Chapter 7-II:
Lipid Metabolism

Oxidation of unsaturated fatty acids

Double bonds
- One: C9
- Two or three: C12, C15

Confront with three problems
- Enoyl-CoA isomerase
- 2,4-dienoyl-CoA reductase
- 3,2-enoyl-CoA isomerase
- 3,5-2,4-dienoyl-CoA isomerase

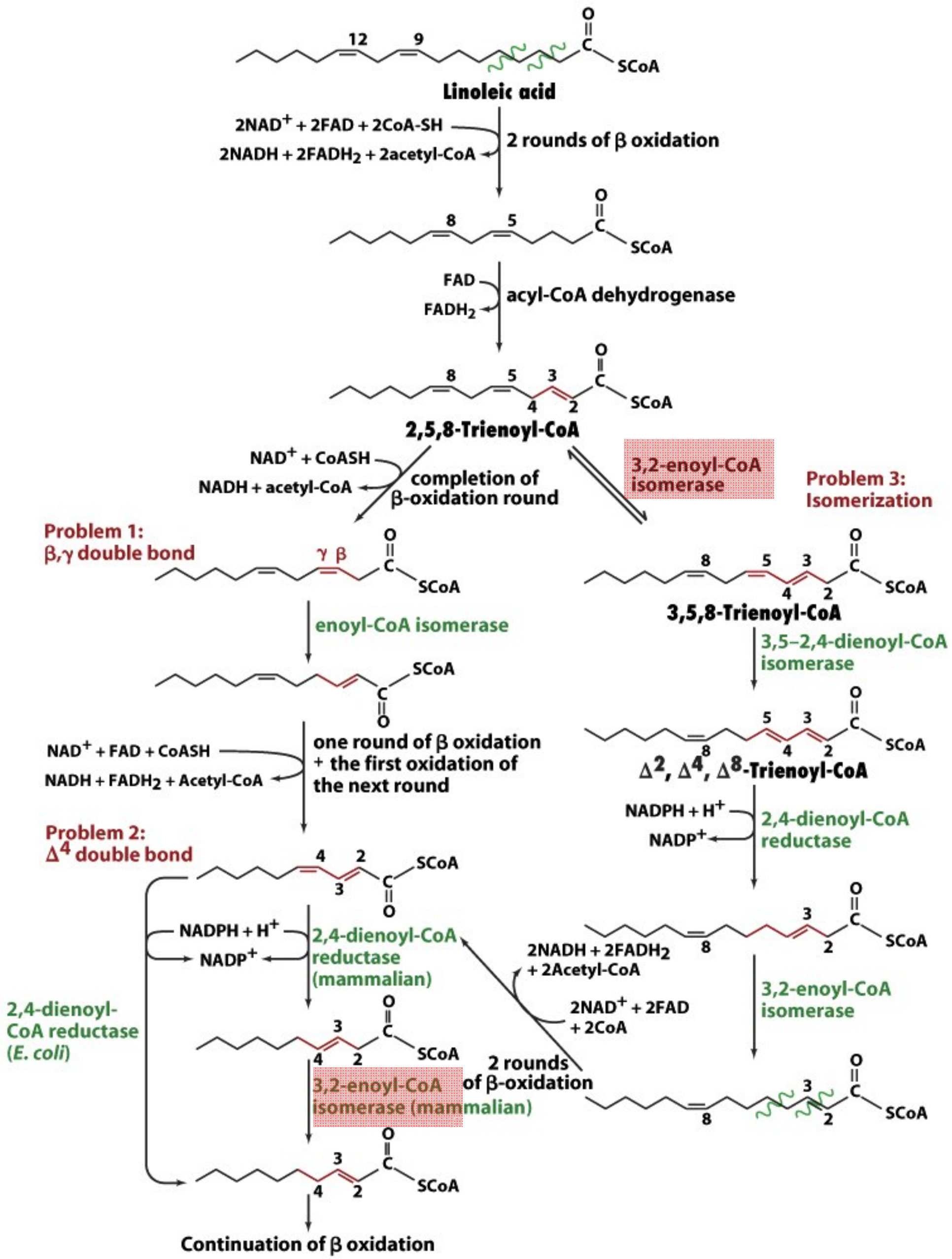


Figure 19-15 Fundamentals of Biochemistry, 2/e

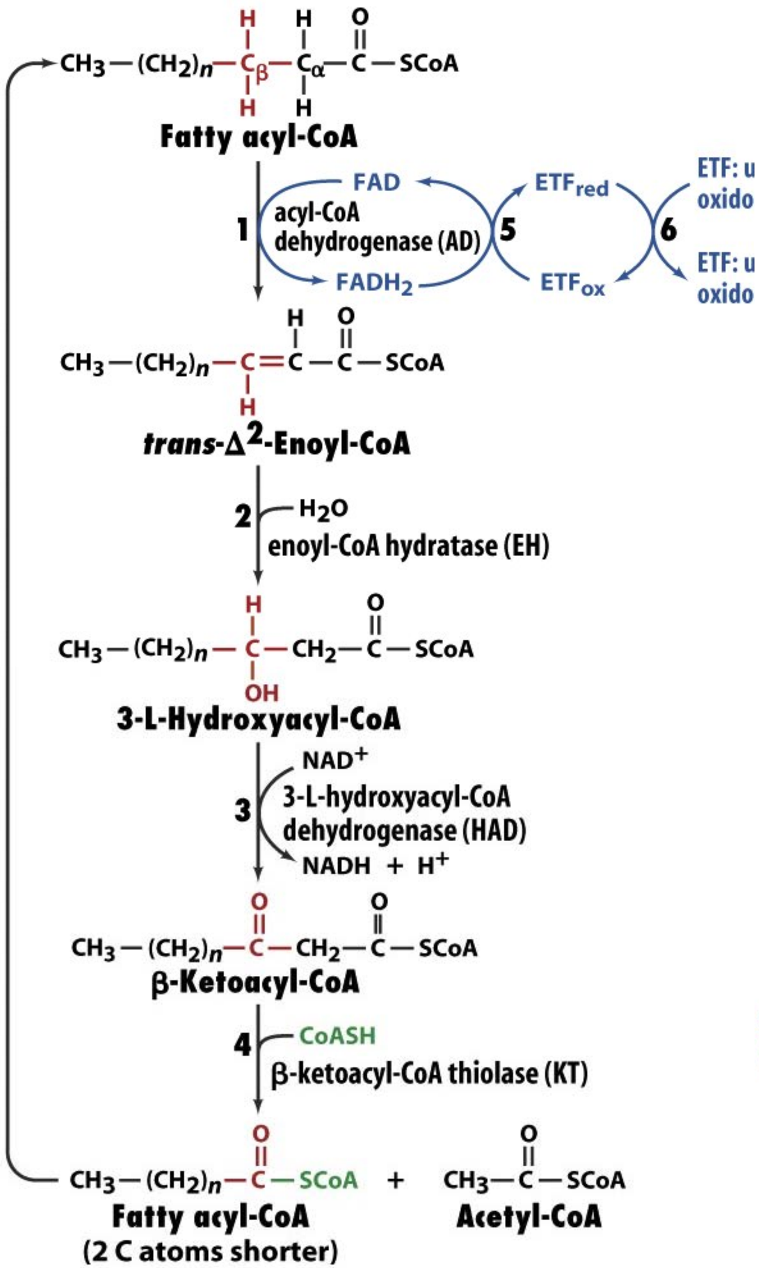


Figure 19-12 Fundamentals of Biochemistry, 2/e

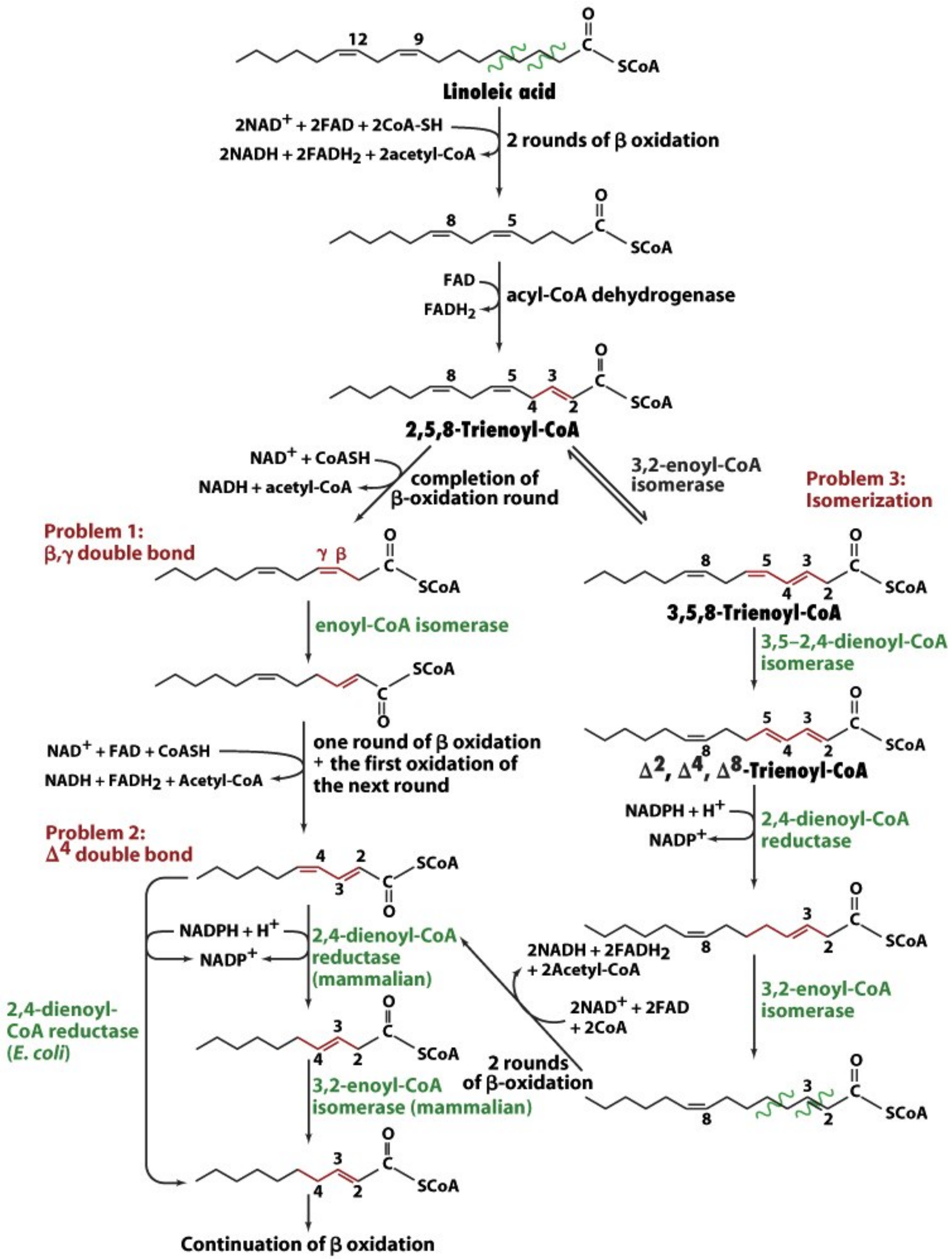
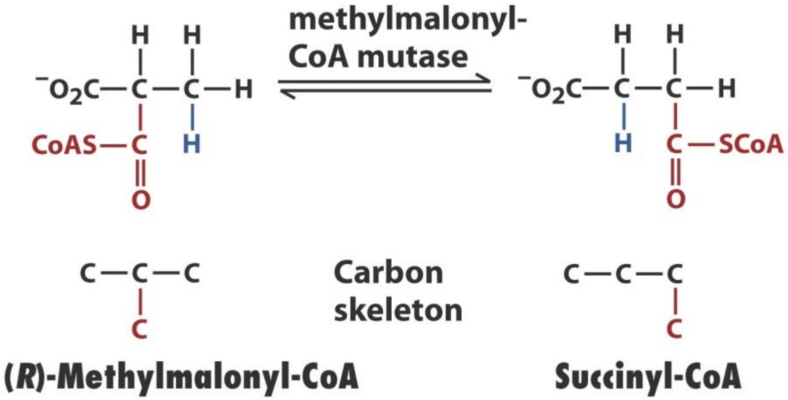


Figure 19-15 Fundamentals of Biochemistry, 2/e

Oxidation of odd-chain fatty acids

The end product is propionyl-CoA
Converted to succinyl-CoA
Entry into the citric acid cycle



Unnumbered figure pg 642 Fundamentals of Biochemistry, 2/e

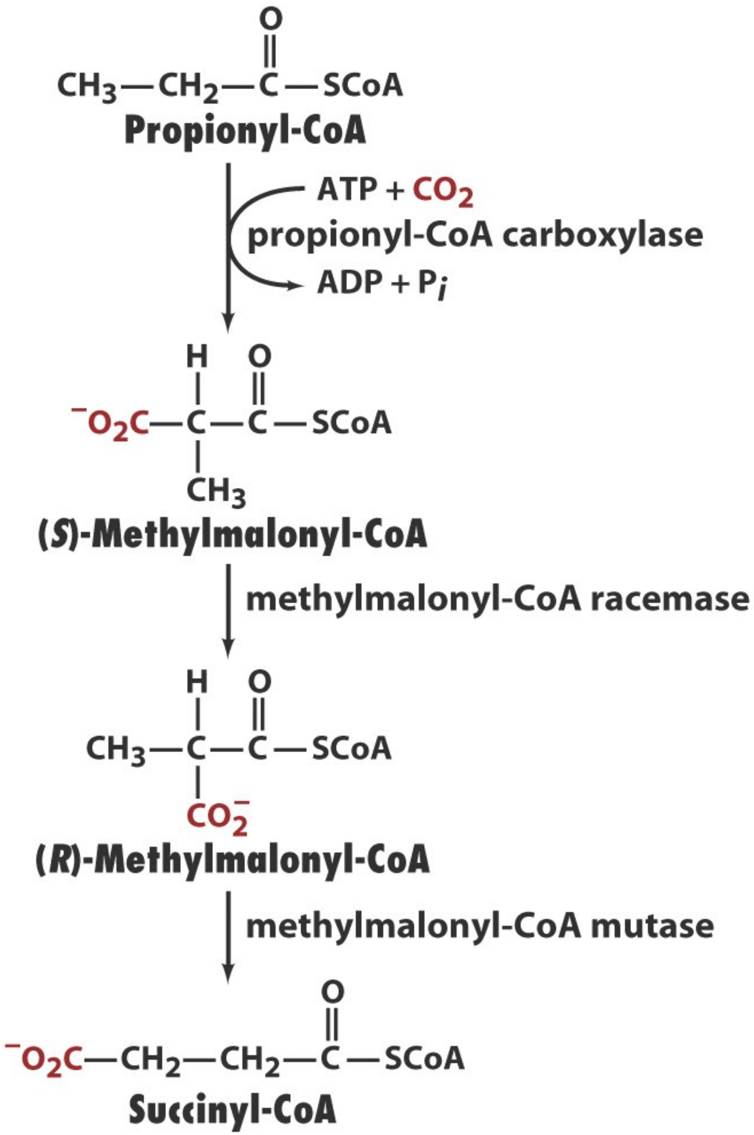


Figure 19-16 Fundamentals of Biochemistry, 2/e

Methylmalonyl-CoA mutase

Prosthetic group: 5’-deoxyadenosylcobalamine (AdoCbl, coenzyme B12)

