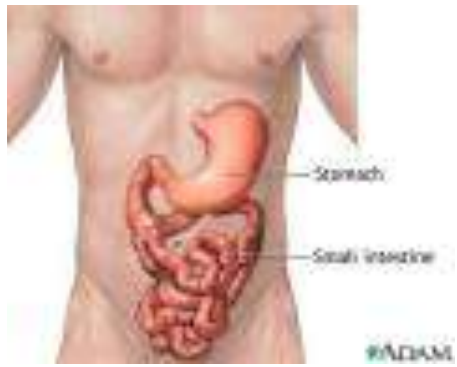
1) Lipid Digestion, Absorption and Transport

Major form of energy: triacylglycerol/fat/triglycerides



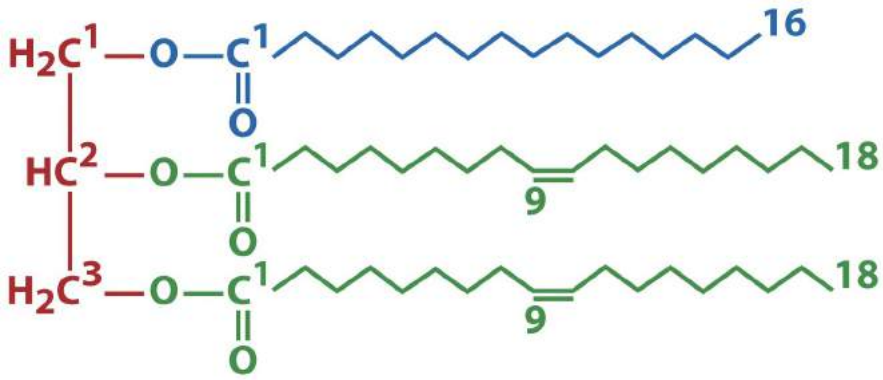
- 90% of dietary lipid
- oxidized to CO_2 and H_2O
- 6 times more energy/weight of glycogen
- water insoluble
- emulsified by **bile salts/bile acids** in small intestine
- digestion at lipid/water interface
- cut at pos 1 and 3 by lipase (triacylglycerol lipase)
  TAG -> 1,2-diacylglycerol -> 2-acylglycerol
- FA uptake by enterocytes, bind to I-FABP

Energy Content of Food Constituents

Constituent	ΔH(kJ · 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).

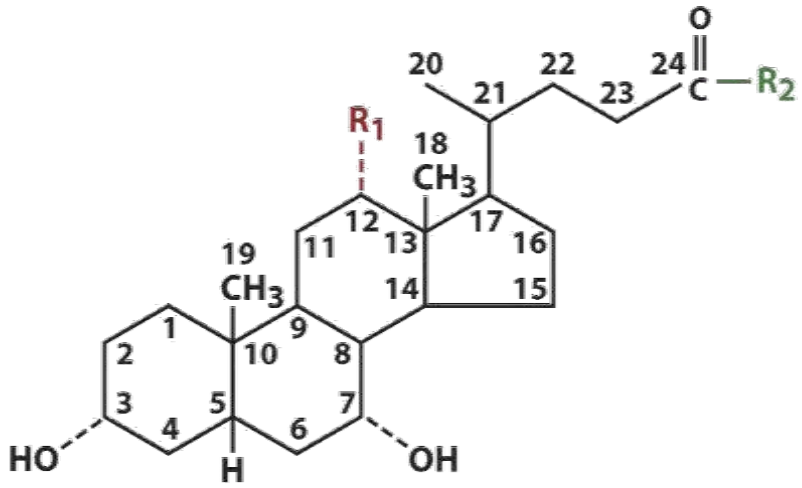
Fat storage: anhydrous !
⇒ Up to 10x more energy per weight than hydrated glycogen



1-Palmitoyl-2,3-dioleoyl-glycerol

Bile acids

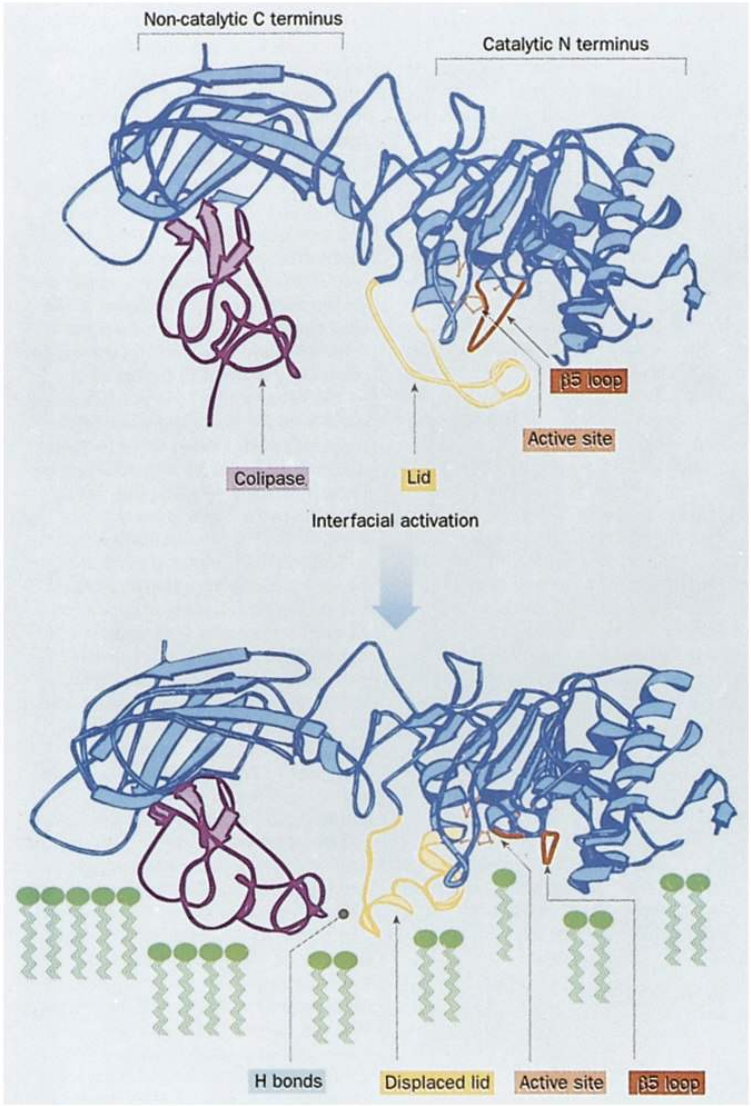
- have detergent character to help solubilize and absorb lipids in the gut
- made in the liver, secreted as glycin or taurine conjugates into the gallblader for storage
- from gallbladder secreted into small intestine, where lipid digestion and absorption mainly takes place



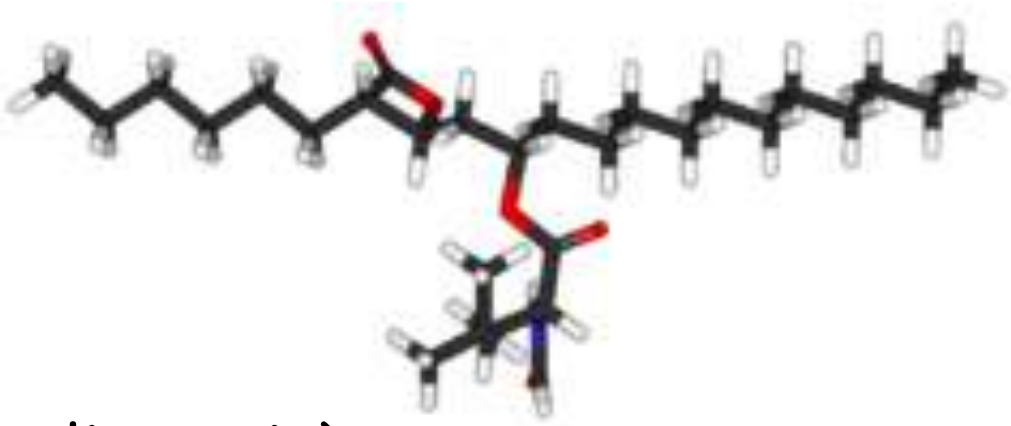
	$R_1 = OH$	$R_1 = H$
$R_2 = OH$	Cholic acid	Chenodeoxycholic acid
$R_2 = NH—CH_2—COOH$	Glycocholic acid	Glycochenodeoxycholic acid
$R_2 = NH—CH_2—CH_2—SO_3H$	Taurocholic acid	Taurochenodeoxycholic acid

Mechanism of interfacial activation of triacylglycerol lipase in complex with procolipase

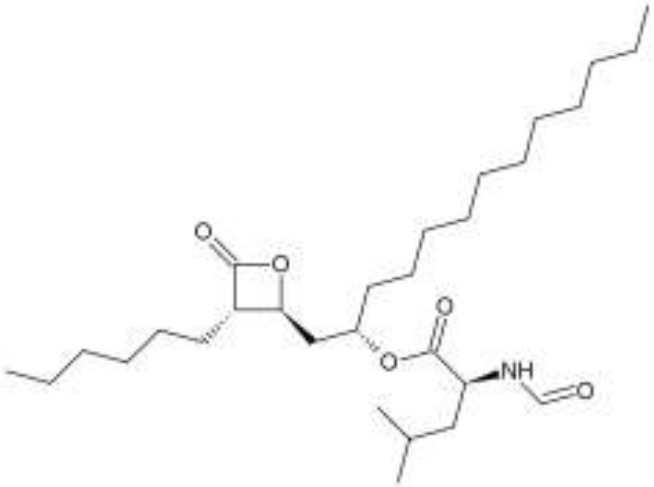
- **Pancreas Lipase** = TAG lipase
- Degrades TAG to 2-acylglycerol
- Lipase activation by colipase
- Interfacial activation
- Activity depends on surface area
- Alpha/beta hydrolase fold
- 25 AS lid structure
- catalytic triad, Asp-Ser-His, related to serine proteases
- hydrolysis similar to peptidase



Orlistat

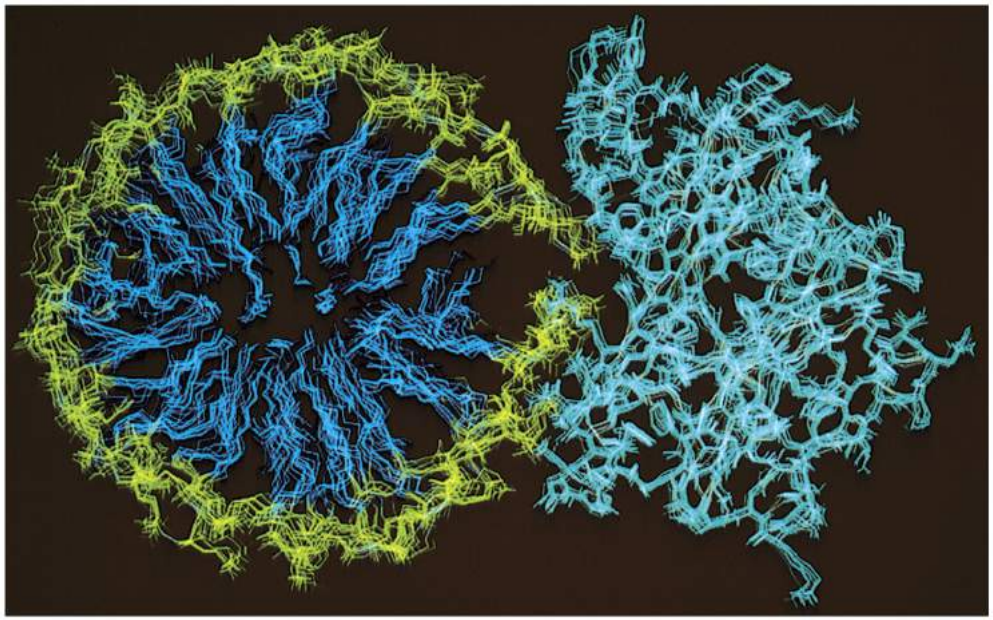


- Xenical, Roche (tetrahydrolipstatin)
- **treat obesity by inhibiting lipid absorption -> reduce caloric intake**
- Inhibits pancreas lipase
- side effect, oily and loose stool
- Recommended "to bring a change of clothes with you to work"

