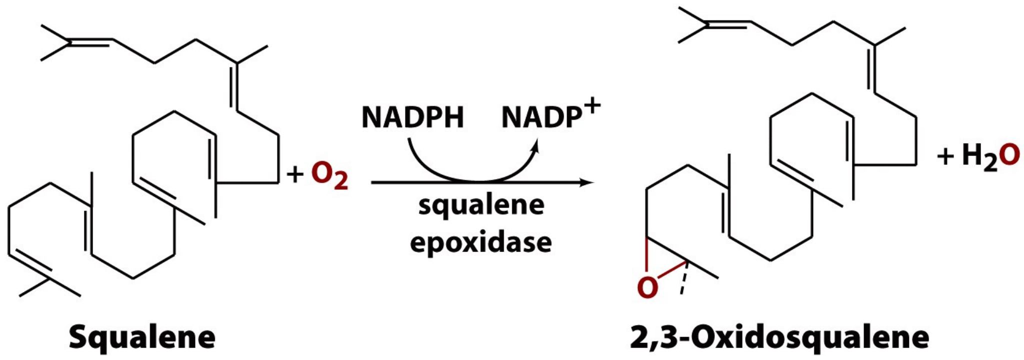


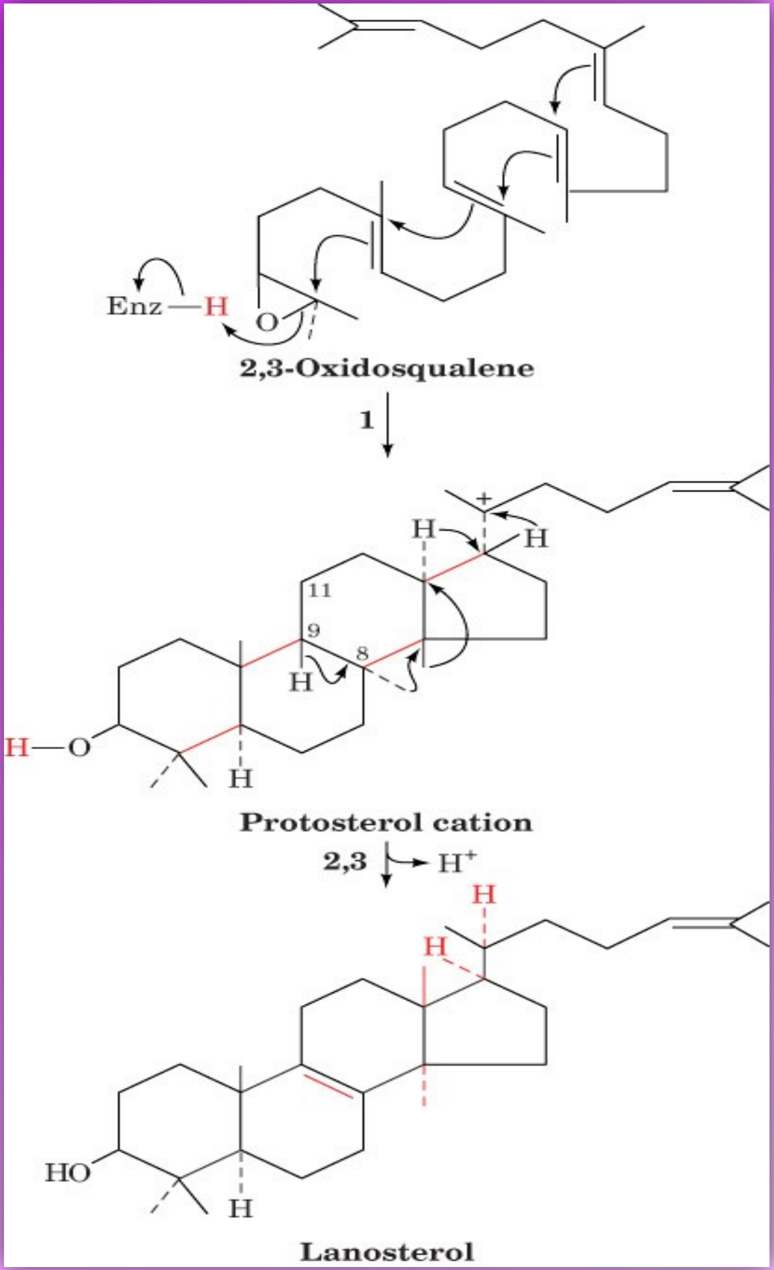
Two possible mechanisms for the prenyltransferase reaction



Action of squalene synthase

The squalene epoxidase reaction





The oxidosqualene cyclase reaction

Lanosterol is converted to cholesterol via a 19-step process in the ER membrane.