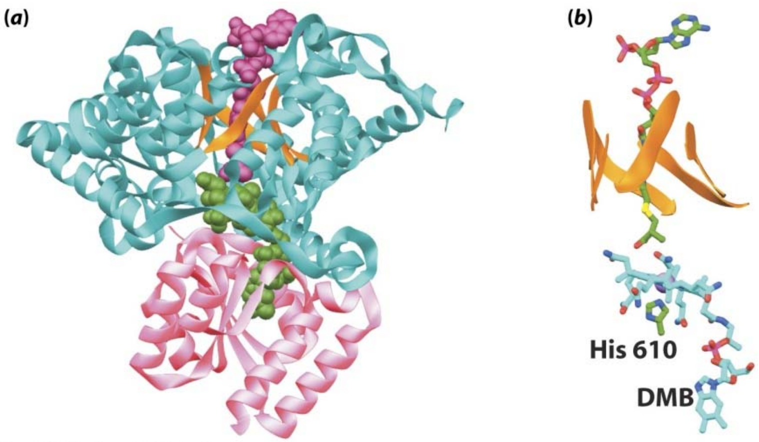
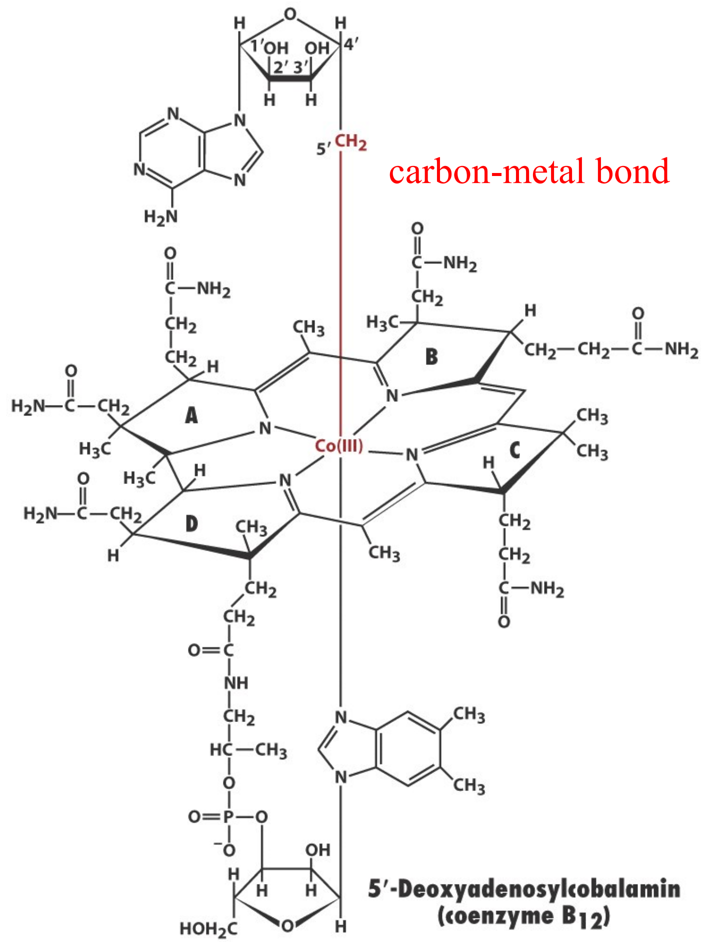


Figure 19-18 Fundamentals of Biochemistry, 2/e



5′-Deoxyadenosylcobalamin (coenzyme B_{12})

Figure 19-17 Fundamentals of Biochemistry, 2/e

Homolytic cleavage of
the cobalamin C-Co bond

Co functions as a reversible
free radical generator

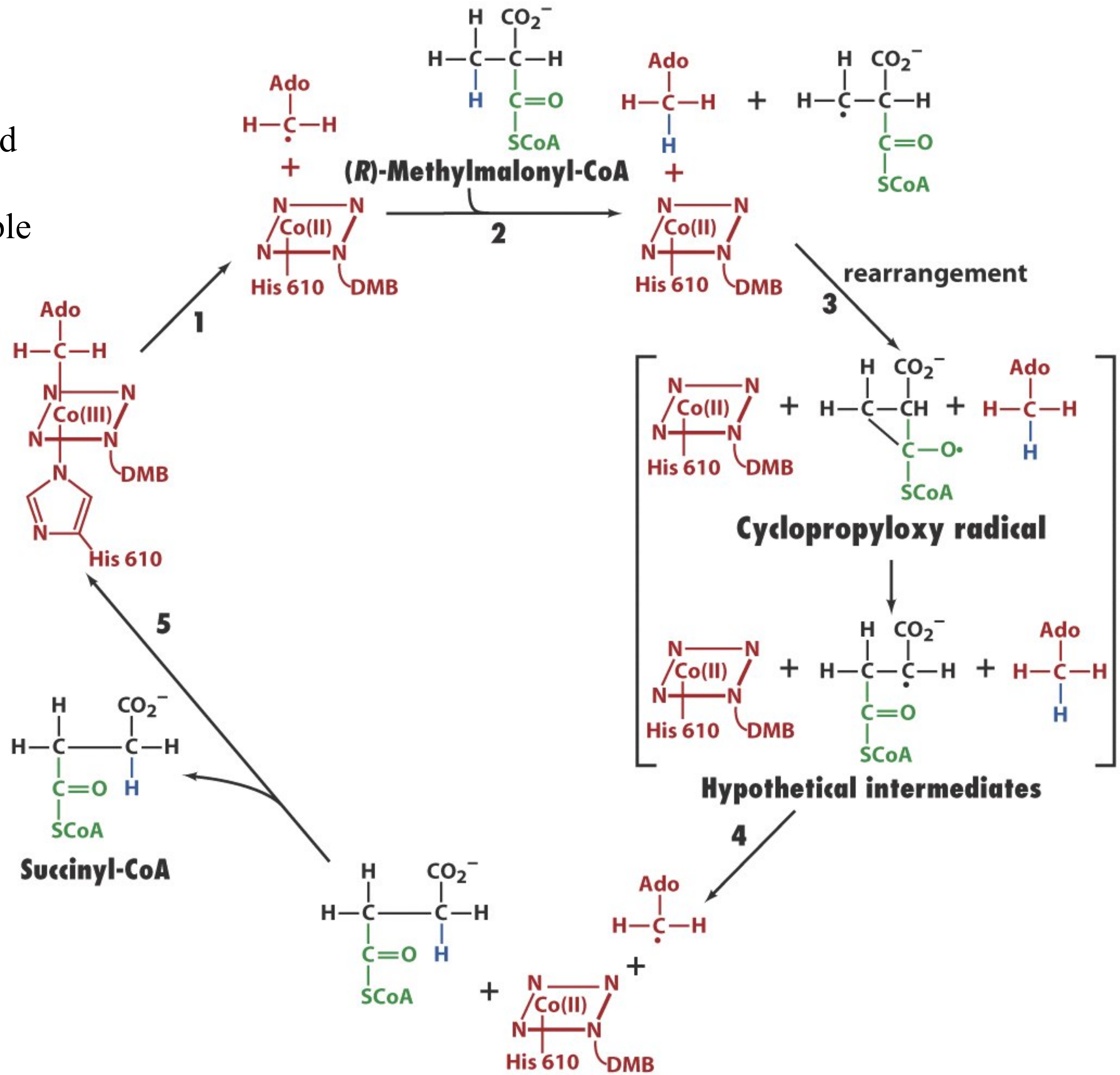
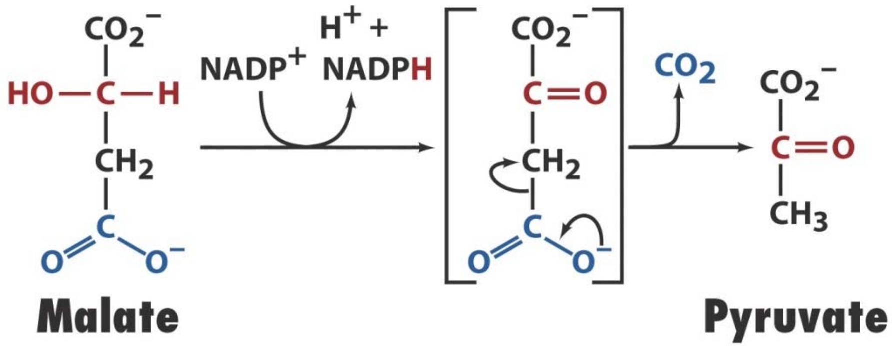


Figure 19-19 Fundamentals of Biochemistry, 2/e

Succinyl-CoA to malate
Transport to the cytosol
Oxidative decarboxylation to pyruvate and CO2



Unnumbered figure pg 648 Fundamentals of Biochemistry, 2/e

Peroxisomal β oxidation

Animal cells: very long chains or branched chains
Plant cells: exclusively in the peroxisomes and glyoxysomes

NADH transport electron to O_2 to generate H_2O_2
Animal cells: very long chain fatty acids (>22 chains) are shortened and transported to mito
Three enzymes

- Acyl-CoA oxidase
- Peroxisomal enoyl-CoA hydratase and 3-L-hydroxyacyl-CoA dehydrogenase
- Peroxisomal thiolase

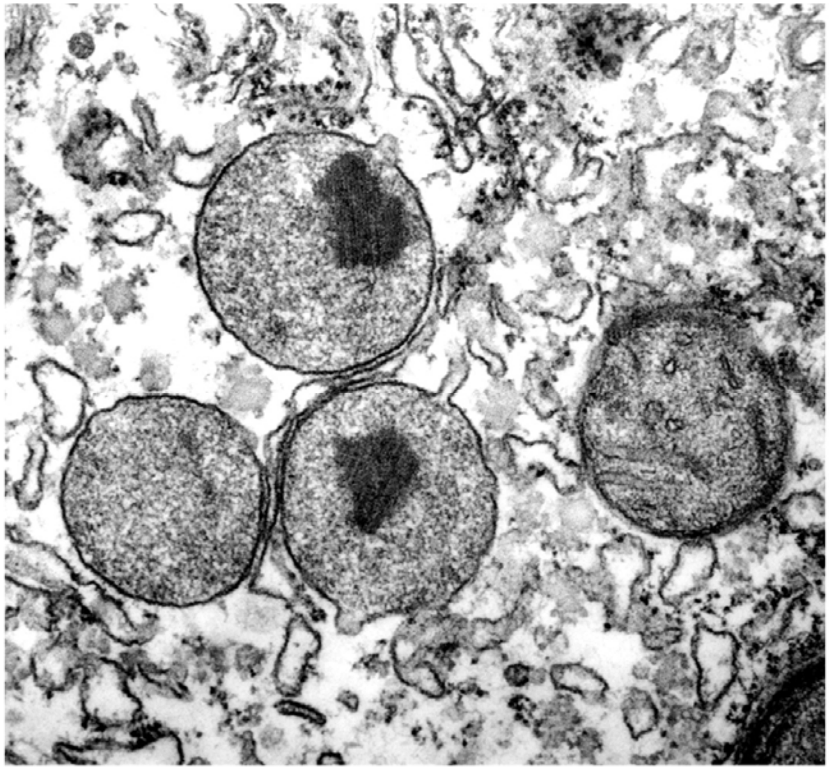


Figure 19-20 Fundamentals of Biochemistry, 2/e

Ketone bodies

Ketogenesis: acetyl-CoA to acetoacetate or D-β-hydroxybutyrate

Important metabolic fuels for heart & skeletal muscle

During starvation the brain depends on ketone bodies

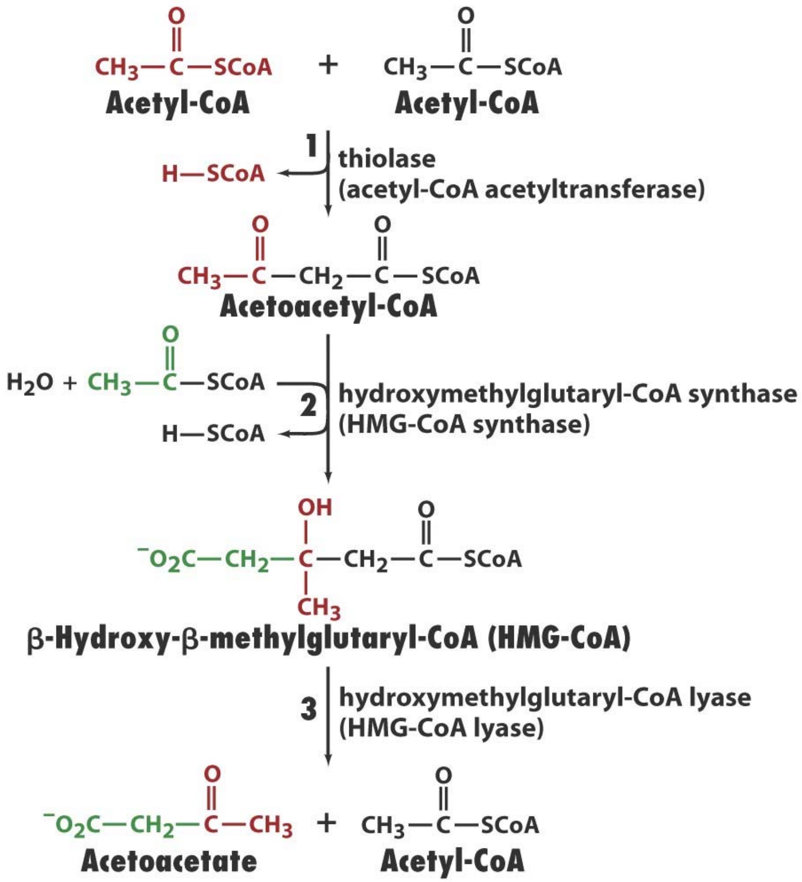
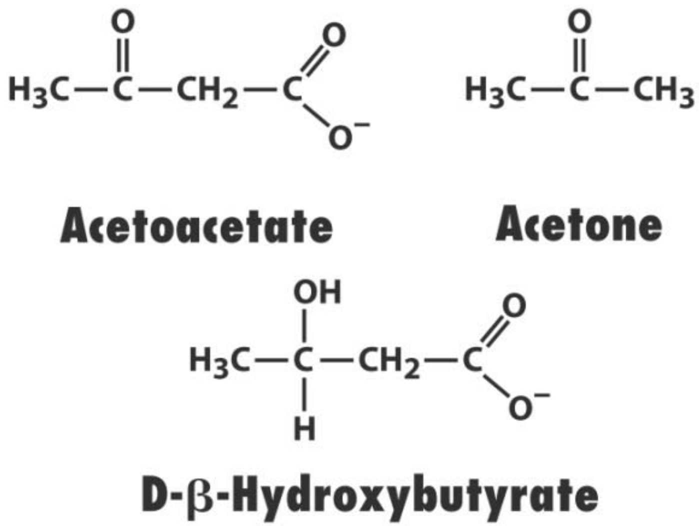


Figure 19-21 Fundamentals of Biochemistry, 2/e



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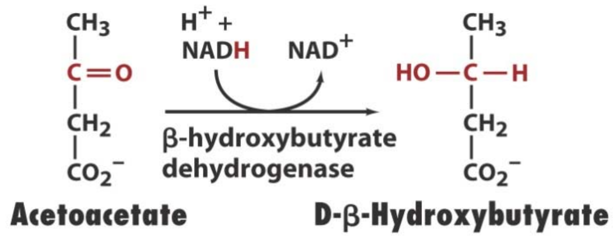
Acetoacetate formation

Ketone bodies to acetyl-CoA

ketosis



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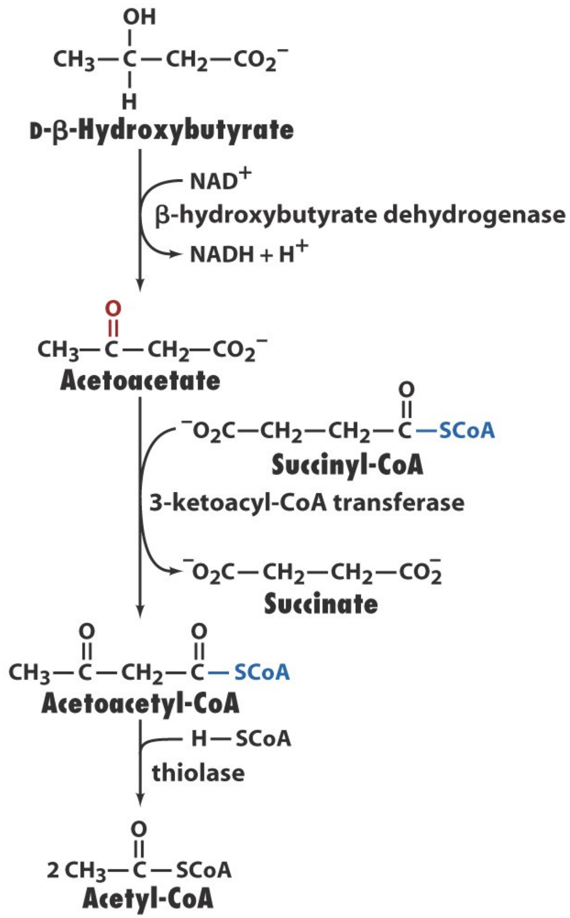

Figure 19-22 Fundamentals of Biochemistry, 2/e
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Fatty acid biosynthesis

Reverse of β-oxidation process

In humans, fatty acids are predominantly formed in the liver and lactating mammary glands, and to a lesser extent, the adipose tissue.