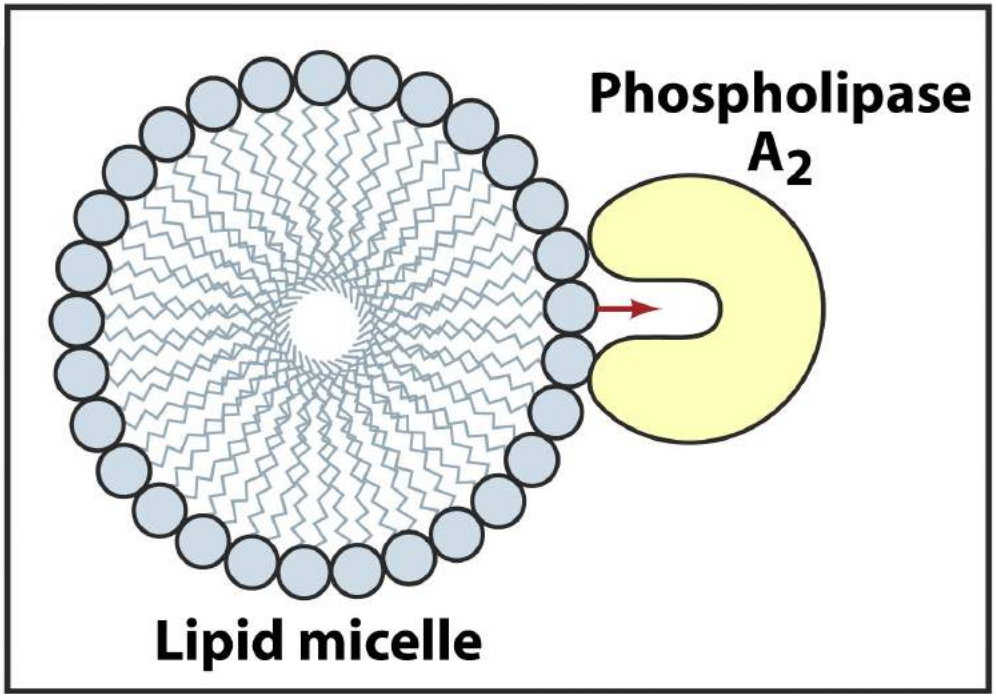


- Avoid high fat food !

Substrate binding to phospholipase A_2



- No interfacial activation
- No conformational change
- Upon interfacial binding
- Why ??



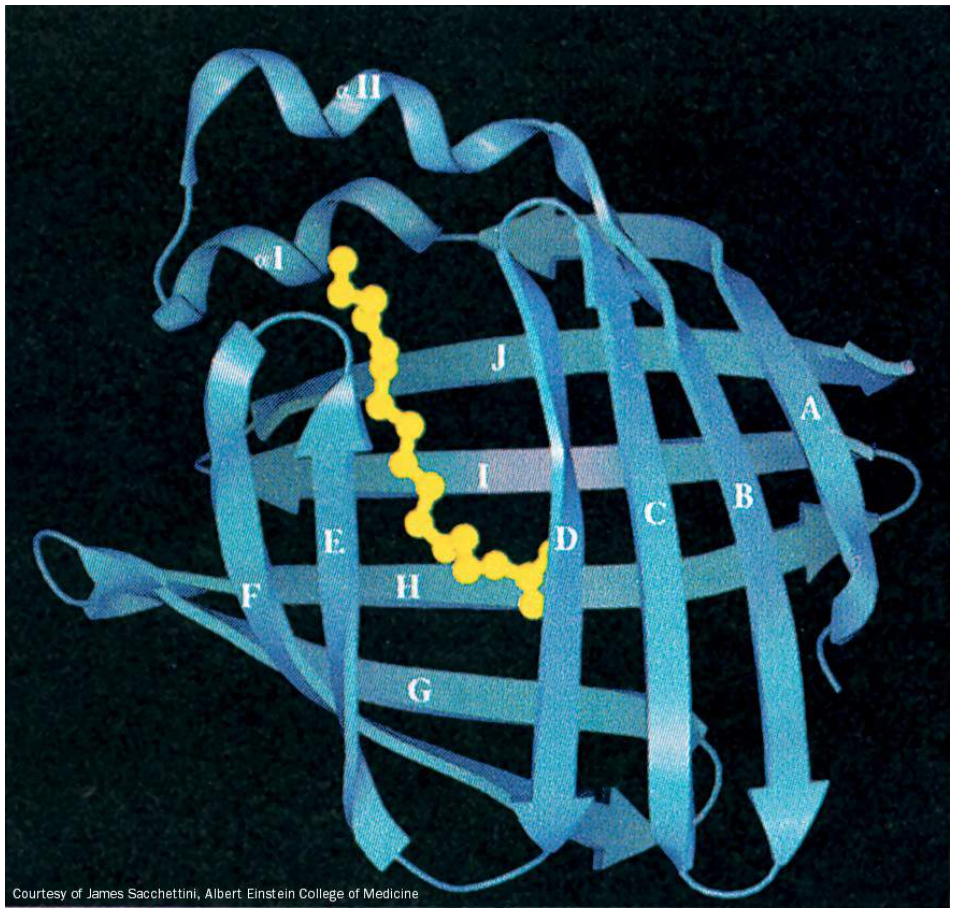
LIPID ABSORBTION by enterocytes

As micelles with bile salts and PC (lecithin)
Or lipid-protein complexes
also for Vit A,D,E, K

Inside the cell:

- **I-FABP**, increases solubility of FAs in the cytosol of **enterocytes**
- Protect cells from their detergent effect
- β-clam structure (Muschel)

X-Ray structure of rat intestinal fatty acid-binding protein



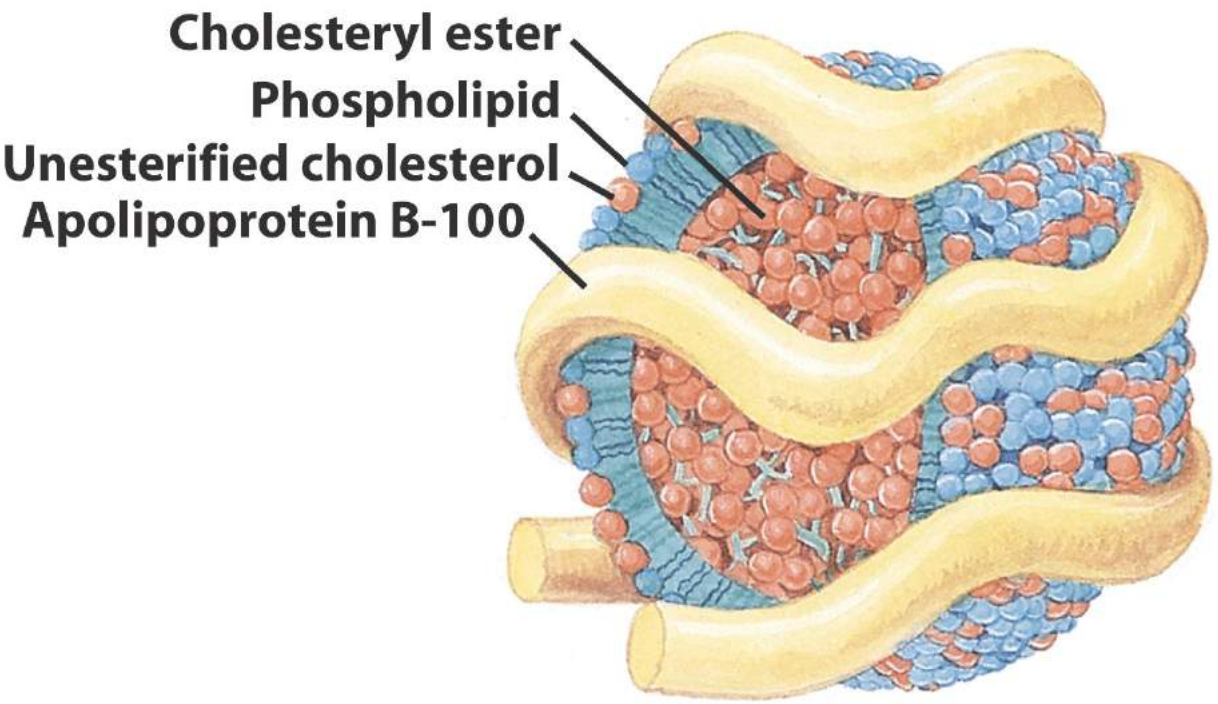
Courtesy of James Sacchettini, Albert Einstein College of Medicine

B) Lipids are transported as Lipoproteins

- How dos an organism transport water insoluble substances, i.e. lipids ?