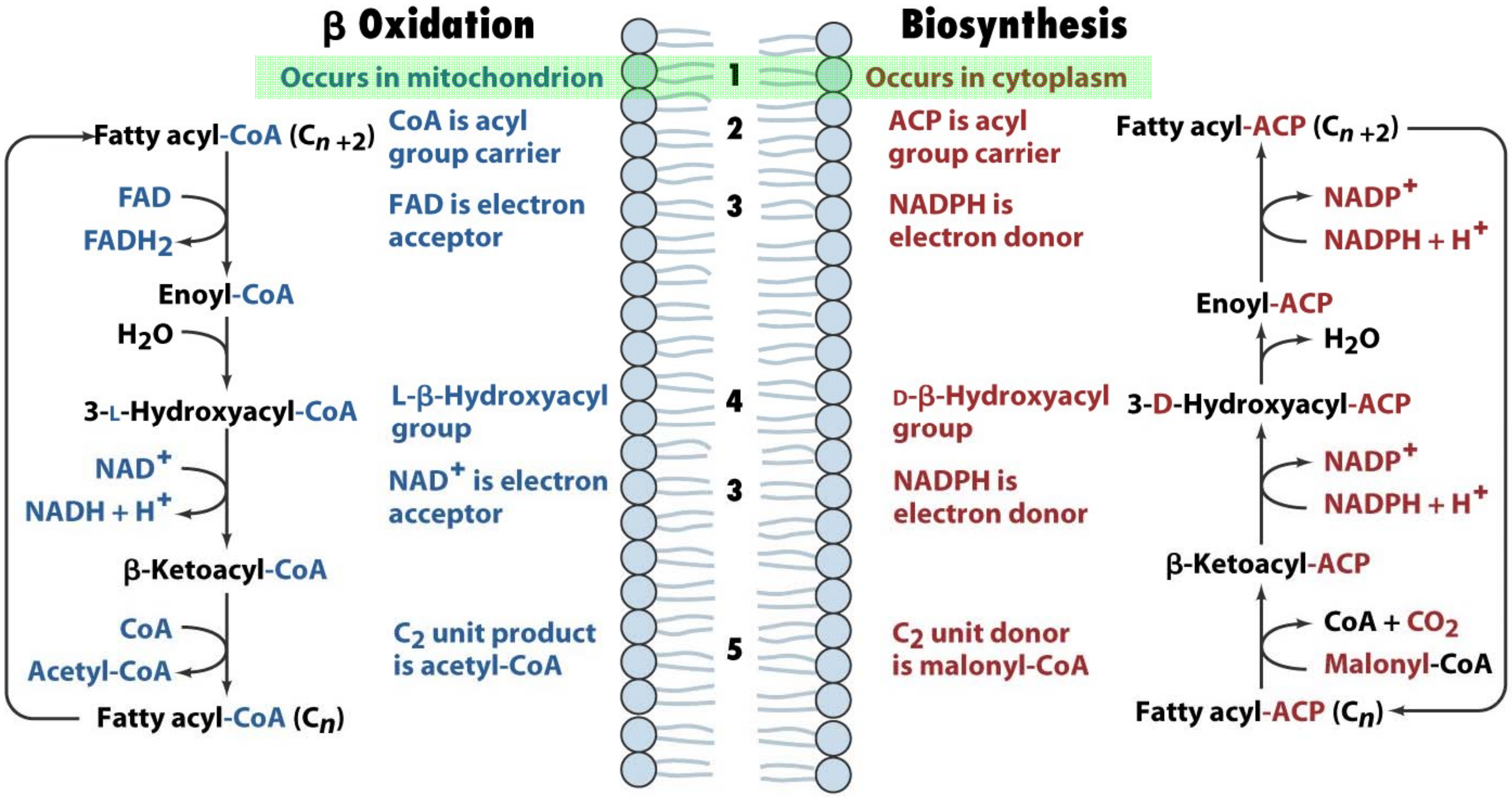


Figure 19-23 Fundamentals of Biochemistry, 2/e

Acetyl group transfer from mito to cytosol

tricarboxylate transport system
ATP-citrate lyase

Citrate + CoA + ATP →
acetyl-CoA + oxaloacetate + ADP + Pi

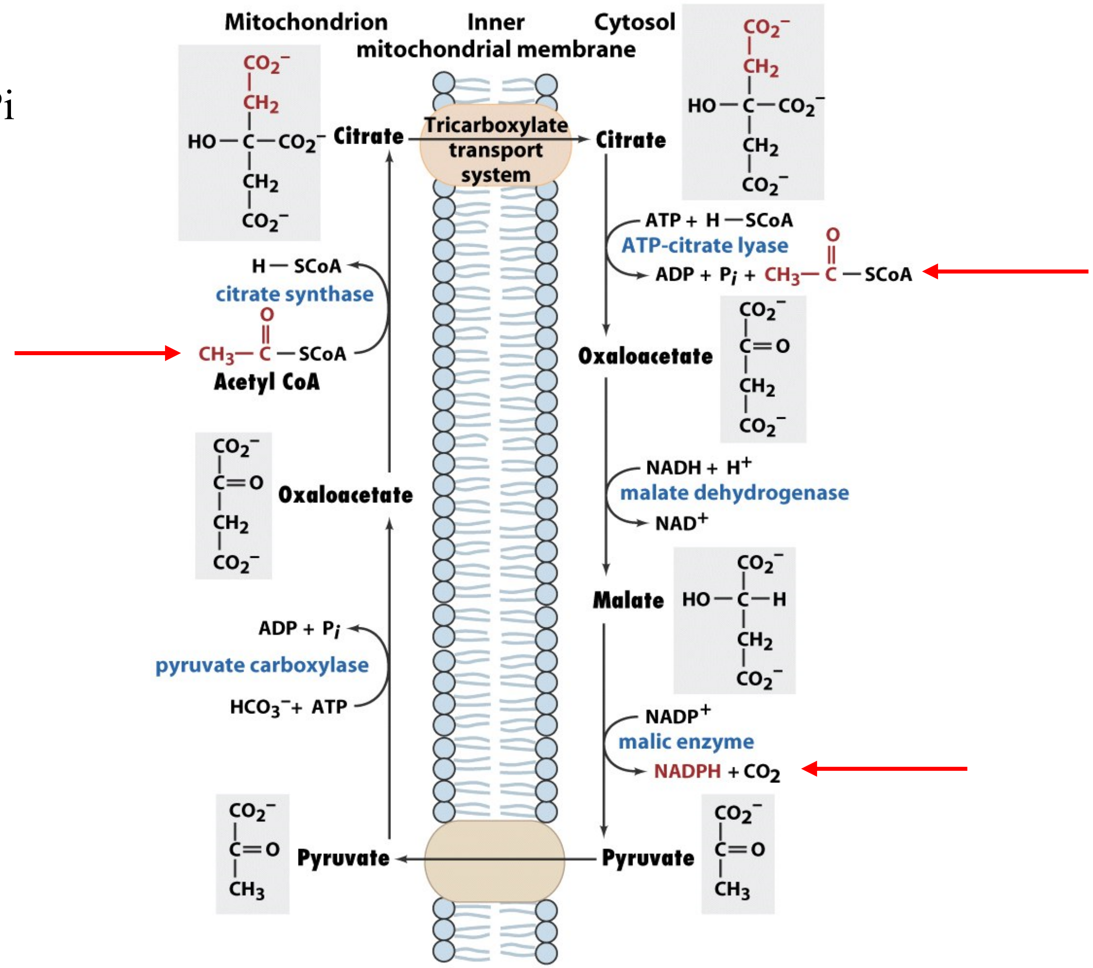


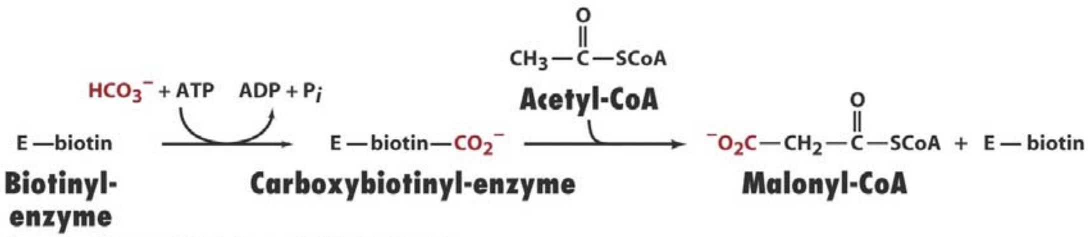
Figure 19-24 Fundamentals of Biochemistry, 2/e

Acetyl-CoA carboxylase (ACC)

The first committed step of fatty acid synthesis & r.d.s.

Allosteric and covalent regulation

CO_2 activation and carboxylation



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Mammalian ACC: two isoforms

adipose tissue, α-ACC; heart muscle, β-ACC; liver, both

Heart muscle does not synthesize fatty acids

What is the function of β-ACC?

Malonyl-CoA strongly inhibits the mito import of fatty acyl-CoA

E. coli ACC

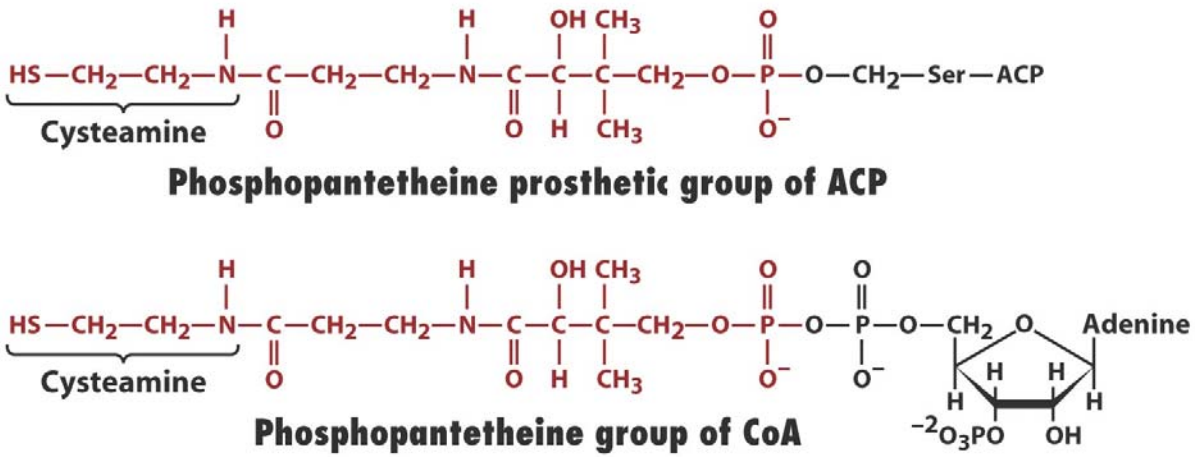
regulated by guanine nucleotides

why? Fatty acid synthesis is coordinated with cell growth

Fatty acid synthase

E. coli by individual enzymes
Plant: in chloroplast by individual enzymes
Yeast: cytosolic 2500-kD multifunctional enzyme α6β6
Animal: 534-kD consisting of two identical polypeptide chains

Acyl-carrier protein (ACP)
  in *E. coli* 10-kD polypeptide
  in animal a part of the multifunctional complex



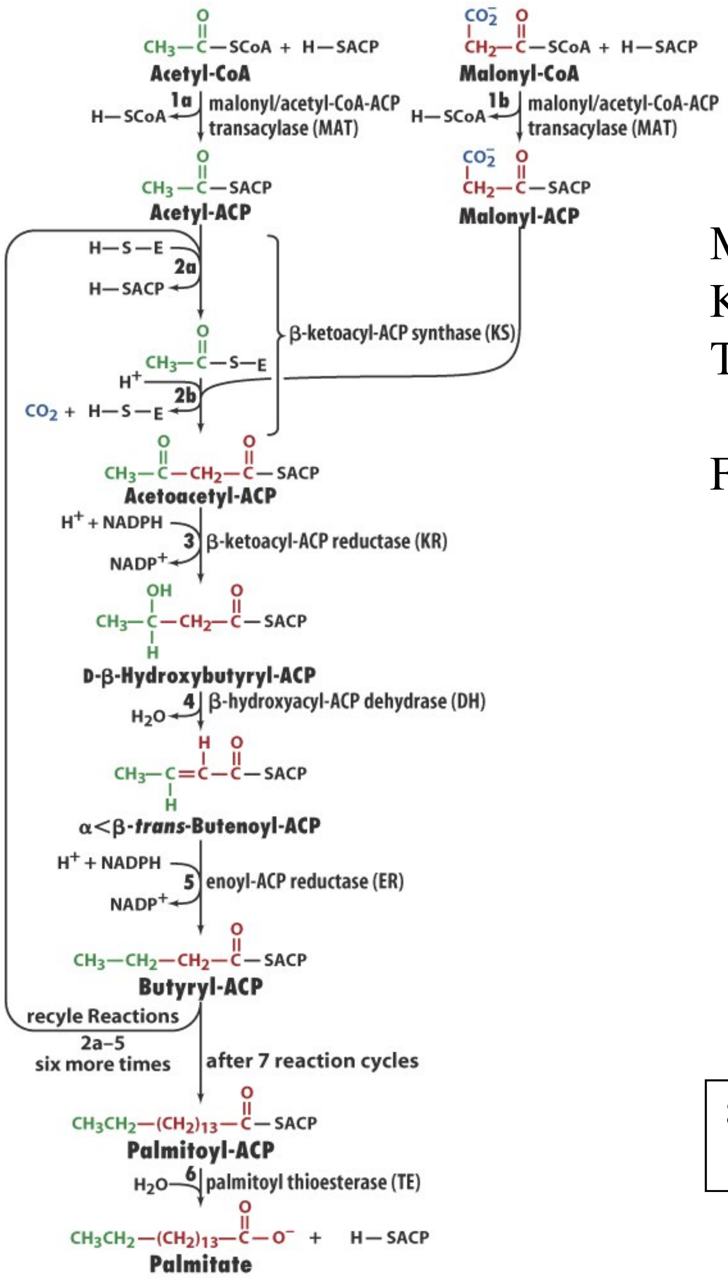


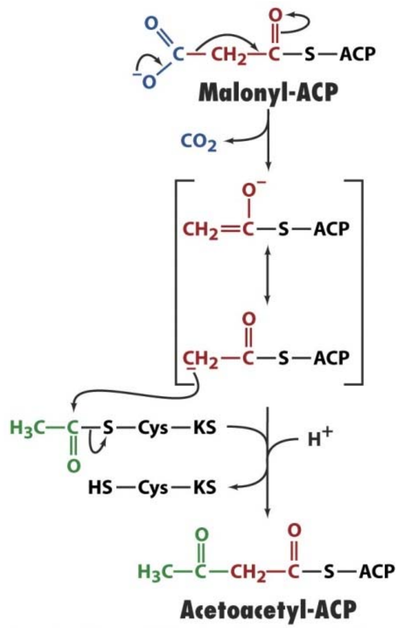
Figure 19-26 Fundamentals of Biochemistry, 2/e

MAT: acetyl or malonyl group transfer to ACP

KS (condensing enzyme)

Two reductions & a dehydration
require two NADPH

Further elongation



Unnumbered figure pg 654 Fundamentals of Biochemistry, 2/e

8 acetyl-CoA + 14 NADPH + 7 ATP →
palmitate + 14 $NADP^+$ + 8 CoA + 6 H_2O + 7 ADP + 7 Pi

Animal fatty acid synthase

Dimers operate in concert: head to tail

7 reactions by 6 discrete active sites (two by MAT)

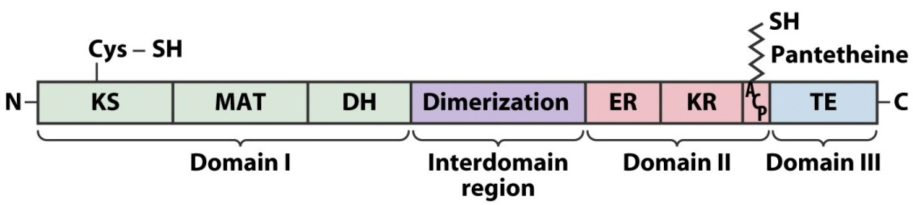


Figure 19-27 Fundamentals of Biochemistry, 2/e

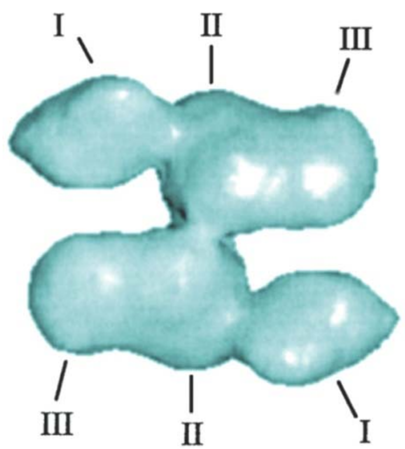
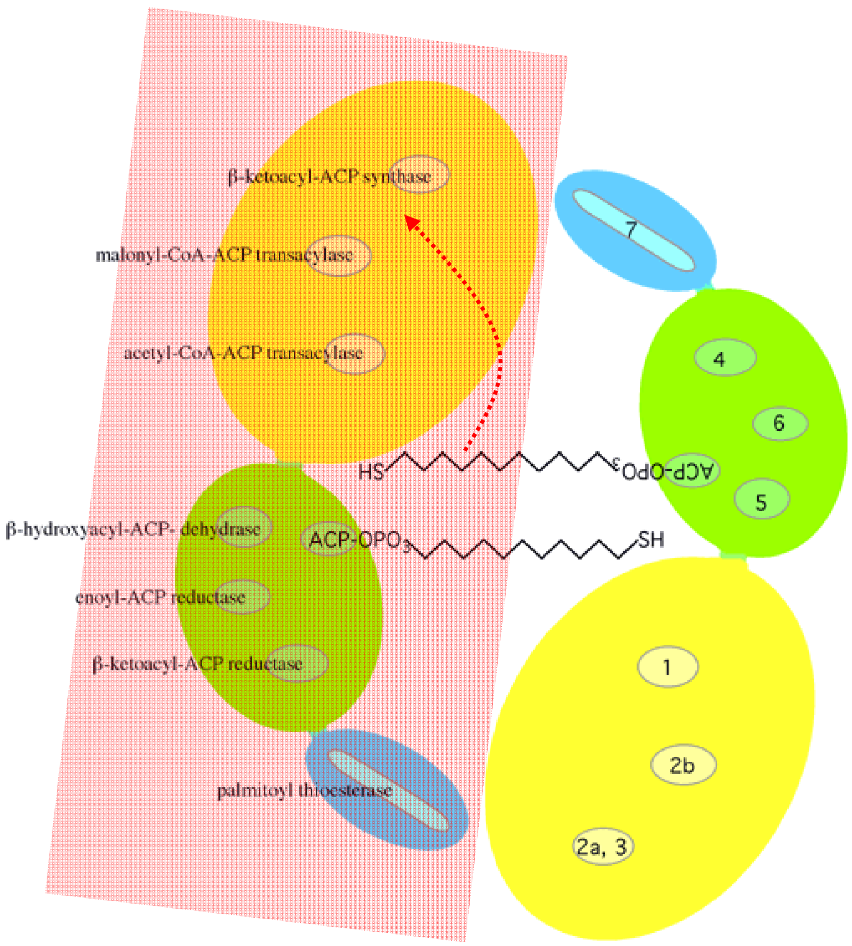


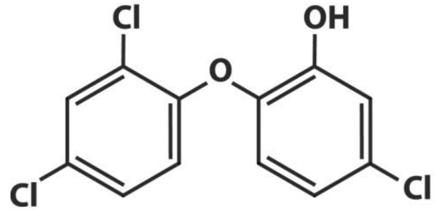
Figure 19-28 Fundamentals of Biochemistry, 2/e

Mammalian Fatty Acid Synthase



Malignant tissues: high levels of fatty acid synthase
An inhibitor of fatty acid synthesis: possible anticancer agent

Triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol)
- antibacterial agent
- inhibits enoyl-ACP reductase
- emergence of resistant strains



Triclosan

Box 19-3 figure 1 Fundamentals of Biochemistry, 2/e

Box 19-3 figure 2 Fundamentals of Biochemistry, 2/e

Elongases and desaturases

Elongases: mito & ER but in different mechanisms

more than C16

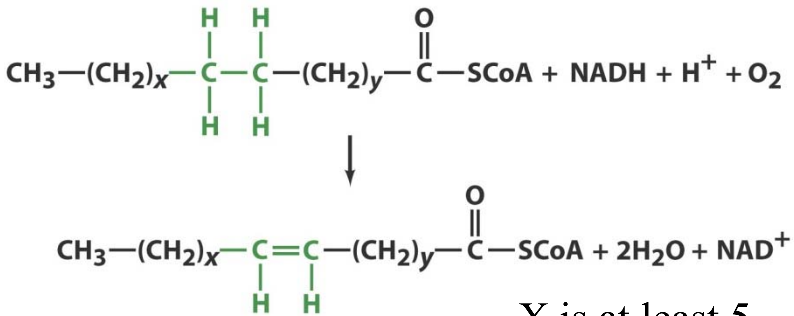
in mito: reversal of fatty acid oxidation

in ER: successive addition of malonyl-CoA

Terminal desaturases

4 enzymes of broad chain-length specificities

Δ^9-, Δ^6-, Δ^5-, Δ^4- fatty acyl-CoA desaturases



Unnumbered figure pg 657 Fundamentals of Biochemistry, 2/e

X is at least 5

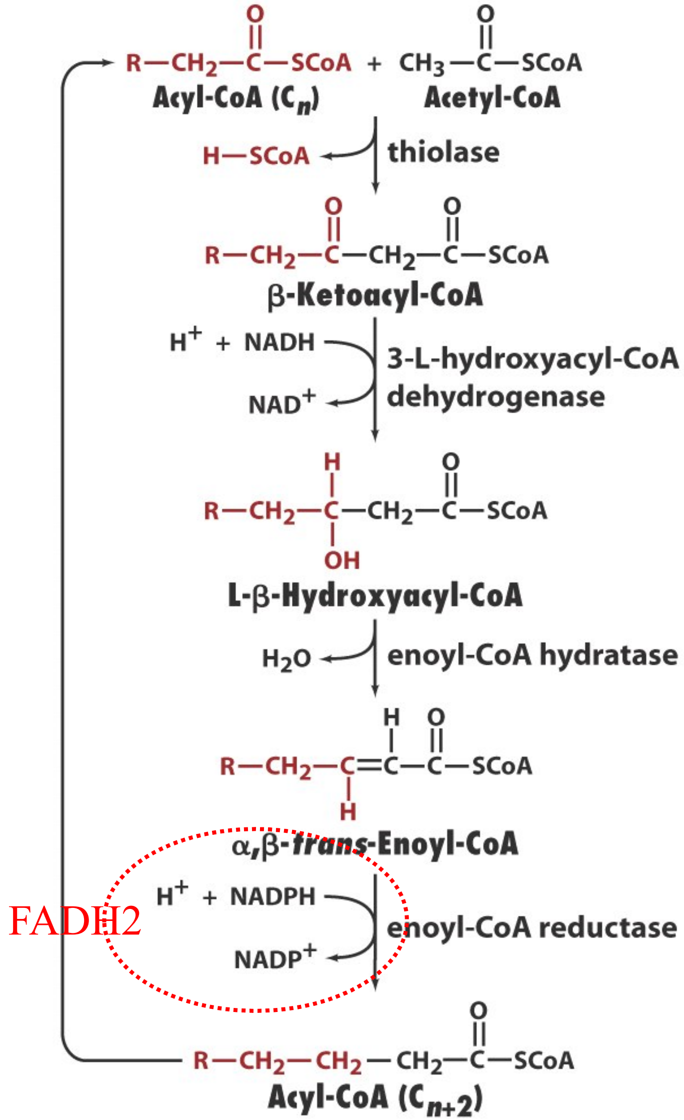


Figure 19-29 Fundamentals of Biochemistry, 2/e

Essential fatty acid:

linoleic acid (9,12-octadecadienoic acid)

A double bond at C6 from methyl end

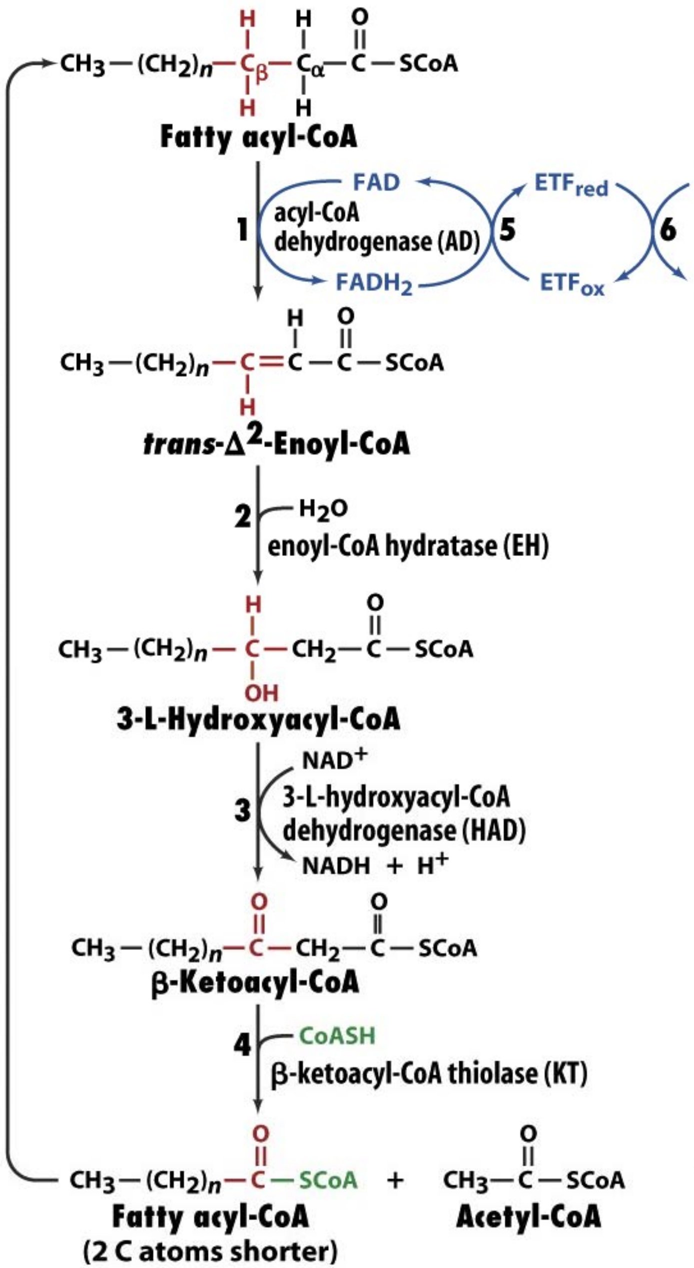


Figure 19-12 Fundamentals of Biochemistry, 2/e

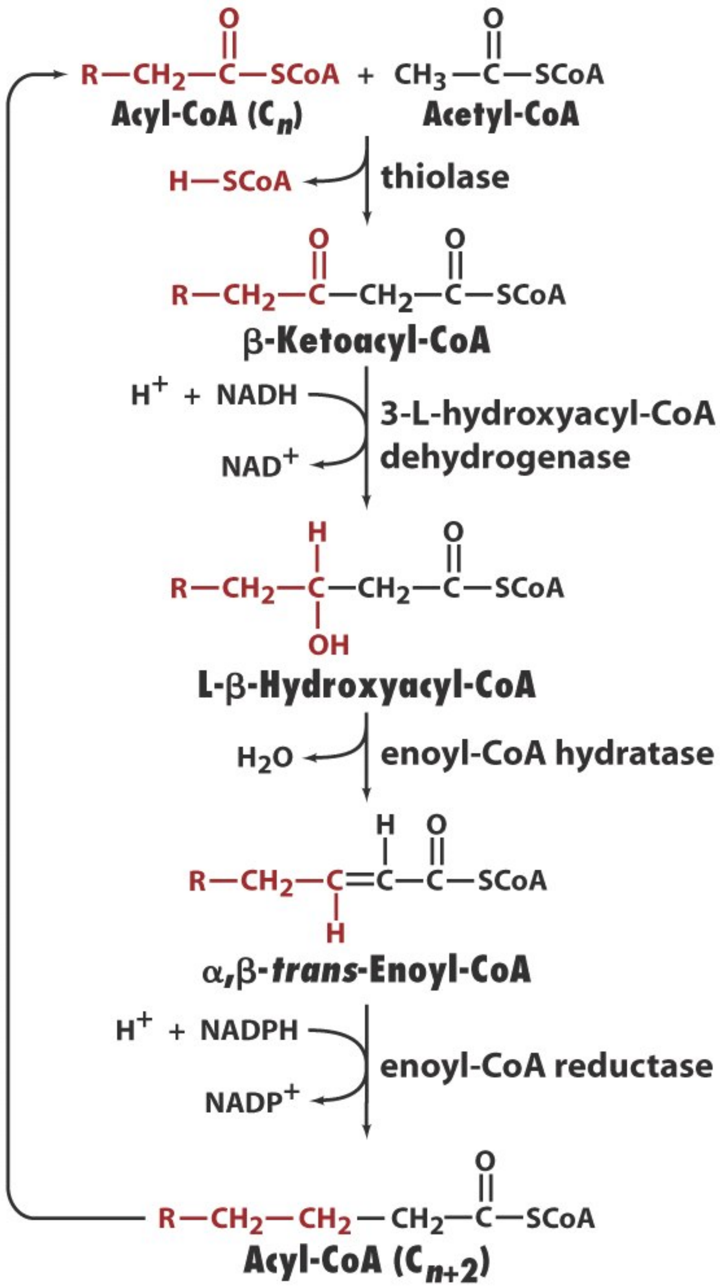


Figure 19-29 Fundamentals of Biochemistry, 2/e

Synthesis of triacylglycerols

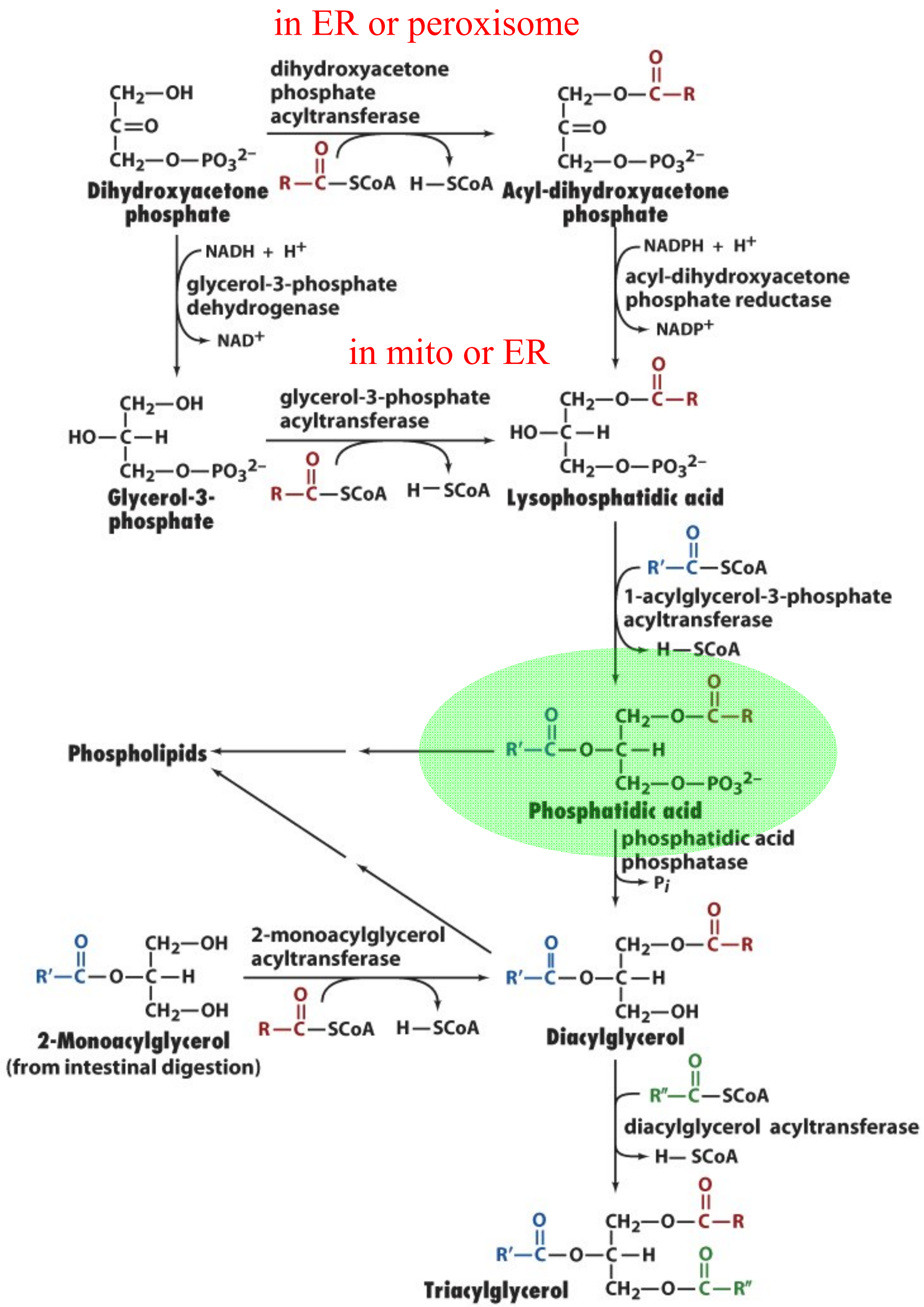


Figure 19-30 Fundamentals of Biochemistry, 2/e

<u>Glyceroneogenesis</u>

important for triacylglycerol biosynthesis
dihydroxyacetone phosphate and glycerol-3-phosphate from glycolysis
oxaloacetate via gluconeogenesis (important in times of starvation)