- In form of lipid/protein complexes, lipoproteins

- The protein wraps around a lipid droplet and thereby makes it soluble



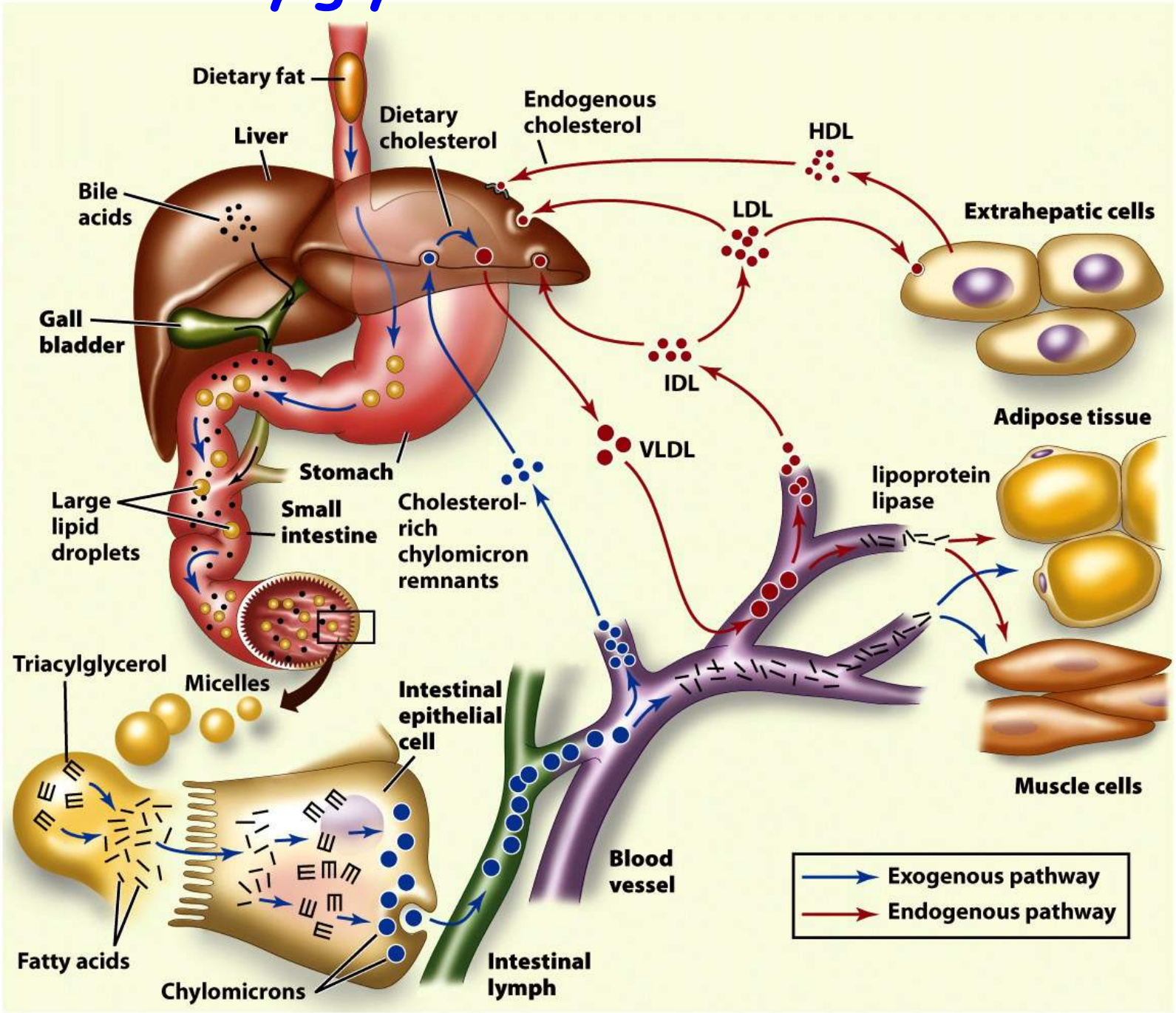
The fate of dietary lipids

- Hydrolyzed lipids are absorbed by the intestinal mucosa
- Converted back to triglycerides !
- Packed into lipoprotein particles, **chylomicrons**
- Released into lymph/blood -> delivered to tissue
- Triglyceride made by liver is packaged into **VLDL** part. ->
- Released into blood
- TAG hydrolyzed in periphery by **lipoprotein lipase** ->
- FA uptake but glycerol back transport to liver and kidney
- TAG in adipose tissue is mobilized by **hormone-sensitive lipase** -> free FA enter blood, bound to serum albumin

Different types of lipoproteins

- **Chylomicrons**, transport from intestine through lymphatic vessels into blood/periphery
- **VLDL**, **IDL**, and **LDL** made by the liver to transport endogenous lipids to periphery
- HDL transport cholesterol from the periphery back to liver
- The more lipids the **LOWER THE DENSITY** of the lipoprotein particle

Plasma triacylglycerol and cholesterol transport



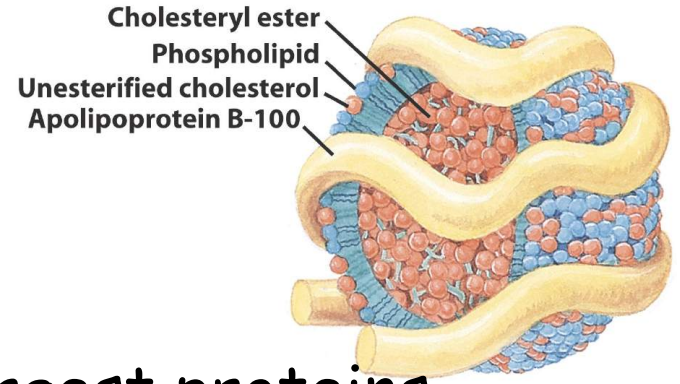
Different types of lipoproteins (2)

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 surface



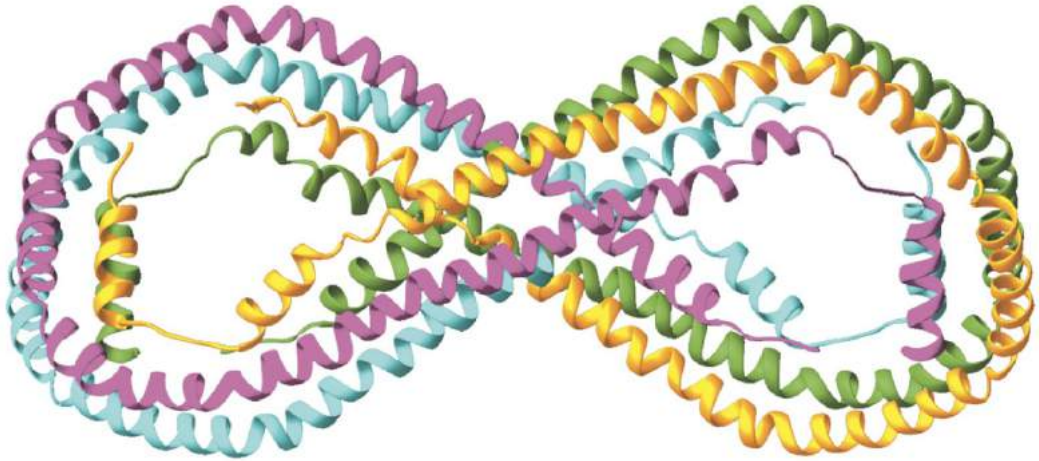
- Apolipoprotein = apoprotein
- Nine different types
- LDL contains apo B-100

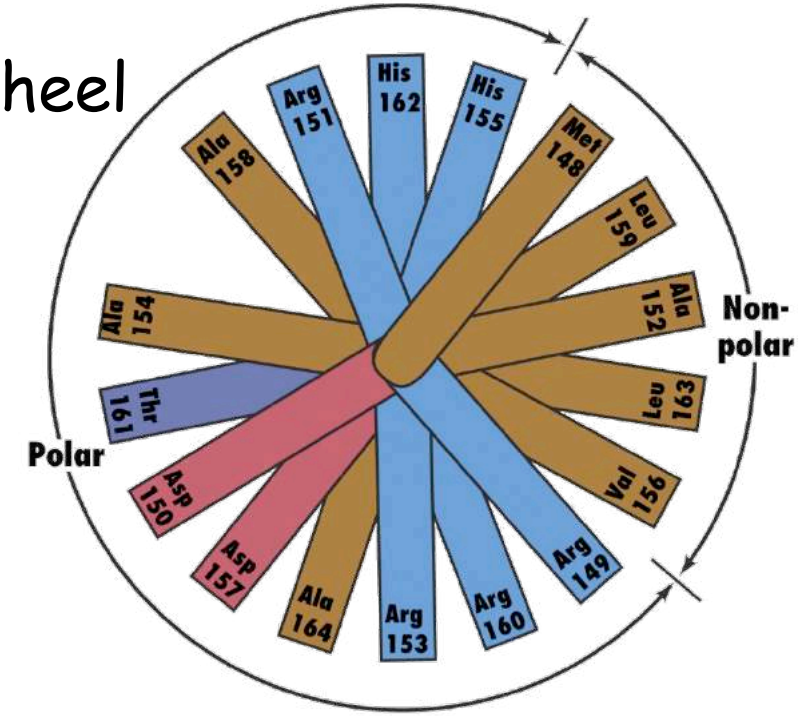
  4536 Aa, monomer, one of the largest proteins

  each LDL particle contains only 1 apo B-100

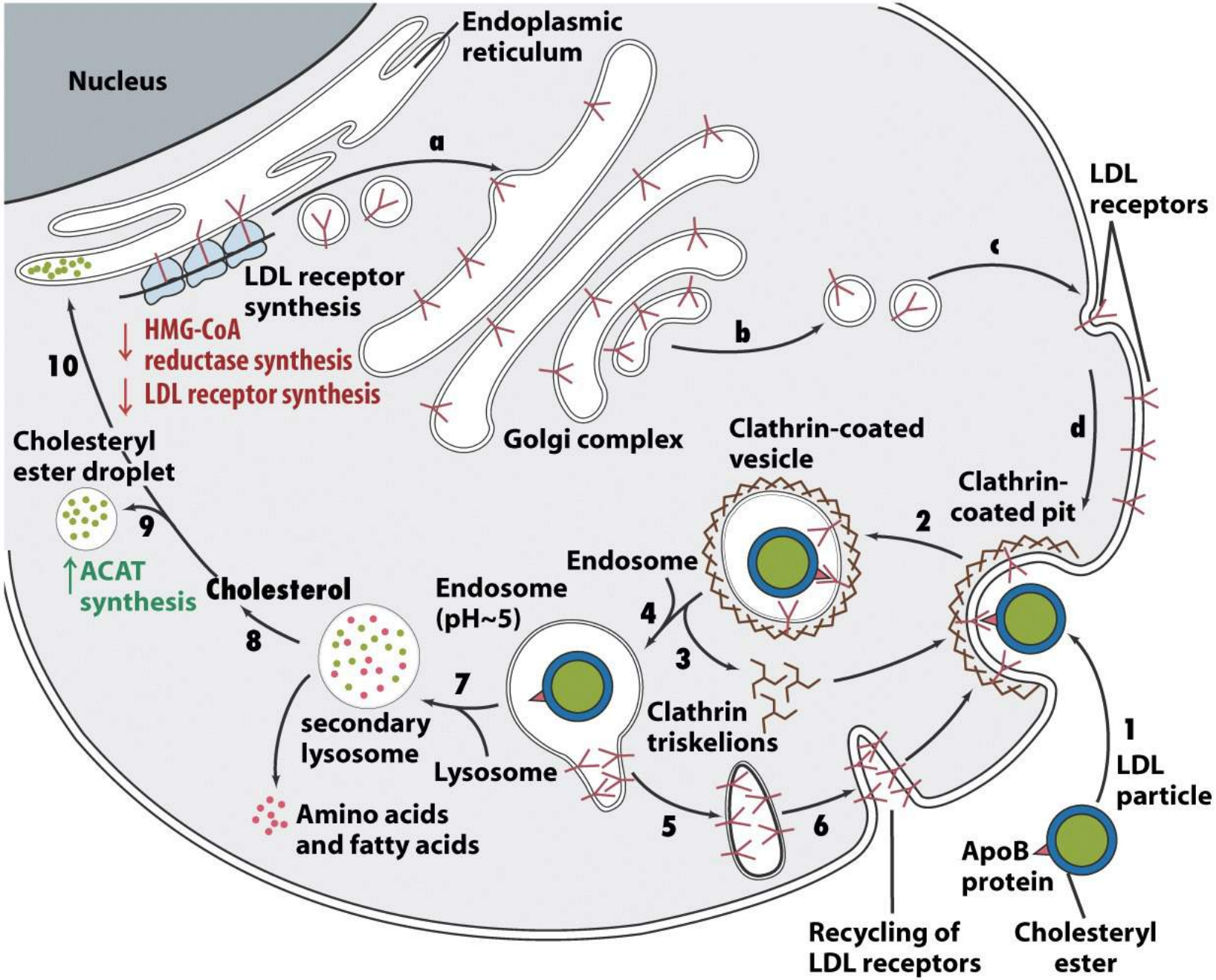
  α-helical

  amphipathic faces -> helical wheel





Cells take up LDL by receptor-mediated endocytosis



2) Fatty acid oxidation

- **Hormone sensitive lipase** releases fatty acids from intracellular TAG stores

- **Lipoprotein lipases** releases fatty acids from lipoproteins into blood stream

- Fatty acids enter blood stream, kept soluble by binding to albumin, ~10^{-6}M -> 2mM