A summary of lipid metabolism

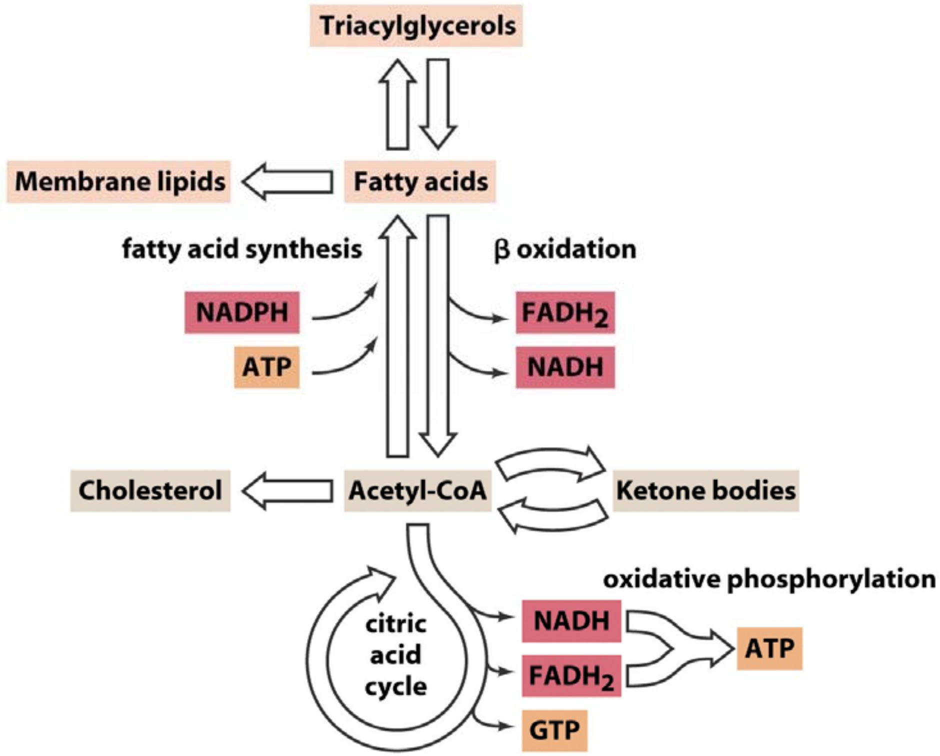


Figure 19-31 Fundamentals of Biochemistry, 2/e

Regulation of
Fatty acid metabolism

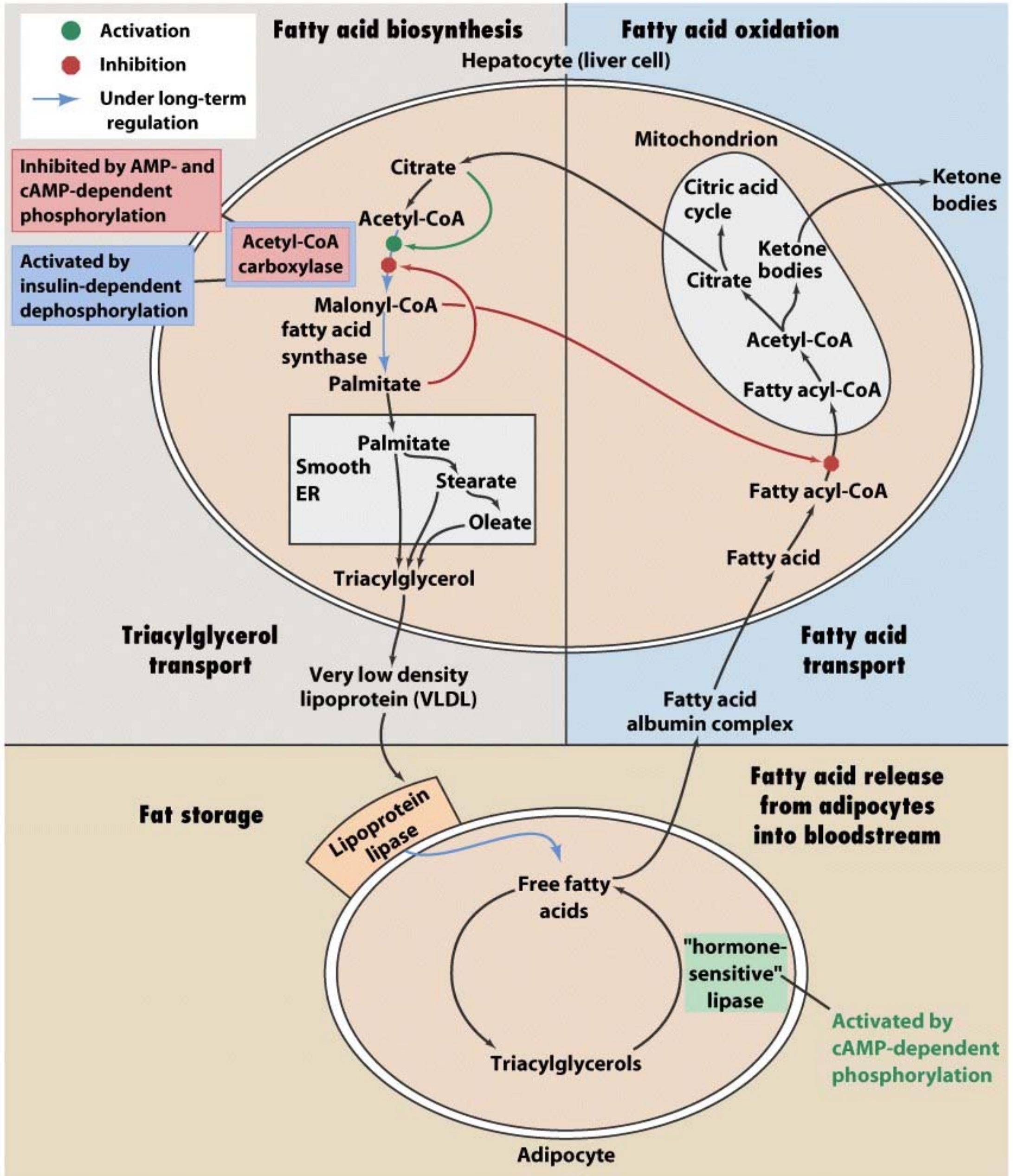


Figure 19-32 Fundamentals of Biochemistry, 2/e

Lipase

Lipoprotein lipase (LPL)

Lipoprotein lipase is found in vascular endothelium. It is activated by insulin, ACTH, TSH, glucagon and thyroid hormone. Its activity is enhanced by heparin. As discussed above, lipoprotein lipase hydrolyzes CM and VLDL to free fatty acids and glycerol and VLDL-remnants, respectively. Apolipoprotein C is essential for activation of LPL.

Hepatic lipase

This enzyme hydrolyzes surface phospholipids on lipoproteins and is responsible for converting VLDL to LDL.

Hormone sensitive lipase

This enzyme is responsible for lipolysis (mobilization of triglycerides from adipose tissue to yield free fatty acids and glycerol). The enzyme is stimulated by catecholamines, growth hormone, thyroxine, corticosteroids and prostaglandins. It is inhibited by insulin. Fatty acids are transported to the liver (free or albumin-bound), where they are taken up and used for energy (beta oxidation), combined with triglycerides to form VLDL or incorporated into ketones. Therefore, lipolysis will increase VLDL production.

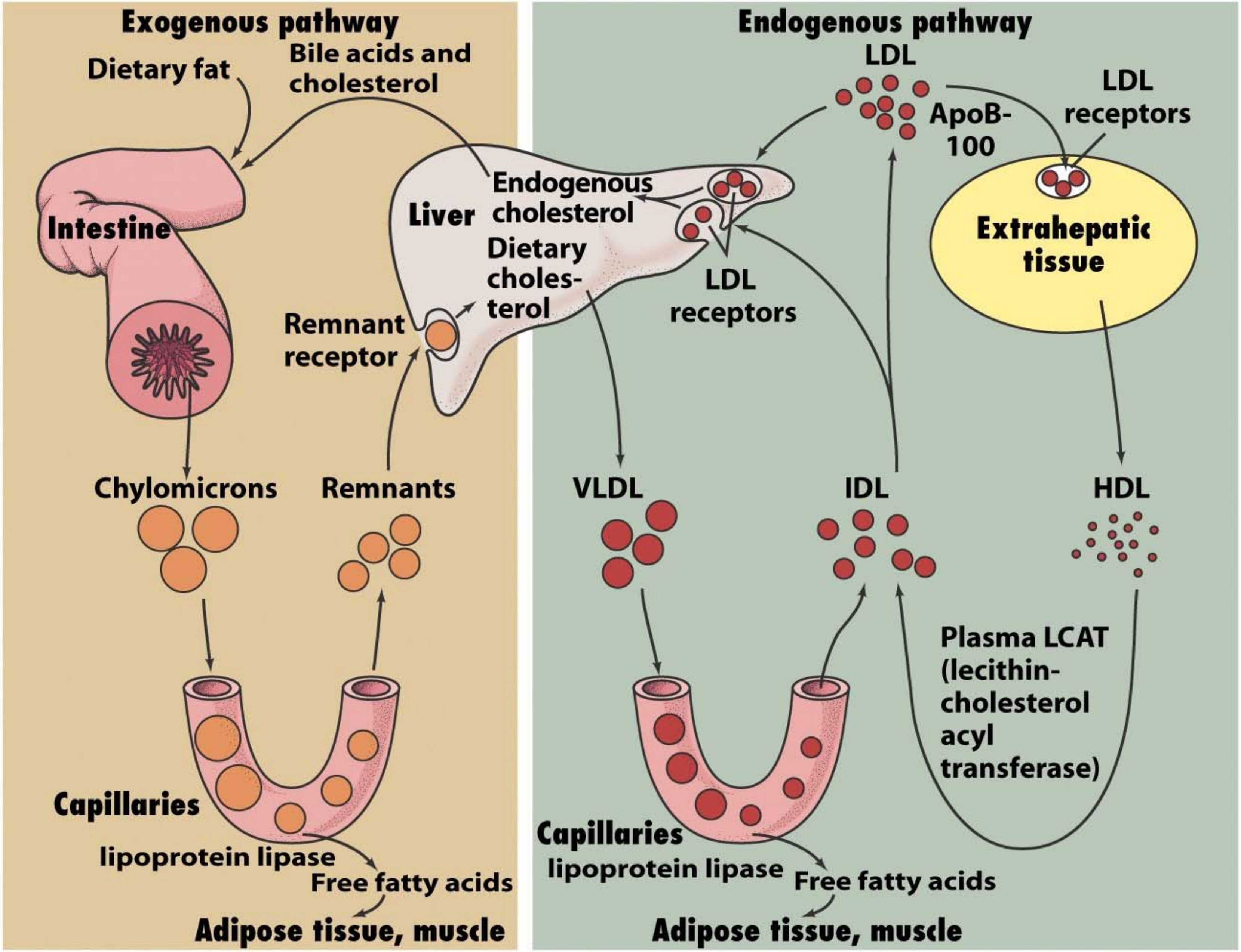


Figure 19-7 Fundamentals of Biochemistry, 2/e

Synthesis of other lipids

Membrane lipids and signal molecules

Synthesis in membranes of the cytosolic side of ER & then transport to their destinations

Gylcerolipids & sphingolipids

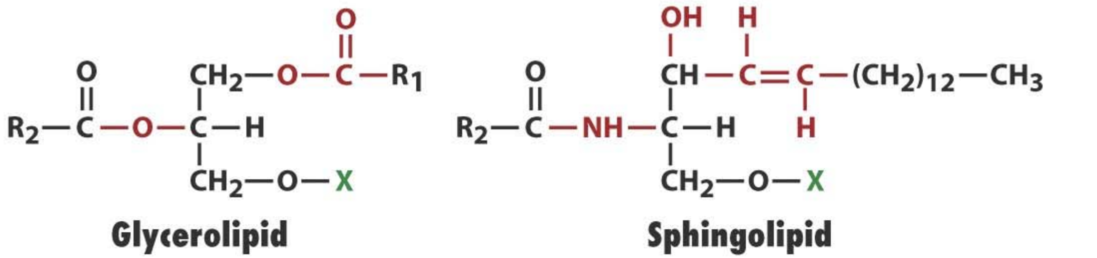
Glycerolipid

glycerophospho lipid

triacylglycerol

Sphingolipid (phospholipid or glycolipid)

phospholipid



X = H	1,2-Diacylglycerol	*N*-Acylsphingosine (ceramide)
X = Carbohydrate	Glyceroglycolipid	Sphingoglycolipid (glycosphingolipid)
X = Phosphate ester	Glycerophospholipid	Sphingophospholipid

Figure 19-33 Fundamentals of Biochemistry, 2/e

Synthesis of glycerophospholipids

C1: saturated
C2: unsaturated
C3: phosphoester group: ethanolamine, choline, serine, etc

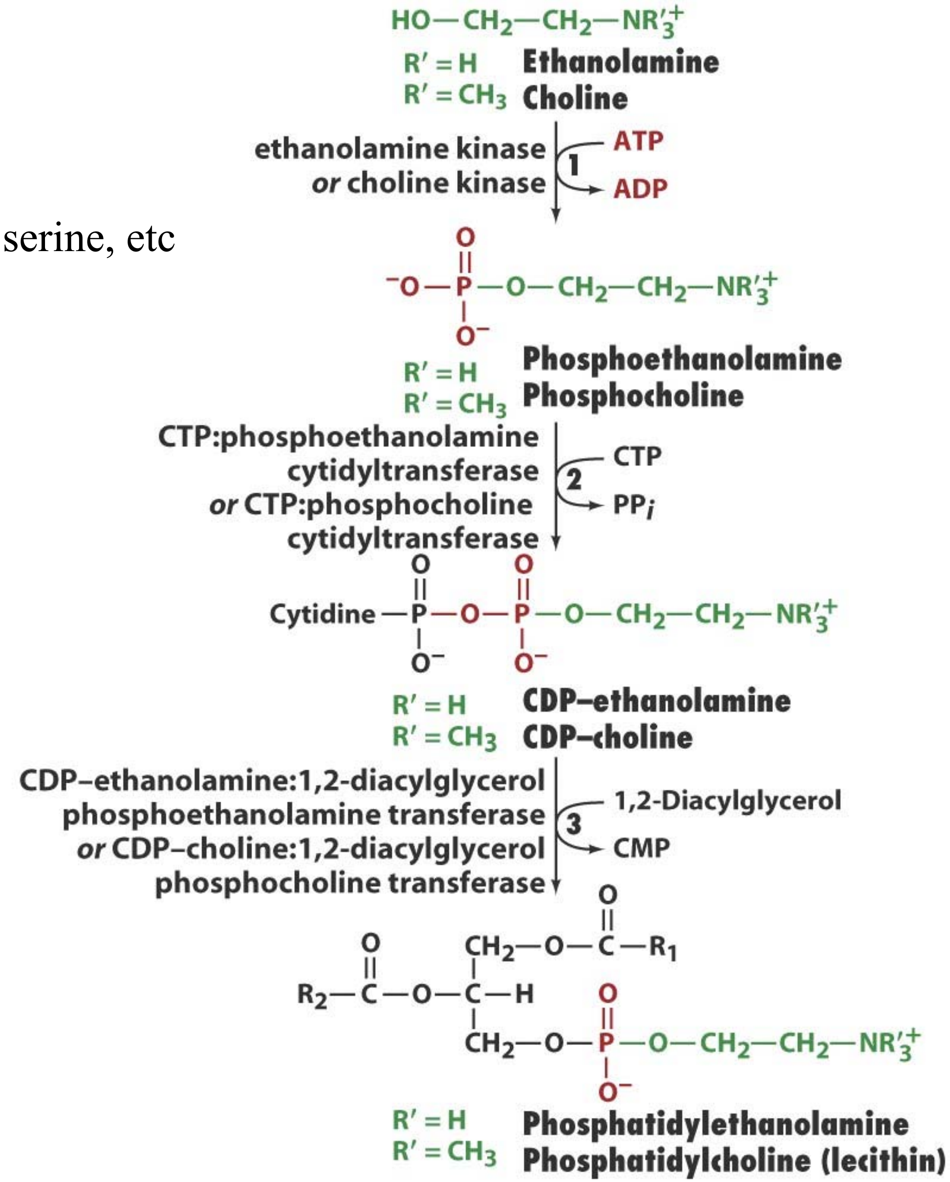
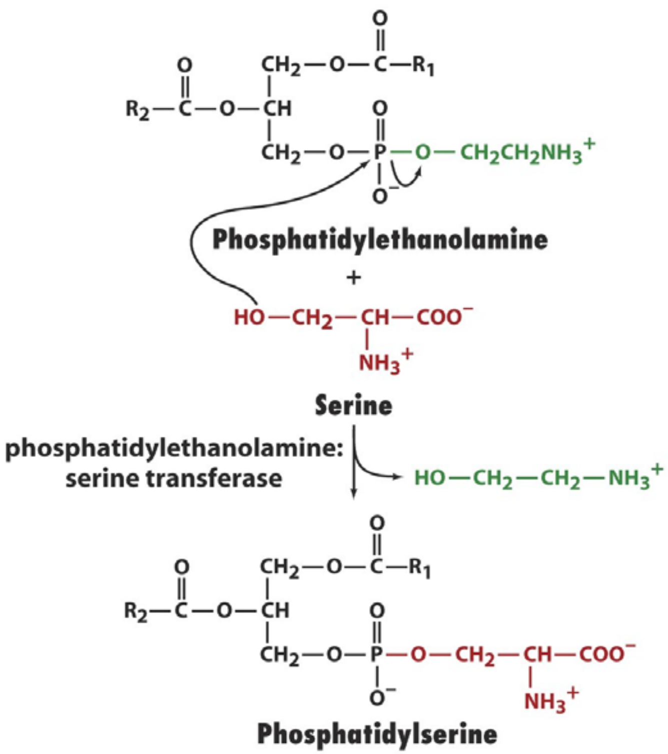
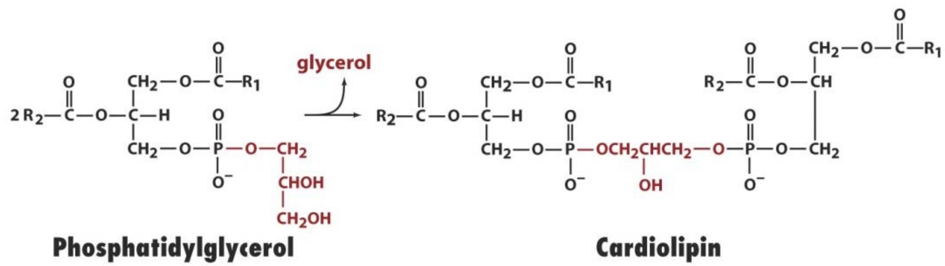