- But **analbuminemia** is not lethal

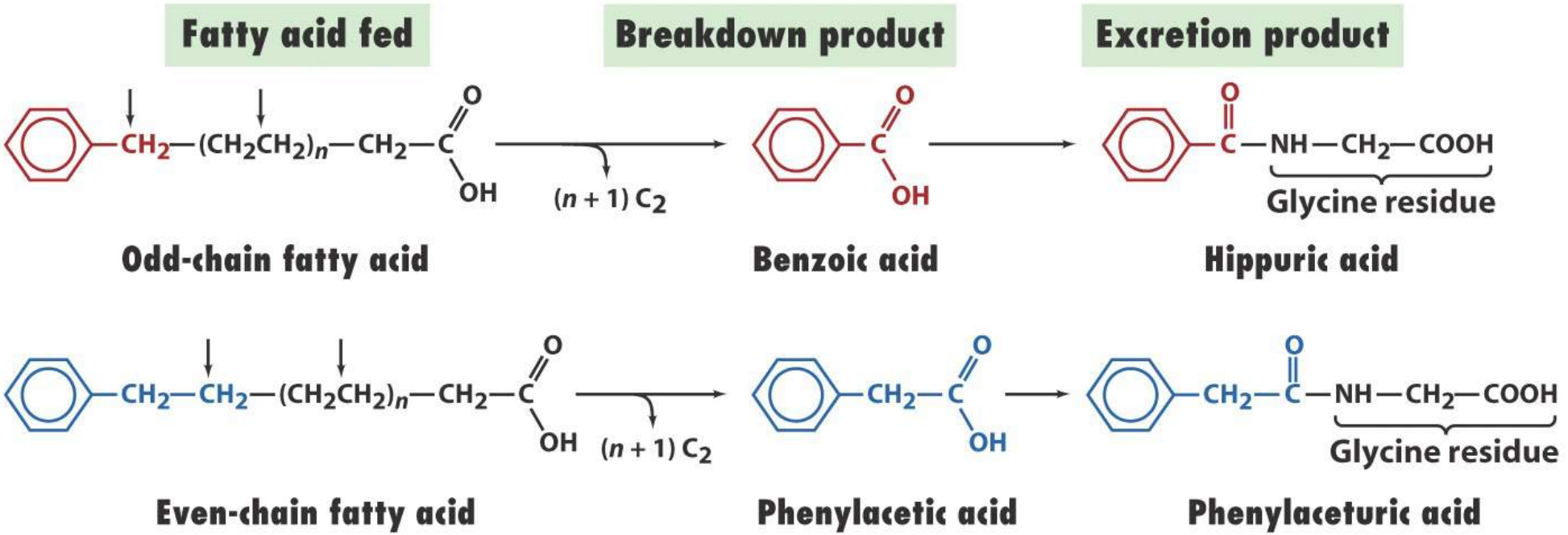
- Intracellular catabolism of fatty acids to produce energy

β-oxidation of fatty acids

- degradation of fatty acid through oxidation of Cβ = β-oxidation
- mitochondria, matrix
- FA need to cross 2 membranes to reach matrix
- not as CoAs but as acyl-carnitine
- CPT-I, cytosol; CPT-II, matrix
- separate pools of mitoch/cytosol.
  - CoAs; ATPs; NAD^+

Franz Knoop's classic experiment indicating that fatty acids are metabolically oxidized at their β-carbon atom

- Phenyl-labeled even- or odd-numbered fatty acids
- Feed to dogs -> what product appears in urine ?



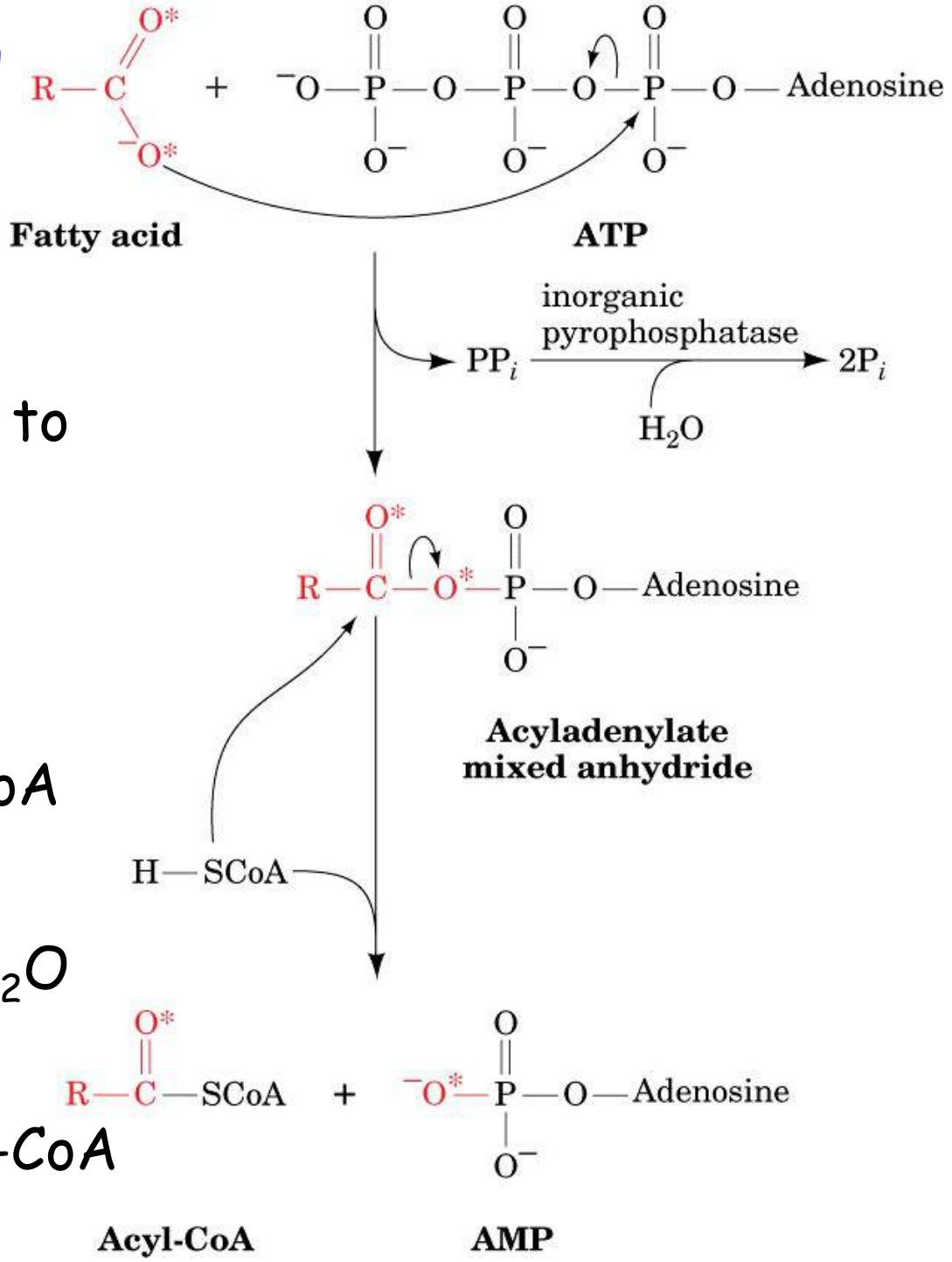
A) Fatty acid activation catalyzed by acyl-CoA synthetase

- Fatty acids need almost always be activated to Acyl-CoAs for subsequent enzymatic reaction
- Activation by acyl-CoA synthetases via acyladenylate intermediate

FA + CoA + ATP <-> Acyl-CoA + AMP + PP_i

High-energy
thioester bond

Mechanism of fatty acid activation catalyzed by acyl-CoA synthetase

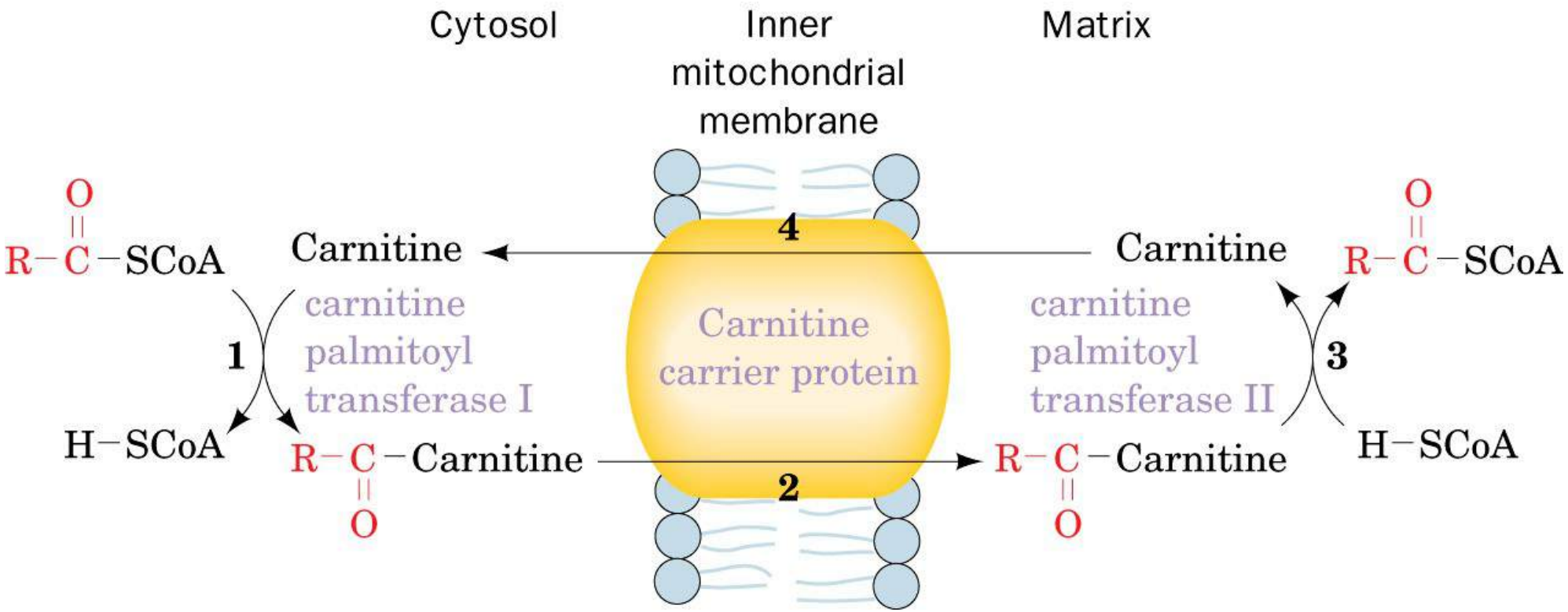


1) Activation of acyl chains to acyl-CoAs in cytosol
2) Requires ATP -> acyl-adenylate intermediated
3) Transesterification to CoA
4) Driven by inorganic pyrophosphatase PP_i -> H_2O $+2P_i$
5) ^{18}O-labels AMP and Acyl-CoA