Figure 19-34 Fundamentals of Biochemistry, 2/e



Unnumbered figure pg 664a Fundamentals of Biochemistry, 2/e



Unnumbered figure pg 664b Fundamentals of Biochemistry, 2/e

Synthesis of PI and PG

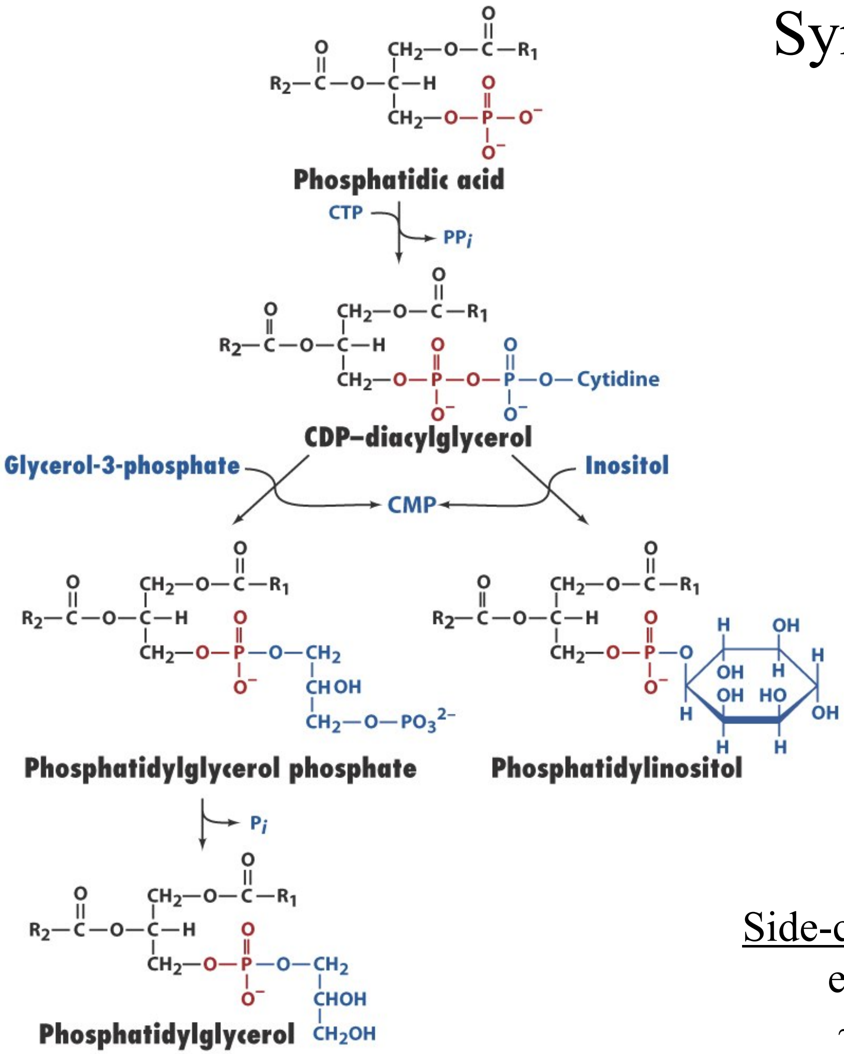


Figure 19-35 Fundamentals of Biochemistry, 2/e

<u>Side-chain specificity: remodeling reactions</u>

exchanged by specific phospholipases & acyltransferases

~80% of brain PI

Stearoyl group (18:0) at C1

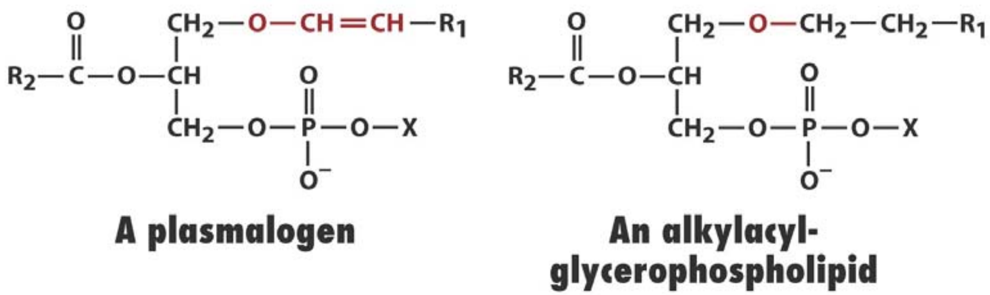
Arachidonic group (20:4) at C2

~40% of lung PC

Palmitoyl groups (16:0) at C1& C2

Biosynthesis of plasmalogen & alkylacylglycerophospholipids

- C1 in ether linkage
- variable abundance among species and tissues
- abundant in nervous, immune, and cardiovascular system



Unnumbered figure pg 666a Fundamentals of Biochemistry, 2/e

Biosynthesis of sphingolipids

Most are glycolipids: carbohydrate units to the C1-OH
Biosynthetic precursors: palmitoyl-CoA & serine

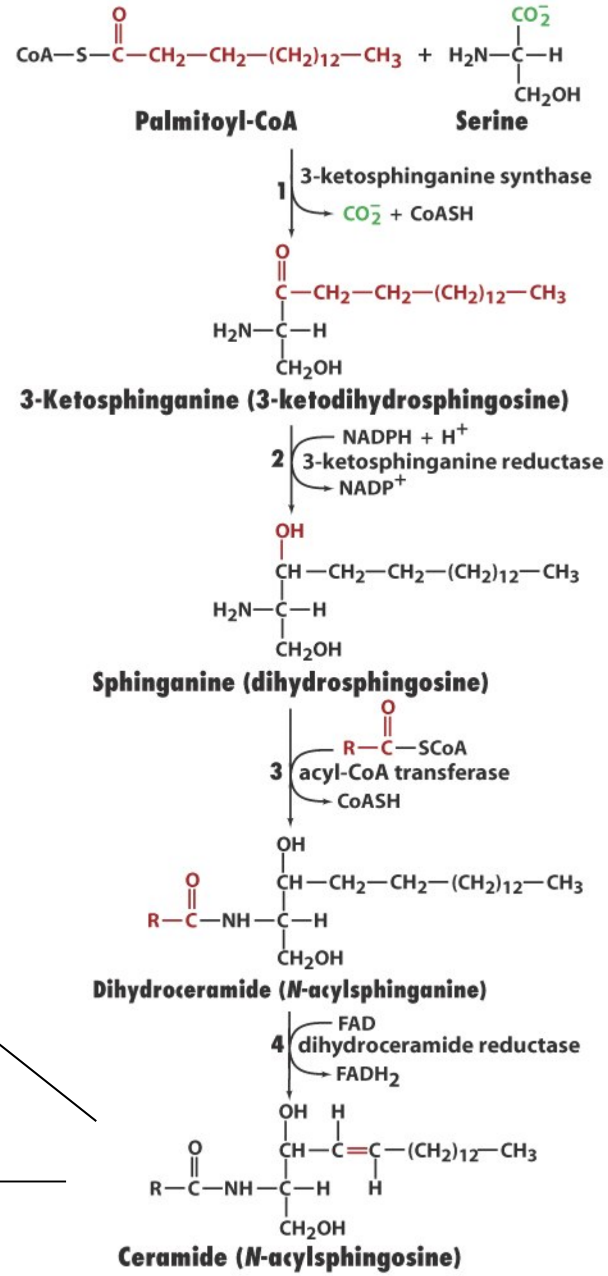
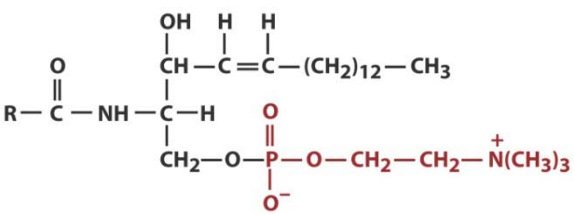


Figure 19-36 Fundamentals of Biochemistry, 2/e

Galactoceramide
Glucoceramide
ganglioside

UDP-hexose

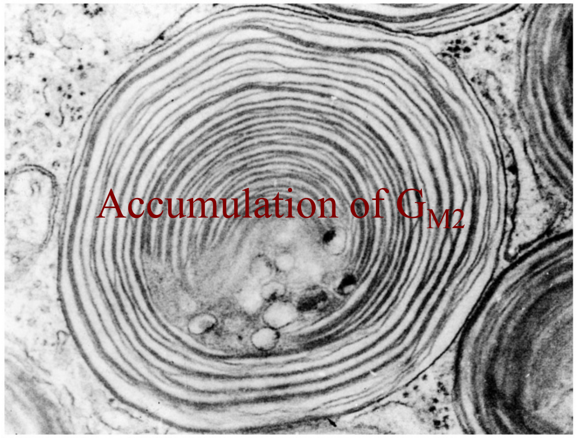
phosphocholine



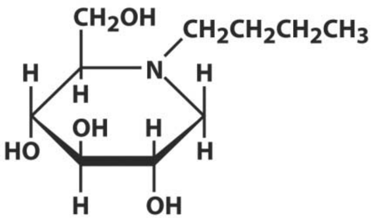
Sphingomyelin

Unnumbered figure pg 666b Fundamentals of Biochemistry, 2/e

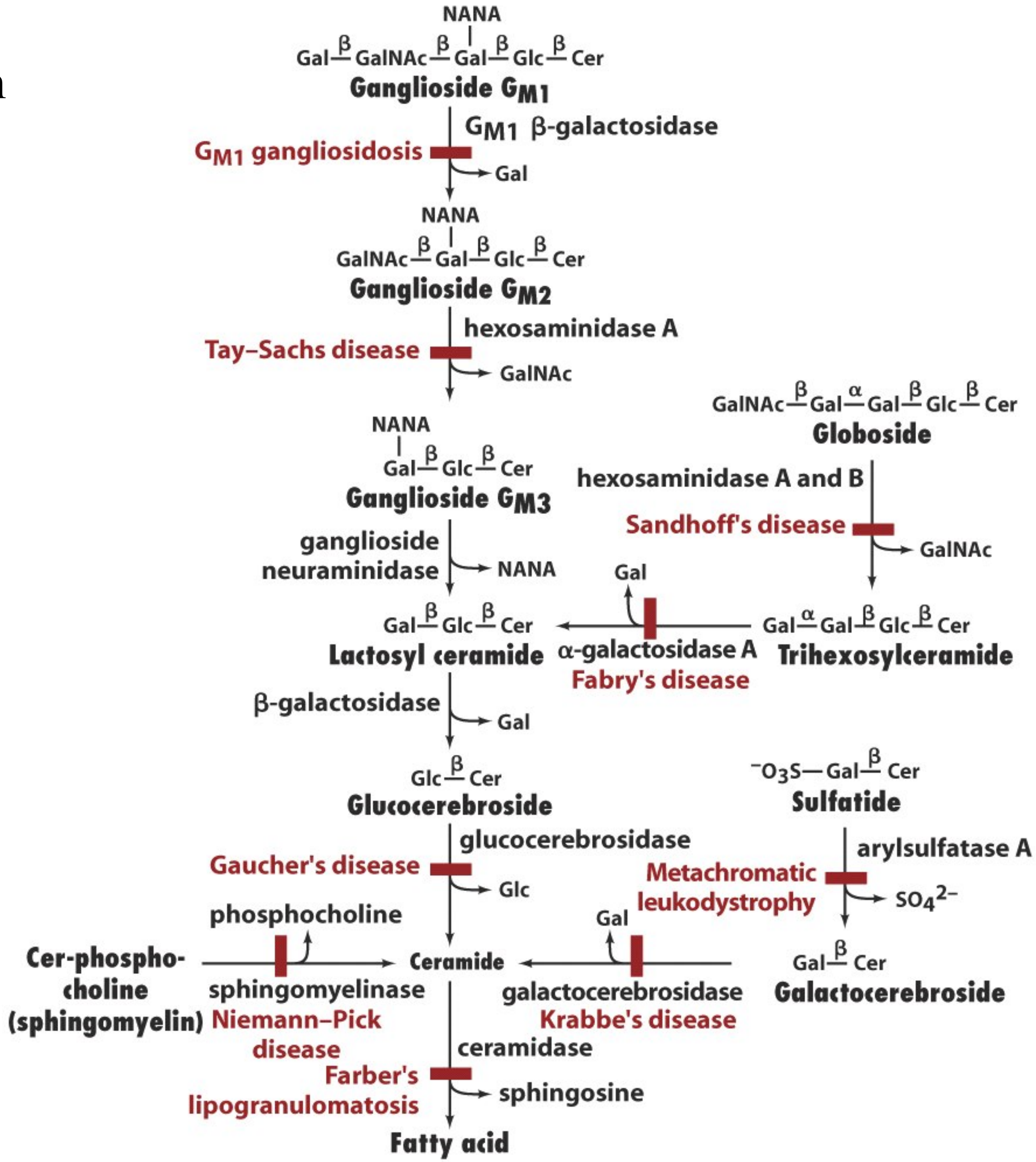
Sphingolipid degradation
and
Lipid storage diseases



Box 19-4 figure 2 Fundamentals of Biochemistry, 2/e



***N*-Butyldeoxynojirimycin**



Box 19-4 figure 1 Fundamentals of Biochemistry, 2/e

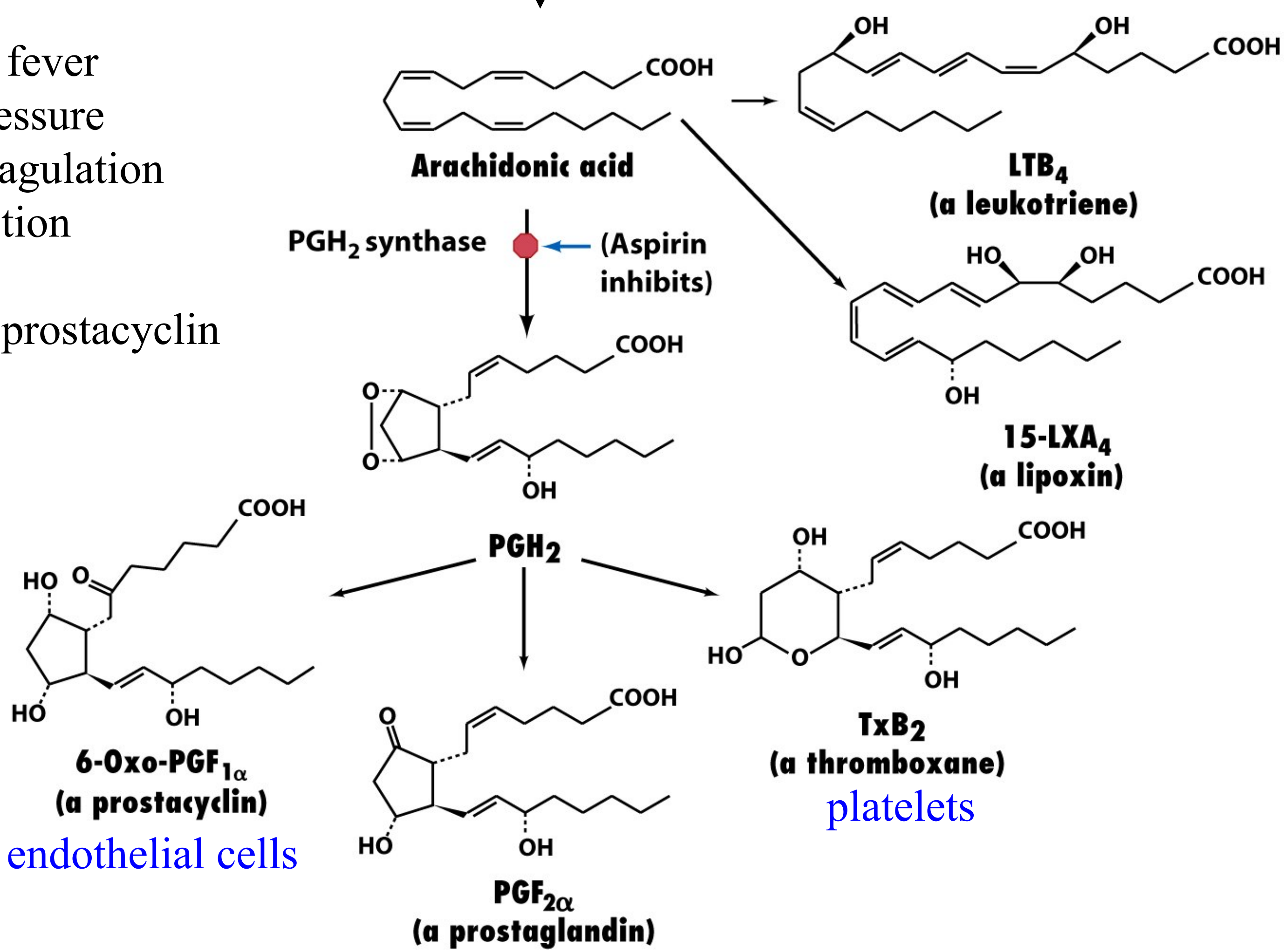
Eicosanoids from arachidonic acid (p 247, Fig. 9-12)

Act at very low conc and locally
Tissue dependent products
Varity of function
- pain and fever
- blood pressure
- blood coagulation
- reproduction

Opposite actions
- thromboxane & prostacyclin

C2 ester of phosphatidylinositol in membrane

phospholipase A2



endothelial cells

platelets

Figure 9-12 Fundamentals of Biochemistry, 2/e

Prostaglandins

Prostaglandin H2 synthase (COX)

Cyclooxygenase & peroxidase

Two isoforms: COX-1 & COX-2

COX-1: constitutive expression in most tissue

COX-2: certain tissue in response to inflammatory stimuli

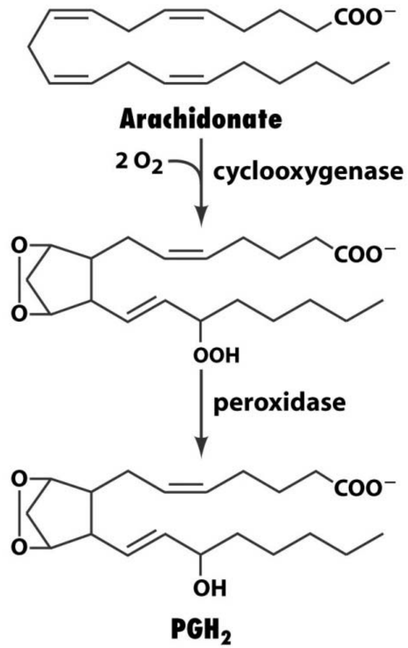
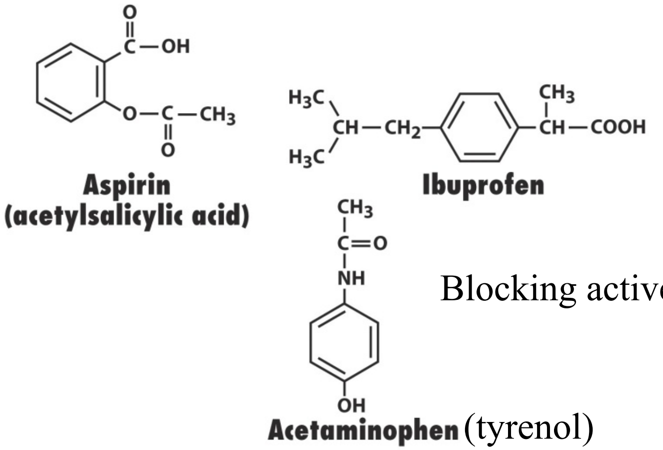


Figure 19-37 Fundamentals of Biochemistry, 2/e

Acetylation of a Ser residue

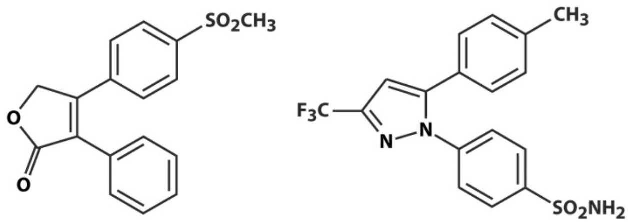


Blocking active site

(tyrenol)

Unnumbered figure pg 670a Fundamentals of Biochemistry, 2/e

COX-2 specific



Rofecoxib (Vioxx) **Celecoxib (Celebrex)**

Unnumbered figure pg 670b Fundamentals of Biochemistry, 2/e

Finding of COX-3: a target of acetaminophen?

Poor binding of acetaminophen to COX-1 & -2

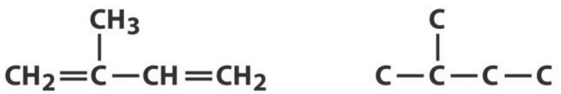
Cholesterol metabolism

<u>Biosynthesis</u>

HMG-CoA synthesis in cytosol: thiolase & HMG-CoA synthase
(in mitochondria for ketone bodies)

Mevalonate (C6): by HMG-CoA reductase (ER membrane protein)
the rate limiting step

Isopentenyl pyrophosphate (C5)



Isoprene (2-methyl-1,3-butadiene)

An isoprene unit

Unnumbered figure pg 671 Fundamentals of Biochemistry, 2/e

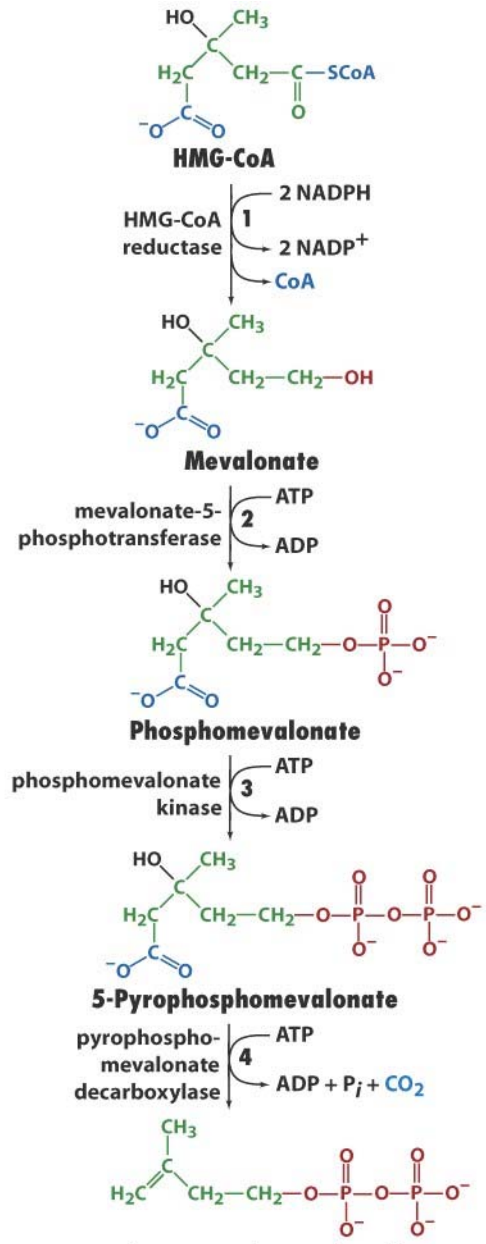
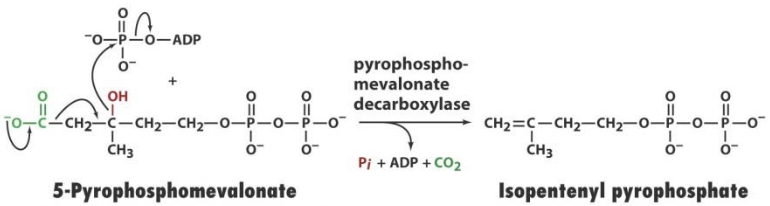
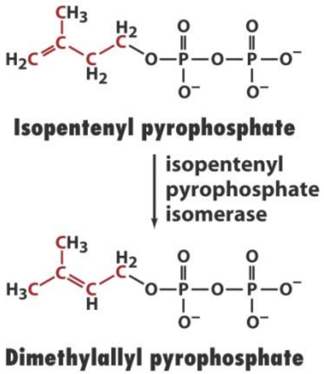
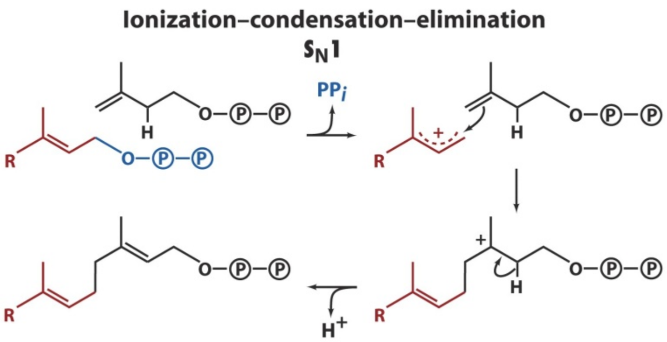


Figure 19-38 Fundamentals of Biochem







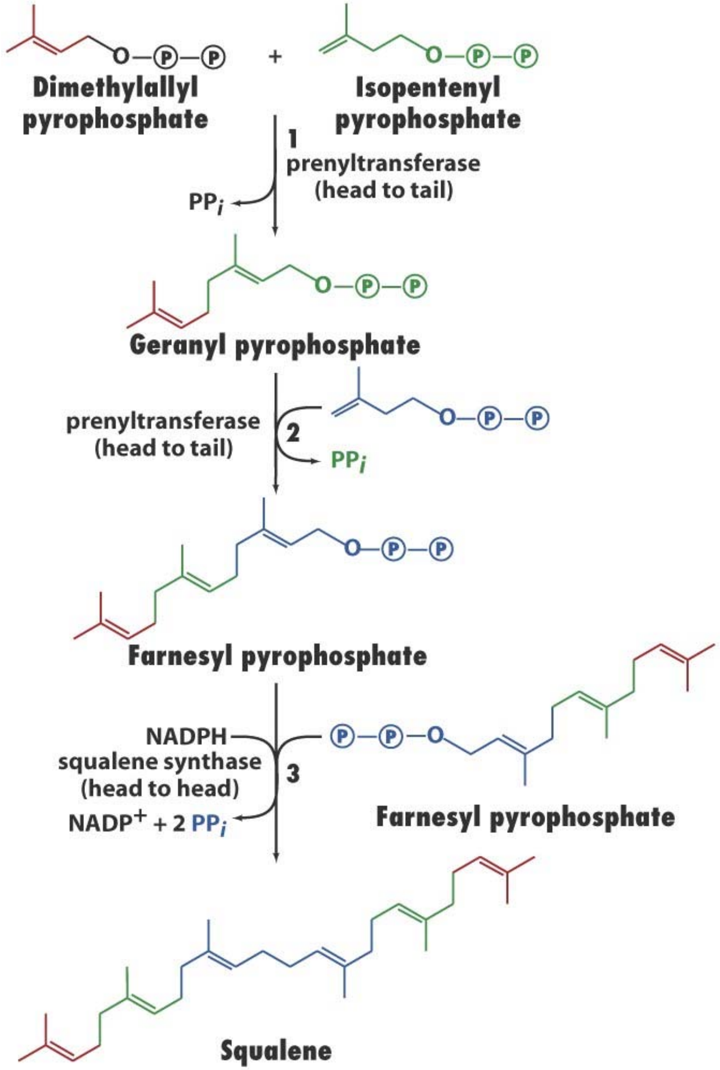
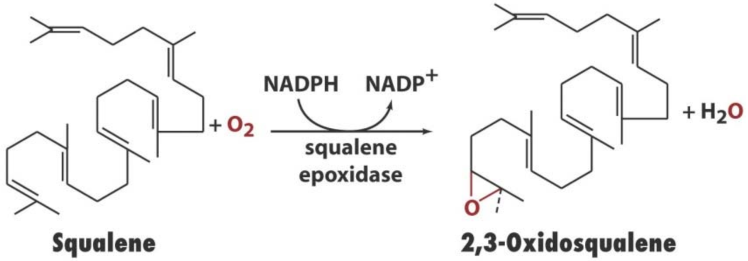
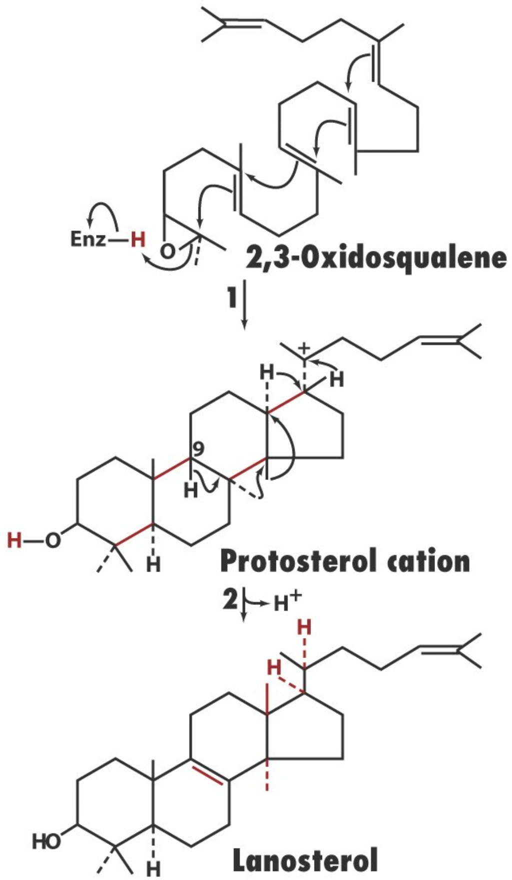
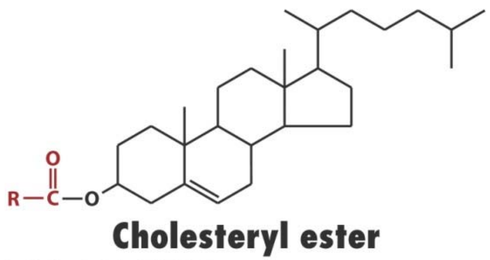
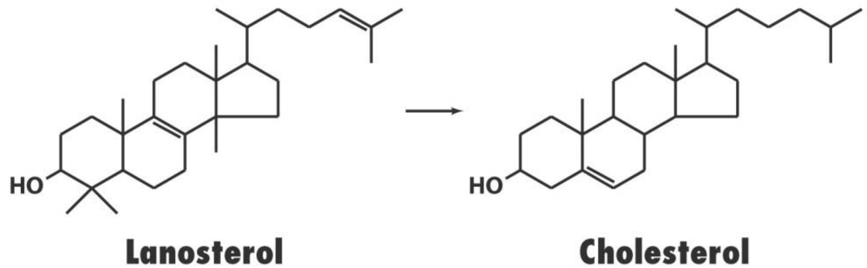


Figure 19-39 Fundamentals of Biochemistry, 2/e


NADPH
NADP+
squalene
epoxidase
+ O2
+ H2O
O
Squalene
2,3-Oxidosqualene


Enz—H
O
2,3-Oxidosqualene
1
H
H
+
9
H
H—O
H
Protosterol cation
2
H+
H
H
HO
H
Lanosterol