B) Transport of fatty acids into the mitochondrial matrix

as: acyl-carnitine, through carnitine carrier protein IMM

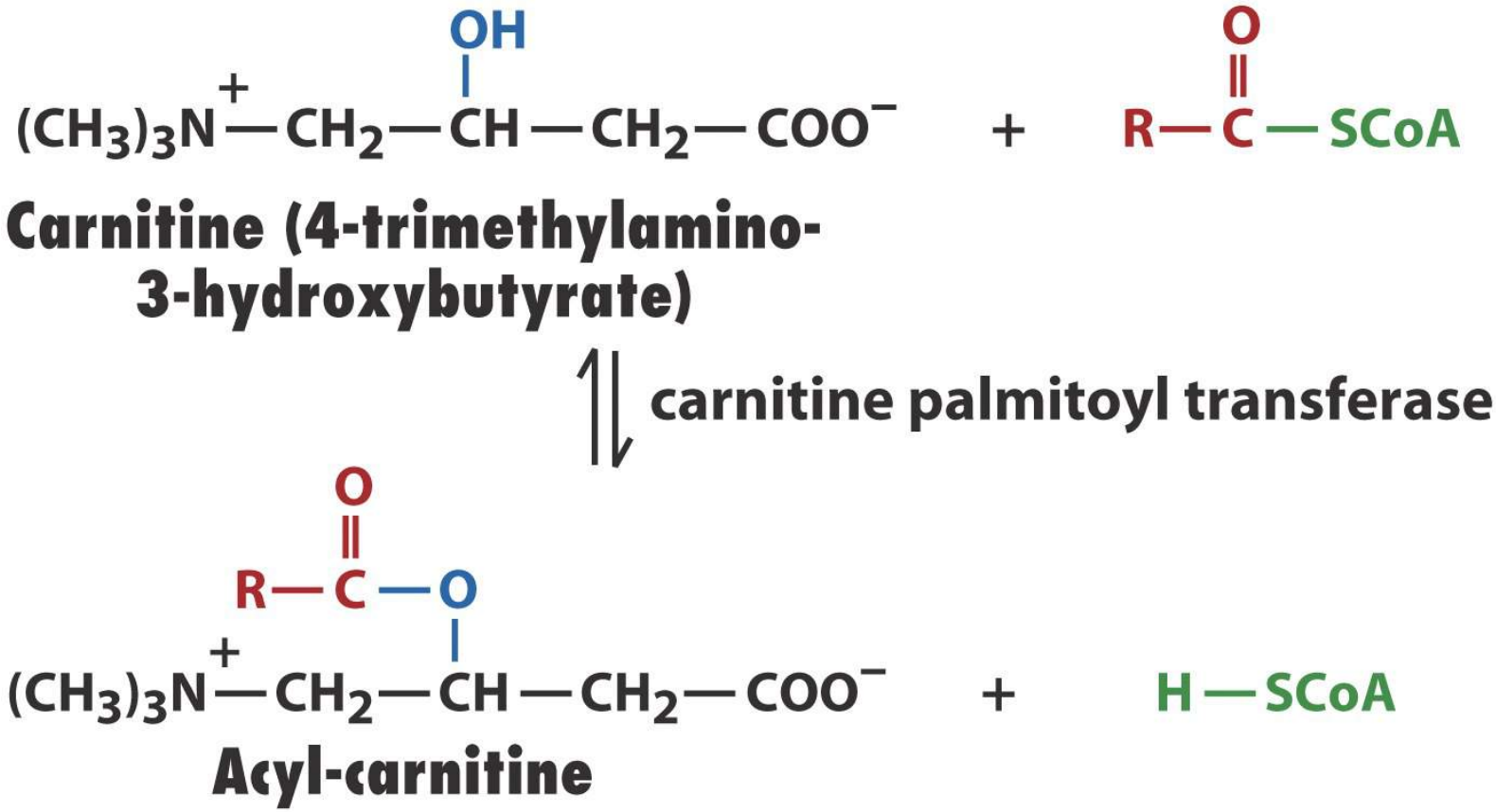
Energy neutral, no ATP required, but highly regulated !!!



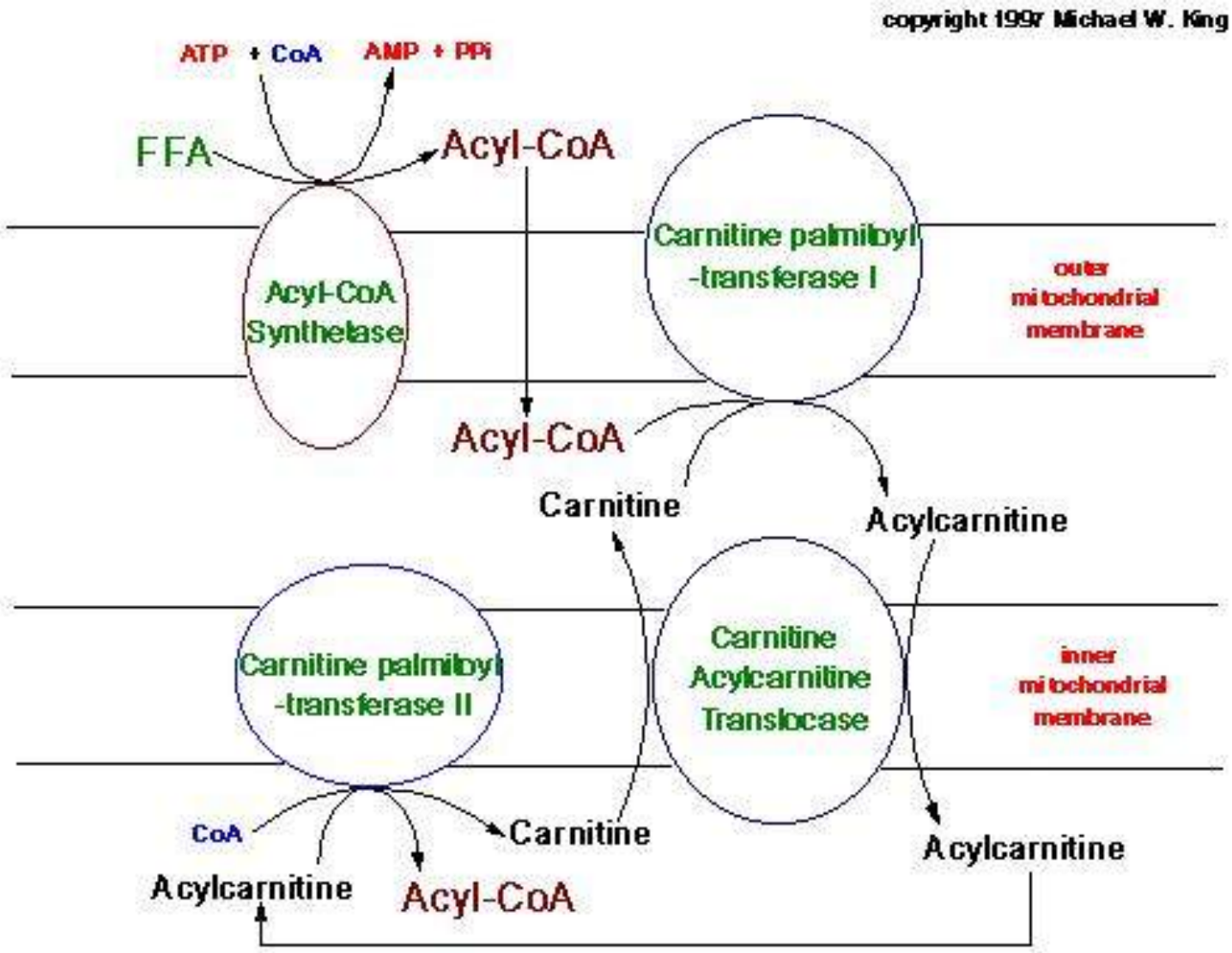
Acylation of carnitine catalyzed by carnitine palmitoyltransferase

2nd step: preparation for mitochondrial import

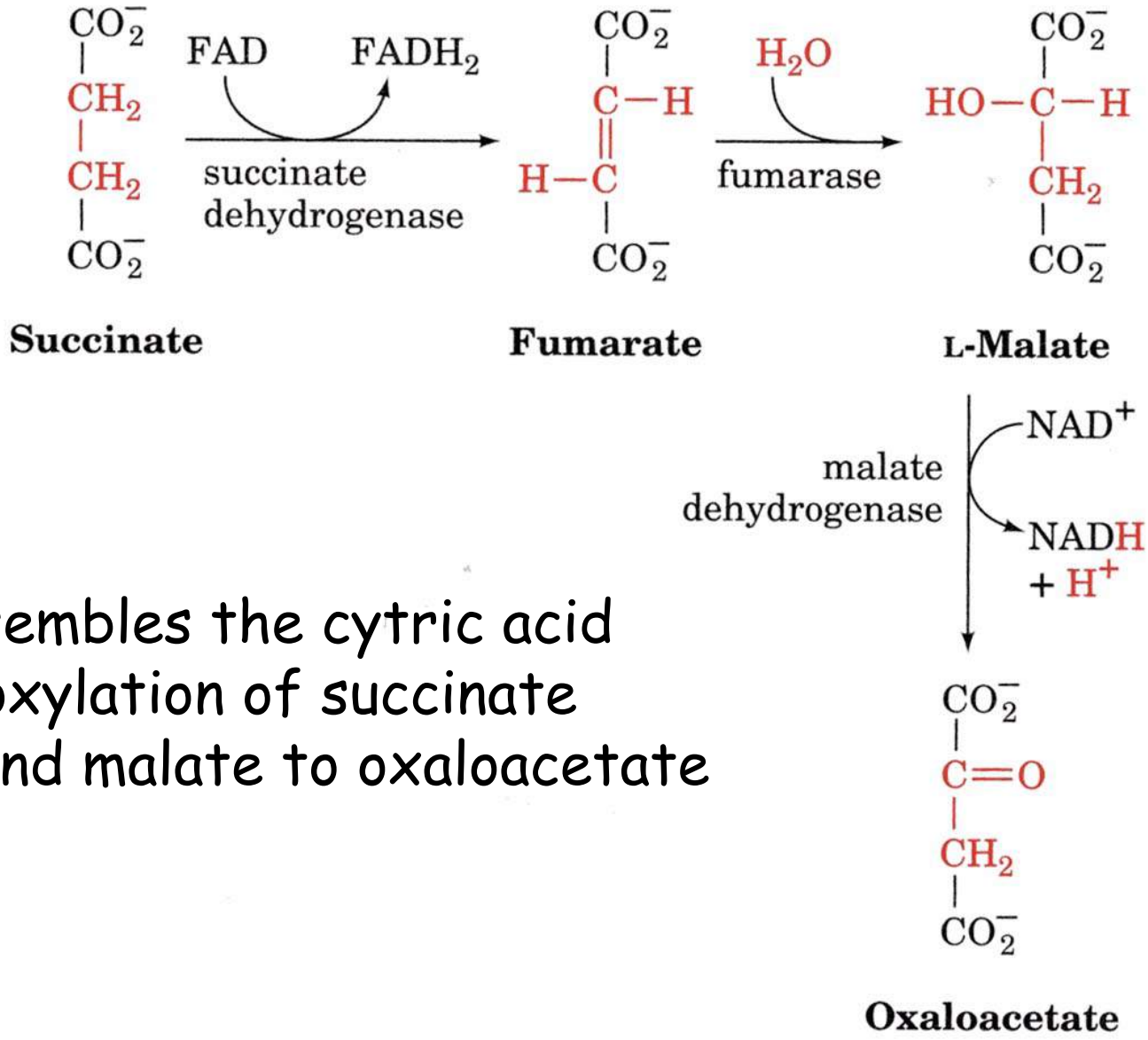
- Transesterification of acyl-CoA to carnitine (no AMP intermediate !)
- catalyzed by CPTI (equilibrium close to 1)



Transport of fatty acids across the mitochondrial double membrane



C) β-oxidation



- Chemically resembles the cytric acid cycle: Decarboxylation of succinate via fumarate and malate to oxaloacetate

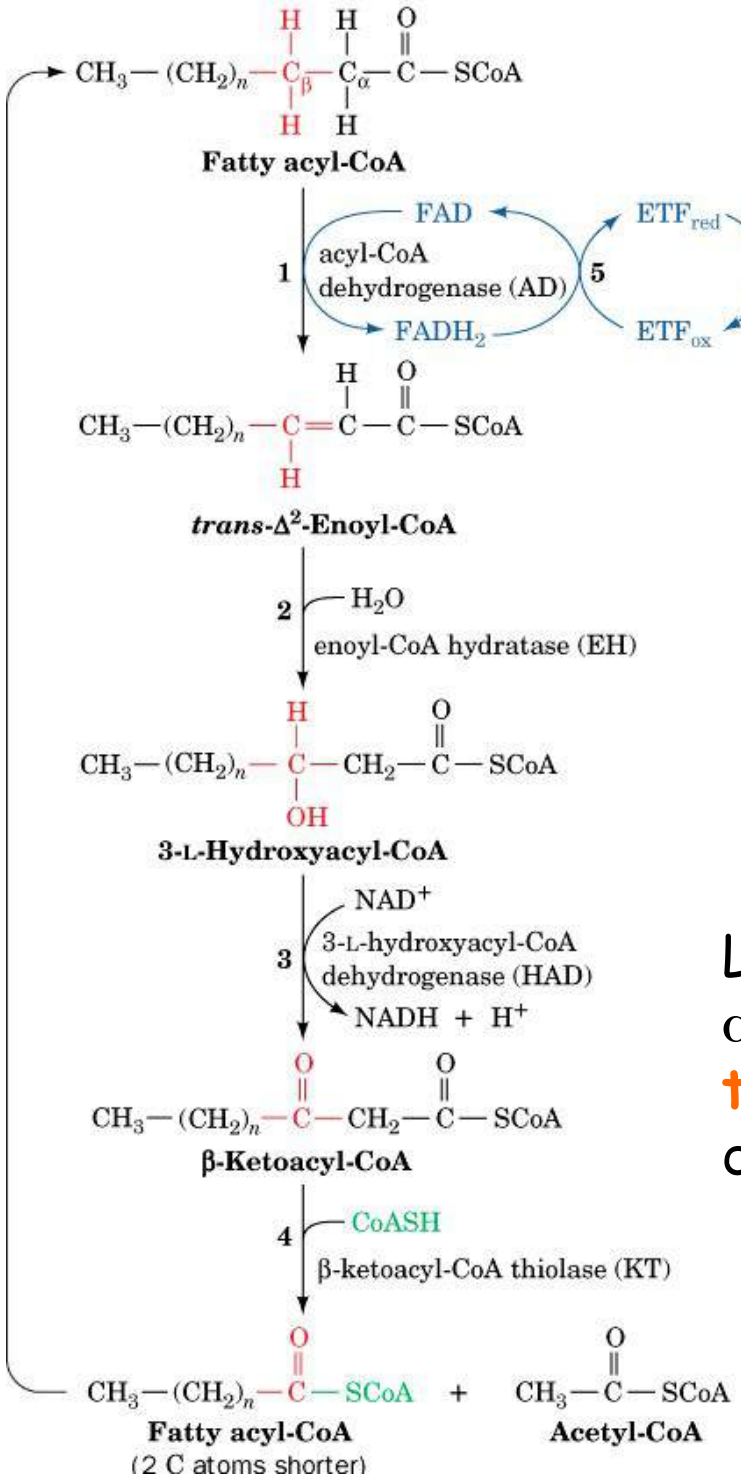
β-oxidation, 4 steps

1. Formation of **trans-α,β double bond**, by FAD-dependent **acyl-CoA dehydrogenase (AD)**

2. Hydration of the double bonds by **enoyl-CoA hydratase (EH)** to form 3-L-hydroxyacyl-CoA

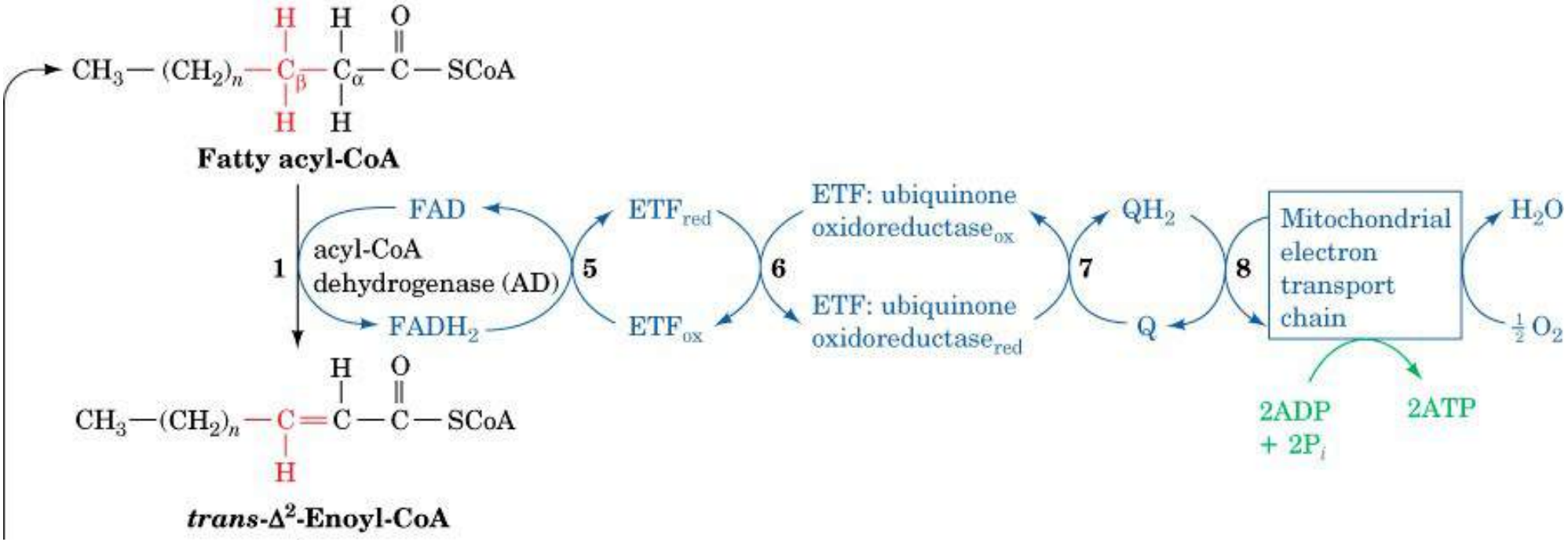
3. NAD^+-dependent dehydrogenation by **3-L-hydroxyacyl-CoA dehydrogenase (HAD)** to form β-ketoacyl-CoA

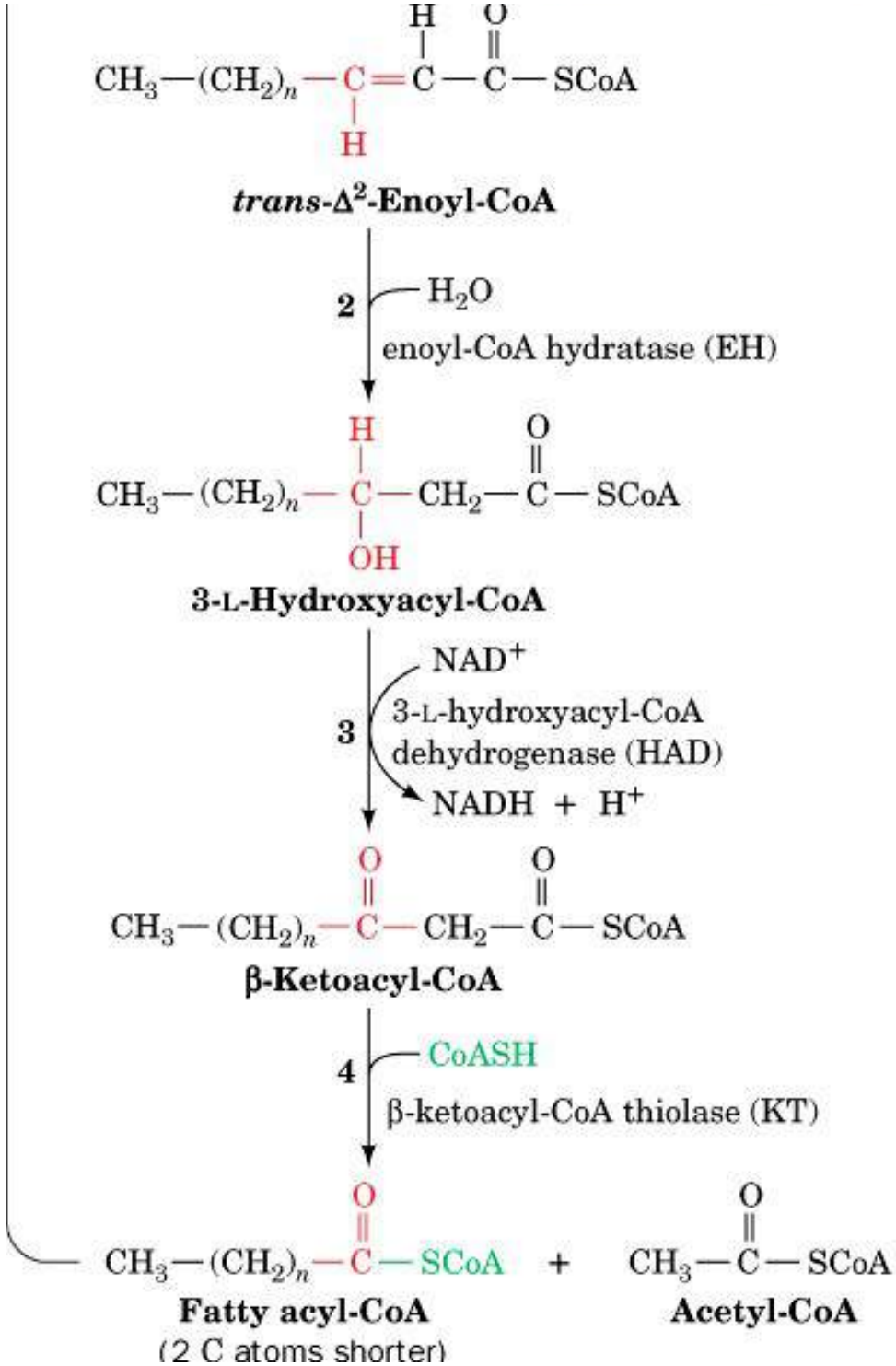
4. Cα–Cβ cleavage by **β-ketoacyl-CoA thiolase (KT, thiolase)** **-> acetyl-CoA and C2 shortened acyl-CoA**



The β-oxidation pathway of fatty acyl-CoA

Long chain versions of EH, HAD and KTs in $\alpha_4\beta_4$ ocatmeric protein, **mitochondrial trifunctional protein** -> channeling, no detectable intermediates


Fatty acyl-CoA
FAD
FADH2
acyl-CoA dehydrogenase (AD)
1
5
6
7
8
ETFred
ETFox
ETF: ubiquinone oxidoreductaseox
ETF: ubiquinone oxidoreductasered
QH2
Q
Mitochondrial electron transport chain
H2O
½ O2
2ADP + 2Pi
2ATP
trans-Δ2-Enoyl-CoA