O
R—C—O
Cholesteryl ester

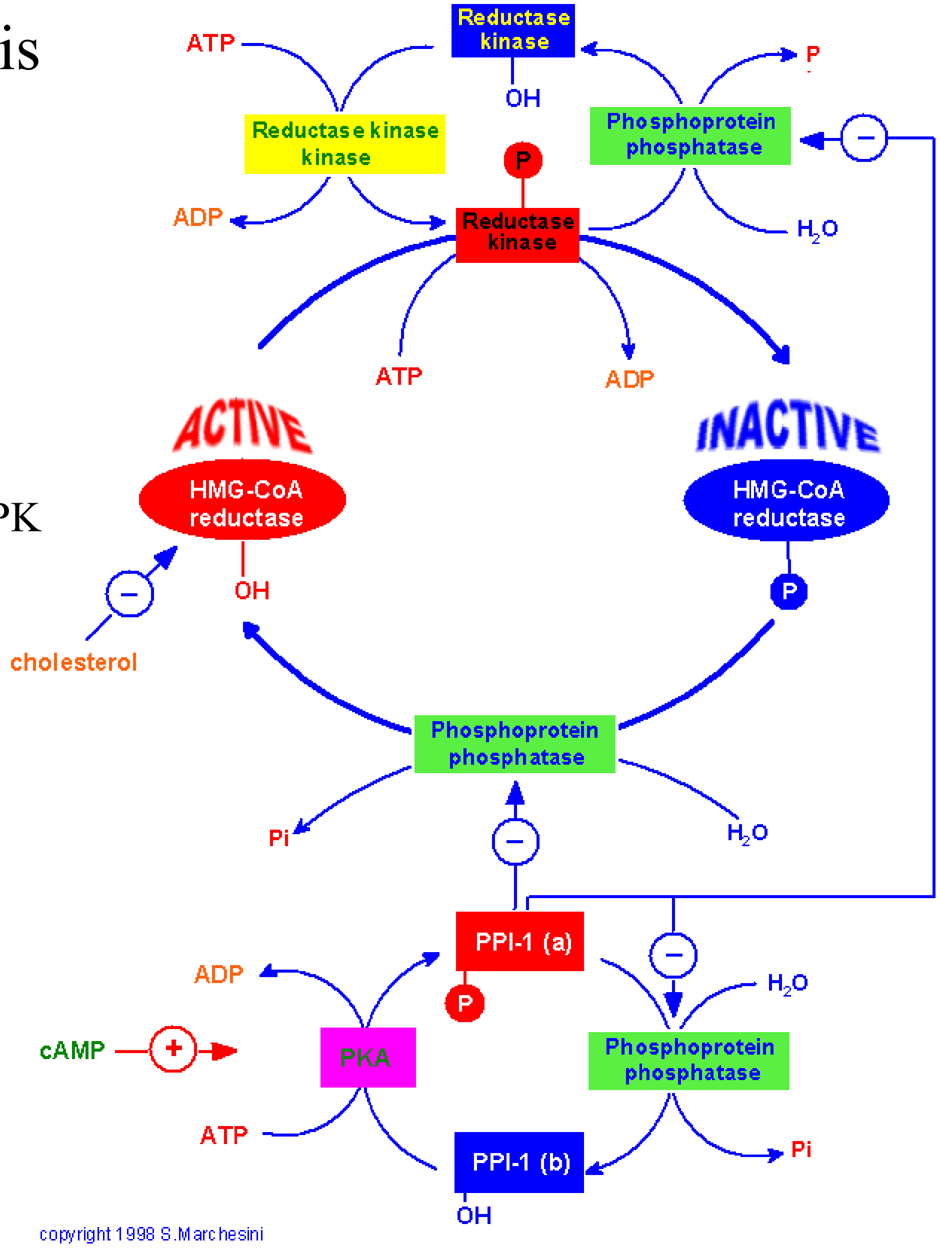

HO
HO
Lanosterol
Cholesterol

Regulation of cholesterol synthesis

The main regulation: HMG-CoA reductase

<u>Short-term regulation</u>
Competitive inhibition
Allosteric effects
Covalent modification: phosphorylation by AMPK

AMPK
http://www.indstate.edu/thcme/mwking/ampk.html



http://www.med.unibs.it/~marchesi/cholest.html

Long-term control: gene expression

the primary regulation

Increased as much as 200-fold along with >20 other genes for synthesis and uptake

Sterol regulatory element (SRE)

SREBP: regulatory & bHLH domains

SCAP: SREBP cleavage-activating protein

    sterol-sensing domain & WD repeat

Activation procedure

- Low cholesterol in ER
- SCAP conformation change
- Transport to golgi apparatus via membranous vesicles
- Site-1 protease
- Site-2 protease
- bHLH binding to SRE

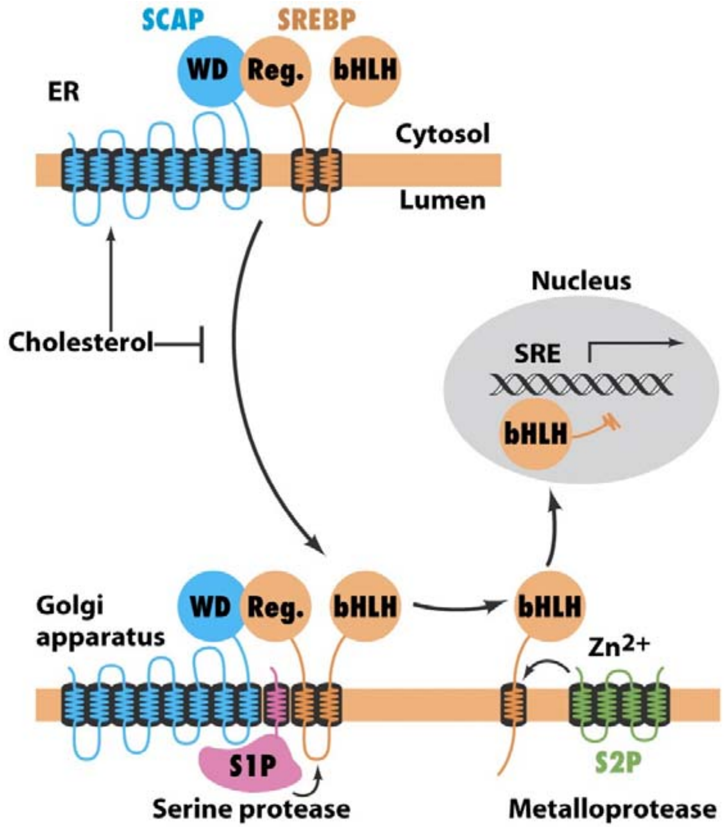


Figure 19-42 Fundamentals of Biochemistry, 2/e

HMG-CoA reductase inhibitors: statins

Hypercholesterolemia
Competitive inhibitor of HMG-CoA reductase
Km for HMG-CoA is ~4 uM
Km for statins is nM range

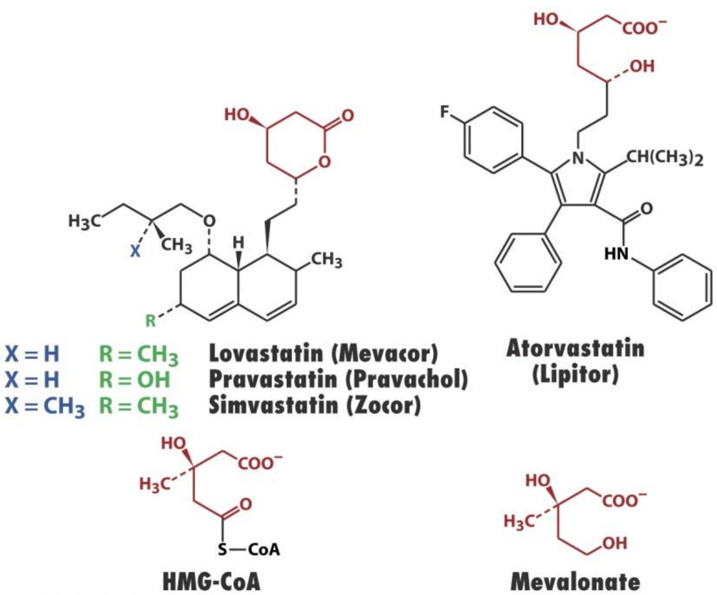
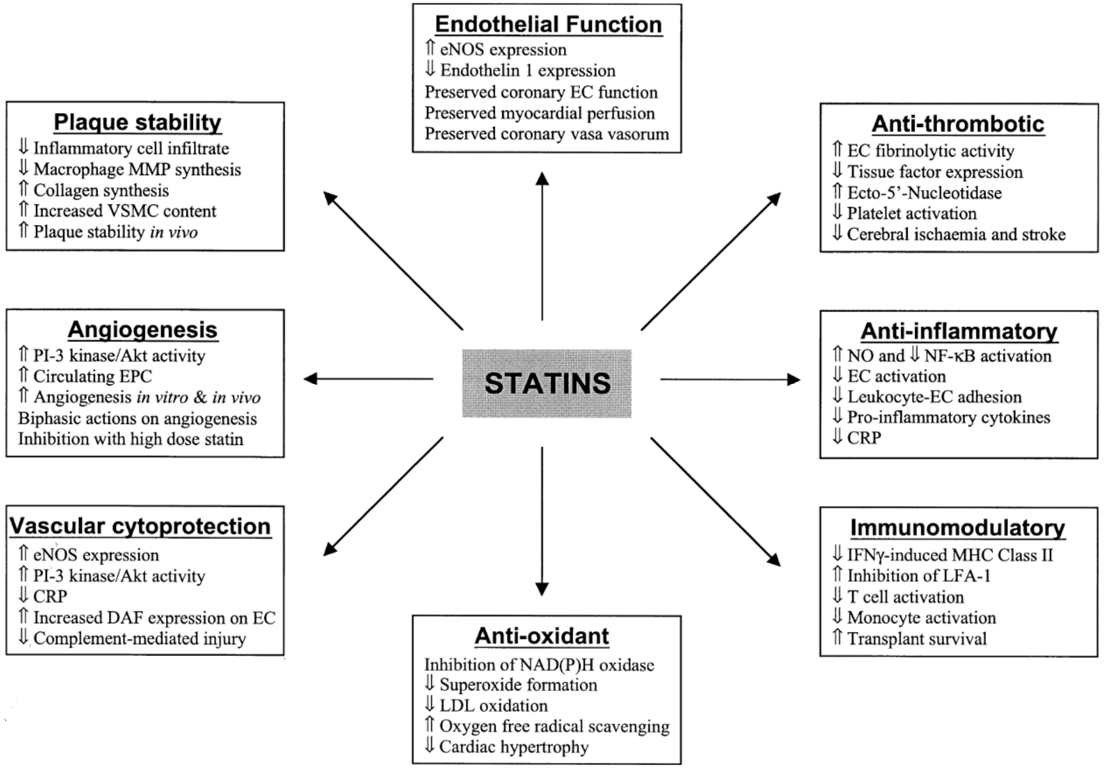


Figure 19-43 Fundamentals of Biochemistry, 2/e



http://www.clinsci.org/cs/105/0251/cs1050251f03.htm?resolution=HIGH

Cholesterol transport and atherosclerosis

Cellular cholesterol concentration depends on
- the rate of cholesterol synthesis
- the ability of cell to absorb cholesterol from circulating lipoproteins

High LDL is a strong risk factor for cardiovascular disease
Accumulation of lipid in vessel walls: Atherosclerosis
- Myocardial infarction (heart attack)
- Stroke (brain)

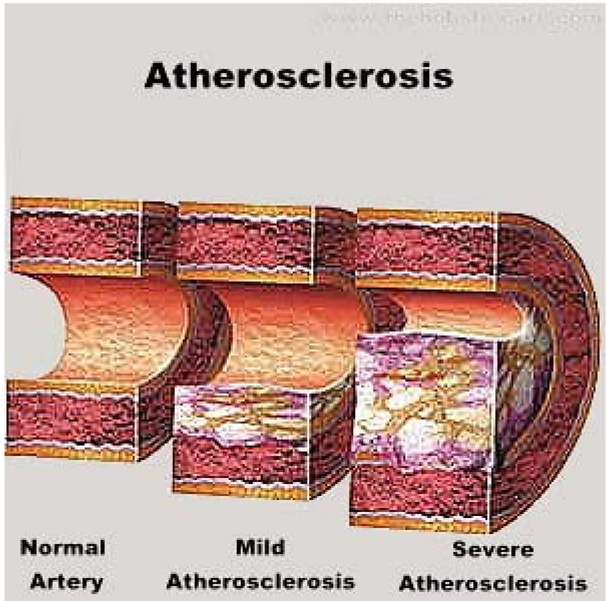
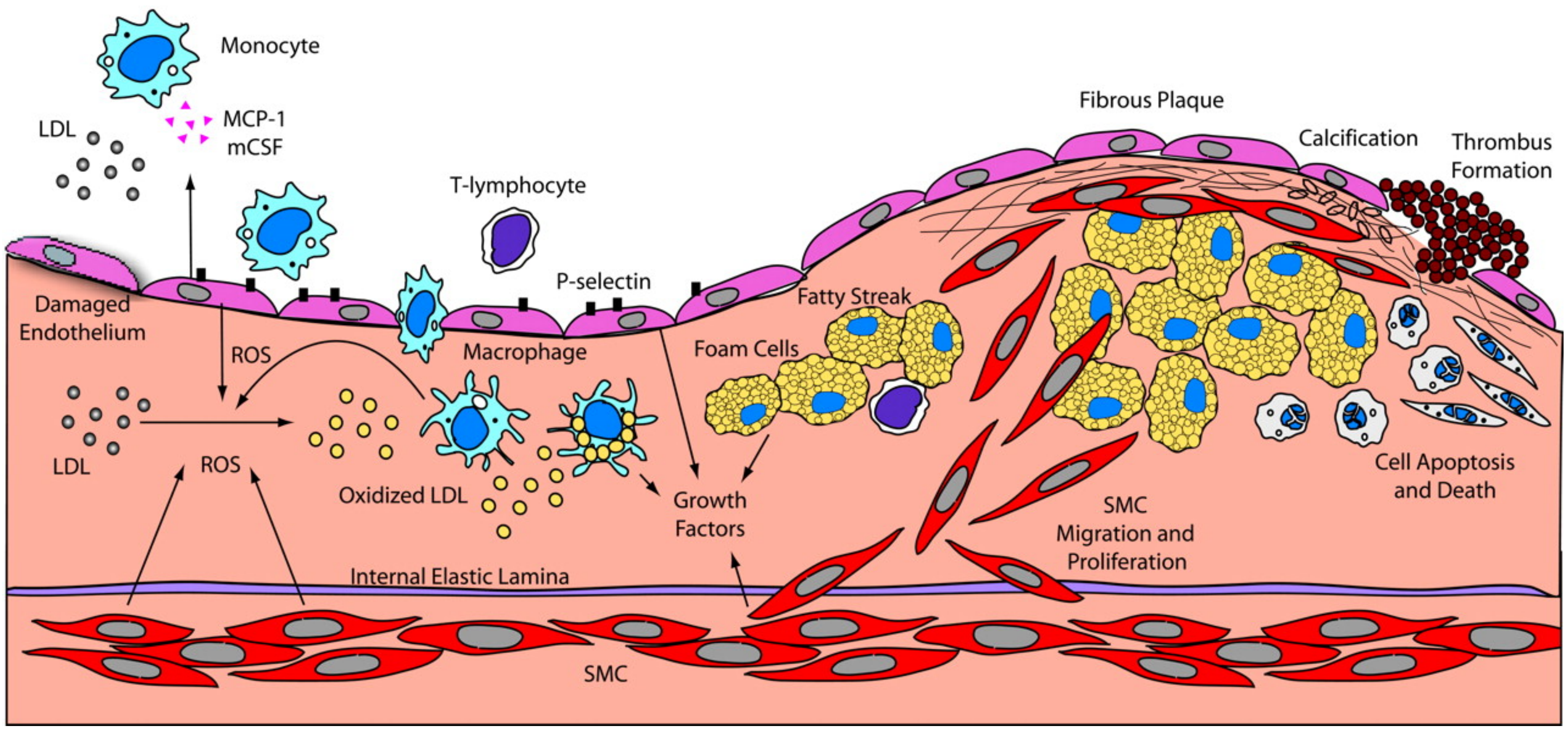


Figure 19-44 Fundamentals of Biochemistry, 2/e



Monocyte
LDL
MCP-1
mCSF
T-lymphocyte
P-selectin
Fibrous Plaque
Calcification
Thrombus
Formation
Damaged
Endothelium
ROS
Macrophage
Fatty Streak
Foam Cells
LDL
ROS
Oxidized LDL
Growth
Factors
SMC
Migration and
Proliferation
Cell Apoptosis
and Death
Internal Elastic Lamina
SMC

Role of the LDL receptors

familial hypercholesterolemia (FH)

Long-term ingestion of a high-fat/high-cholesterol diet

Cholesterol efflux from cells

LDL receptor: FH

ABCA1 (ATP-cassette binding protein A1): Tangier disease

- no HDL synthesis
- accumulation of cholesteryl ester in macrophages
- develop atherosclerosis

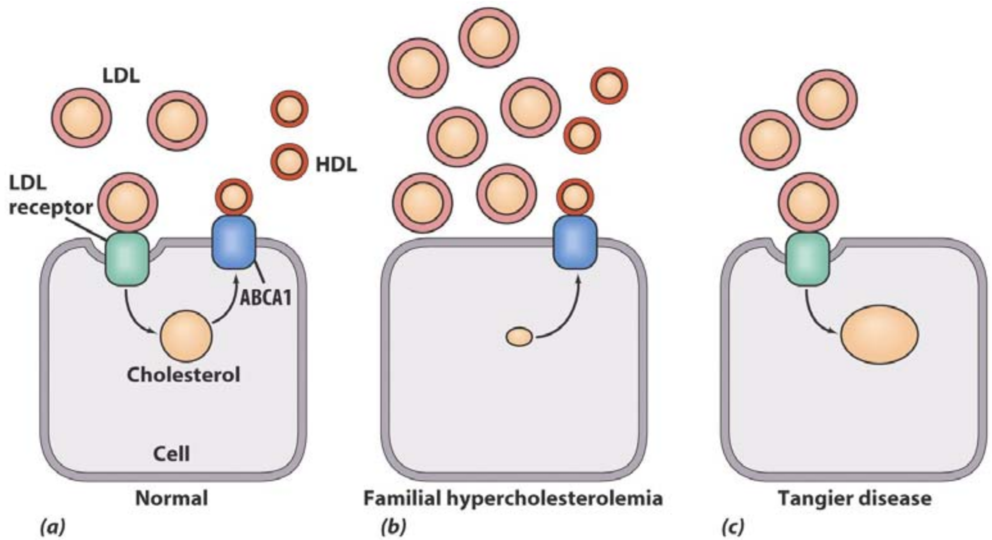


Figure 19-45 Fundamentals of Biochemistry, 2/e