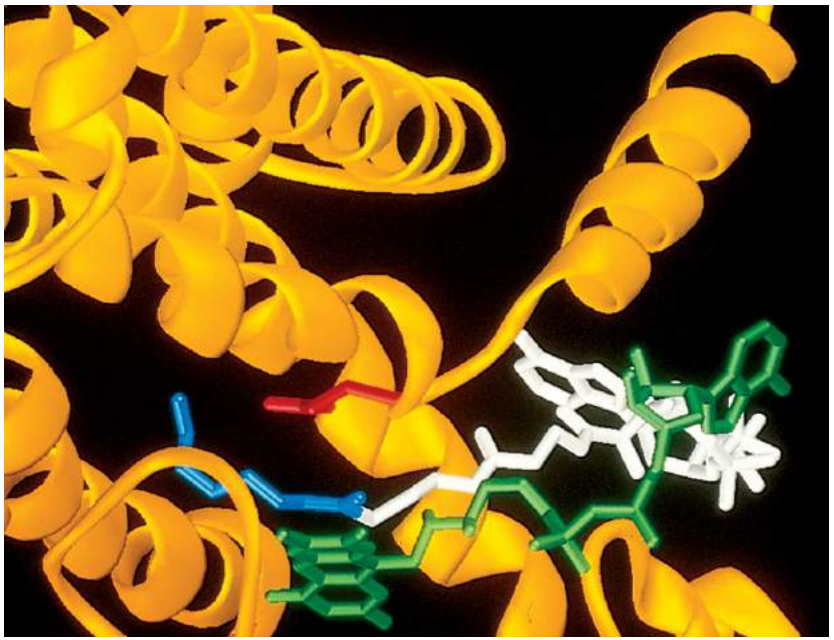

CH3—(CH2)n—C(H)=C(H)—C(=O)—SCoA
trans-Δ2-Enoyl-CoA
2
H2O
enoyl-CoA hydratase (EH)
CH3—(CH2)n—C(H)(OH)—CH2—C(=O)—SCoA
3-L-Hydroxyacyl-CoA
3
NAD+
3-L-hydroxyacyl-CoA dehydrogenase (HAD)
NADH + H+
CH3—(CH2)n—C(=O)—CH2—C(=O)—SCoA
β-Ketoacyl-CoA
4
CoASH
β-ketoacyl-CoA thiolase (KT)
CH3—(CH2)n—C(=O)—SCoA
Fatty acyl-CoA
(2 C atoms shorter)
+
CH3—C(=O)—SCoA
Acetyl-CoA

Acyl-CoA dehydrogenases

- **1st step:** acyl-CoA dehydrogenases (AD)
  - mitos contain 4 such dehydrogenases with different chain length specificities
  - VLCAD (C12-C18), LCAD (C8-C12)
  - MCAD (C6-C10)
  - SCAD (C4-C6)

  - MCAD deficiency linked to 10% of cases of sudden infant death syndrome (SIDS): imbalance between glucose and fatty acid oxidation

  - Reoxidation of $FADH_2$ by mitochondrial electron transport chain -> ATP



MCAD, homo-tetramer
FAD green

Mitochondrial trifunctional protein

2-enoyl-CoAs are further processed by chain length-specific:

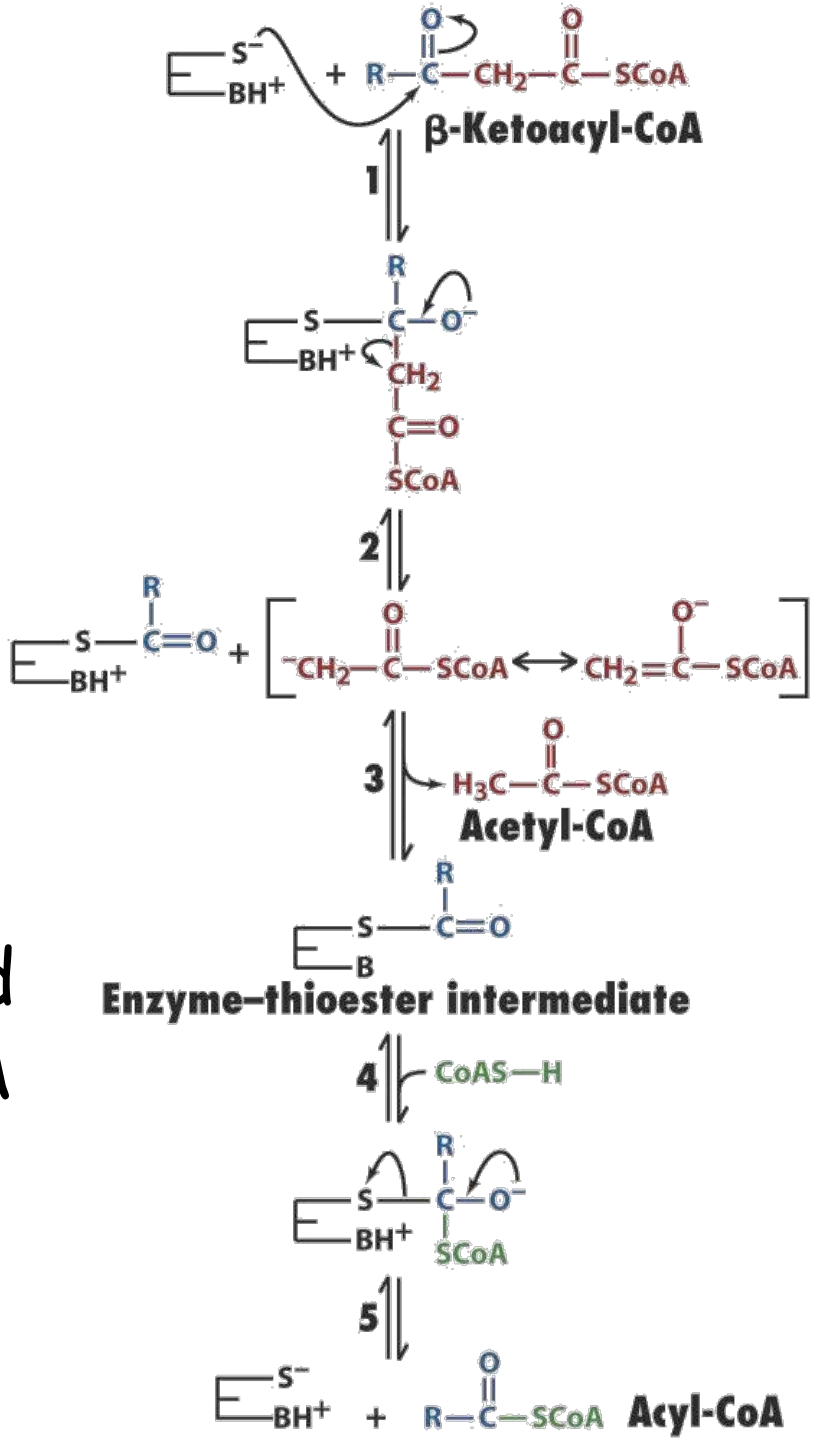
- Enoyl-CoA hydratase (EHs)
- Hydroxyacyl-CoA dehydrogenase (HADs)
- β-ketoacyl-CoA thiolase (KTs)

- Long chain version contained $\alpha_4\beta_4$ octameric protein = **mitochondrial trifunctional protein**
  - α chain contains LCEH and LCHAD
  - β chain LCKT

  (multifunctional protein, more than one enzyme on pp)
  Multienzyme complex
  Channeling of intermediates

Mechanism of action of β-ketoacyl-CoA thiolase

- Final step in β-oxidation
- Via an enzyme thioester bound intermediate to the substrates oxidized β carbon, displaced by CoA



Energy balance of β-oxidation

for C16 palmitic acid: 7 rounds of β-oxidation
-> 8 x acetyl-CoA

Each round of β-oxidation produces:

1 NADH -> 3 ATP
1 FADH2 -> 2 ATP
1 acetyl-CoA -> TCA (1 GTP, 3 NADH, 1 FADH2) (respiration only !)

OVERALL NET YIELD: **106 ATP per C16**

Special cases of β-oxidation

Unsaturated fatty acids

- mono, Δ9 (odd)
- poly, Δ9, Δ12 (odd, even)

-> isomerization, reduction

Odd chain length fatty acids

-> propionyl-CoA in the last cycle

Very long-chain fatty acids (> C22 atoms)

-> first β-oxidation in peroxisomes

Branched chain fatty acids

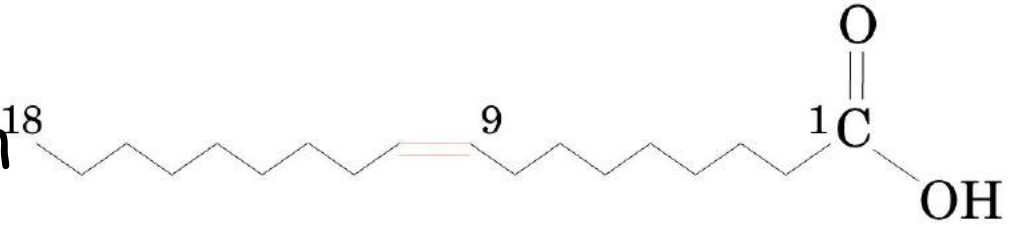
- chlorophyll's phytanic acid

-> α-oxidation, formyl-CoA + propionyl-CoA

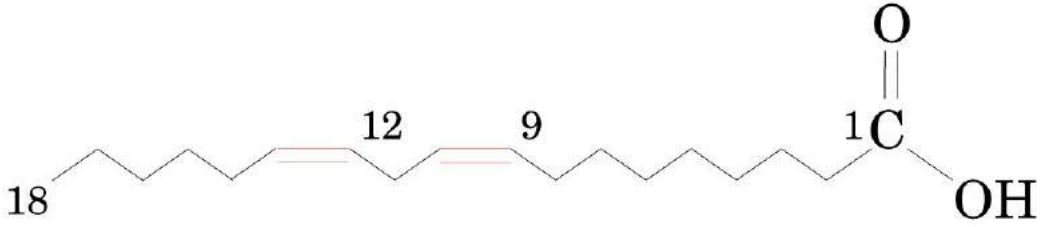
D) Oxidation of unsaturated fatty acids

Structures of two common unsaturated fatty acids,
Usually, *cis* double bond at C9
Additional double bond in C3 intervals, i.e. next at C12
-> odd, even numbered C atoms

Problems for β-oxidation



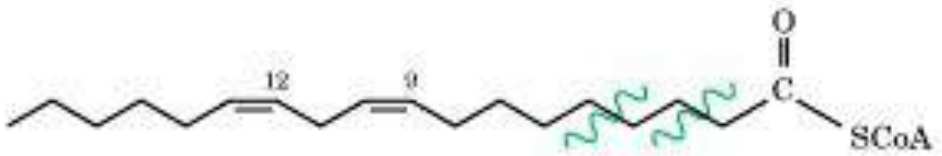
Oleic acid
(9-*cis*-Octadecenoic acid)



Linoleic acid
(9,12-*cis*-Octadecadienoic acid)

Problems for β-oxidation of unsaturated fatty acids

1) Generation of a β, γ double bond
2) A Δ4 double bond inhibits hydratase action
3) Isomerization of 2,5-enoyl-CoA by 3,2-enoyl-CoA isomerase

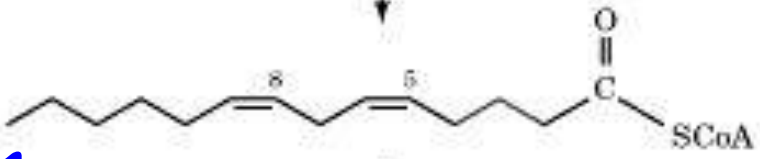


Linoleic acid

$2NAD^+ + 2FAD + 2CoA\text{-}SH$

$2NADH + 2FADH_2 + 2acetyl\text{-}CoA$

2 rounds of β oxidation

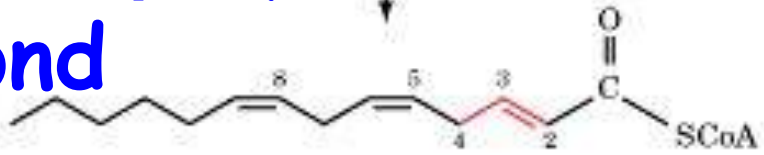


Problem 1: Generation of a β, γ double bond

FAD

$FADH_2$

acyl-CoA dehydrogenase



2,5,8-Trienoyl-CoA

$NAD^+ + CoASH$

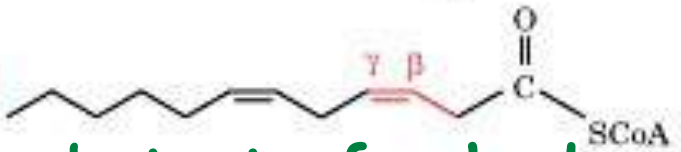
$NADH + acetyl\text{-}CoA$

completion of β-oxidation round

3,2-enoyl-CoA isomerase

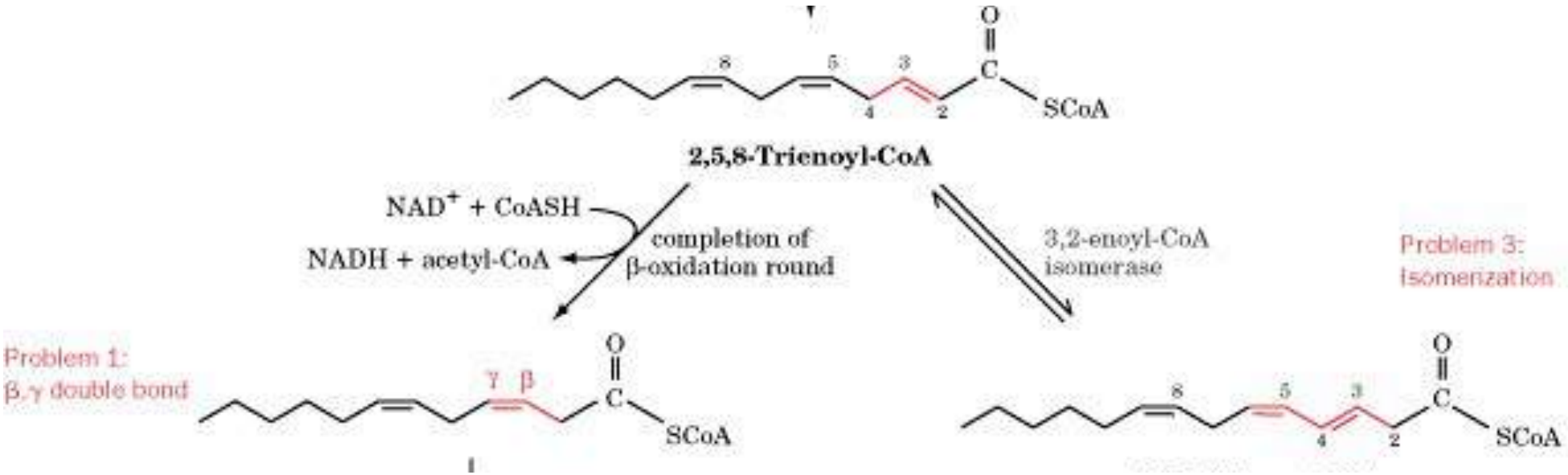
Problem 3: Isomerization

Problem 1: β,γ double bond

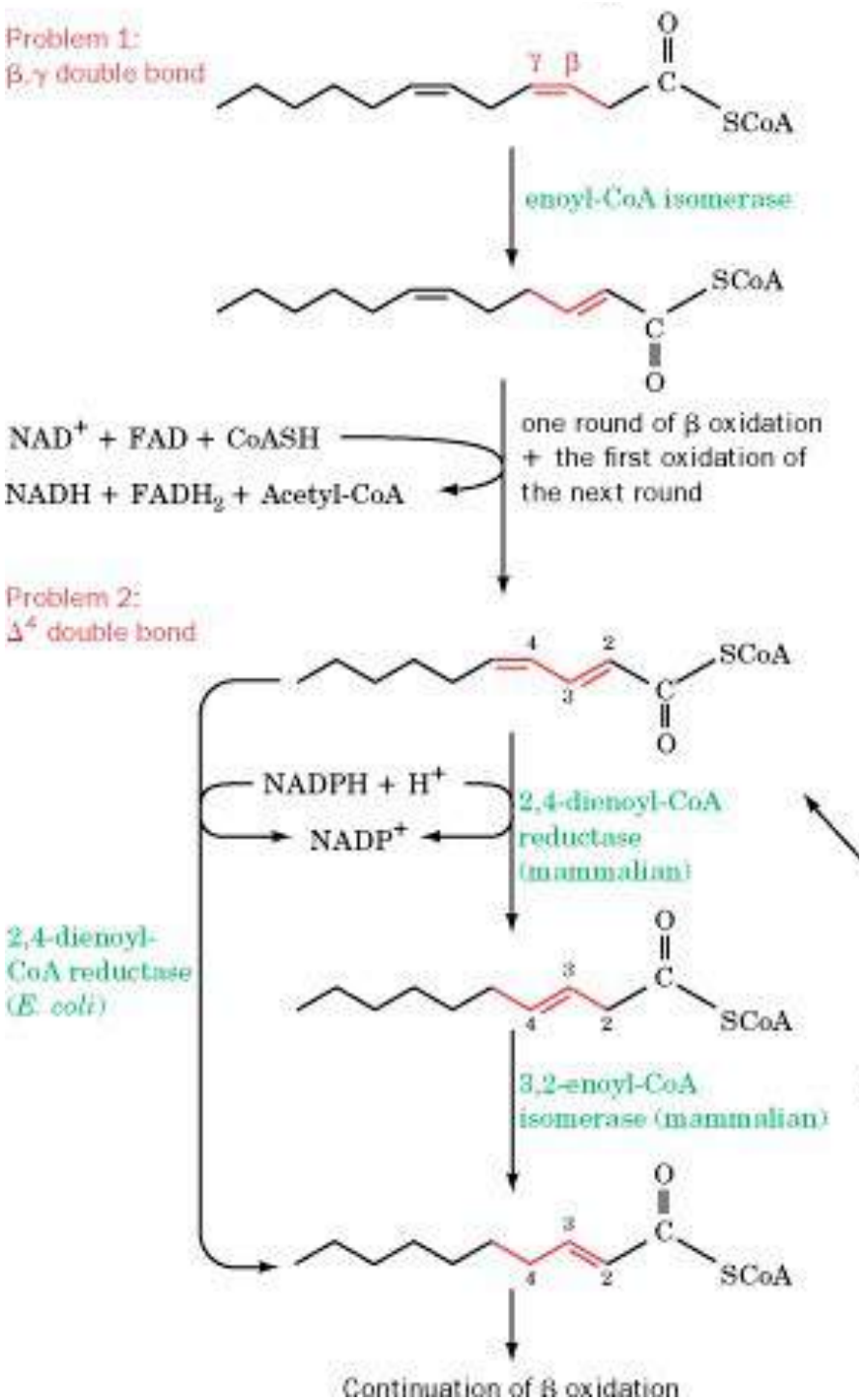


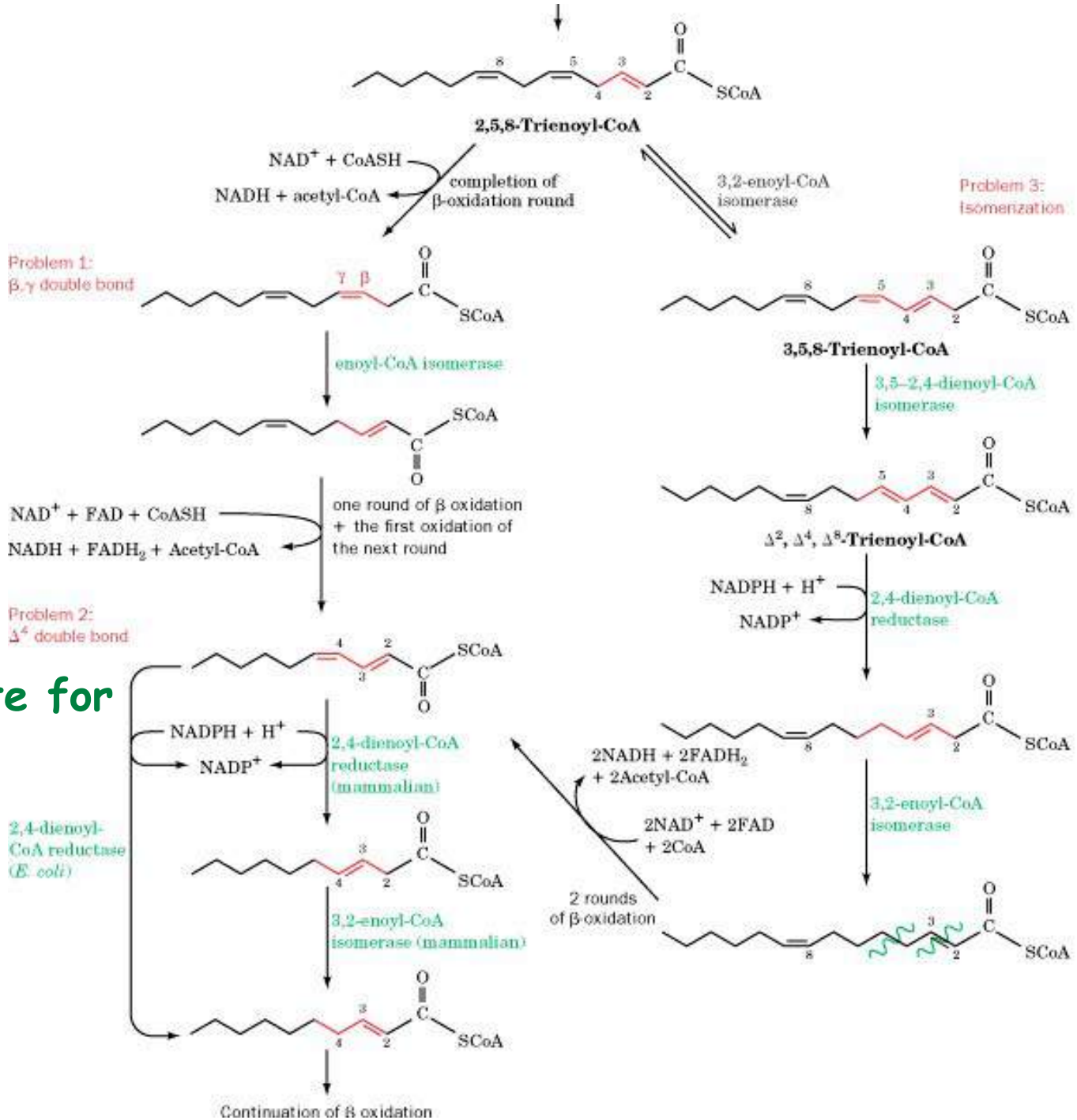
No substrate for hydroxylase

Problem 1: Generation of a β, γ double bond



No substrate for hydroxylase


Problem 1:
β,γ double bond
γ β
O
C
SCoA
enoyl-CoA isomerase
SCoA
C
O
NAD+ + FAD + CoASH
NADH + FADH2 + Acetyl-CoA
one round of β oxidation
+ the first oxidation of
the next round
Problem 2:
Δ4 double bond
4 2
3
SCoA
NADPH + H+
NADP+
2,4-dienoyl-CoA
reductase
(mammalian)
2,4-dienoyl-
CoA reductase
(E. coli)
3
4 2
3,2-enoyl-CoA
isomerase (mammalian)
Continuation of β oxidation



No substrate for hydroxylase

Stability of DB

E) Oxidation of odd chain fatty acids yields propionyl-CoA

- Most naturally FA are even numbered
- Odd numbered FA are rare, some plants and marine organisms
- *Final round of β-oxidation yields propionyl-CoA*
- Propionyl-CoA is converted to succinyl-CoA -> TCA
- Propionate is also produced by oxidation of Ile, Val, Met
- **Ruminant animals**, most caloric intake from acetate and propionate produced by microbial fermentation of carbohydrates in their stomach

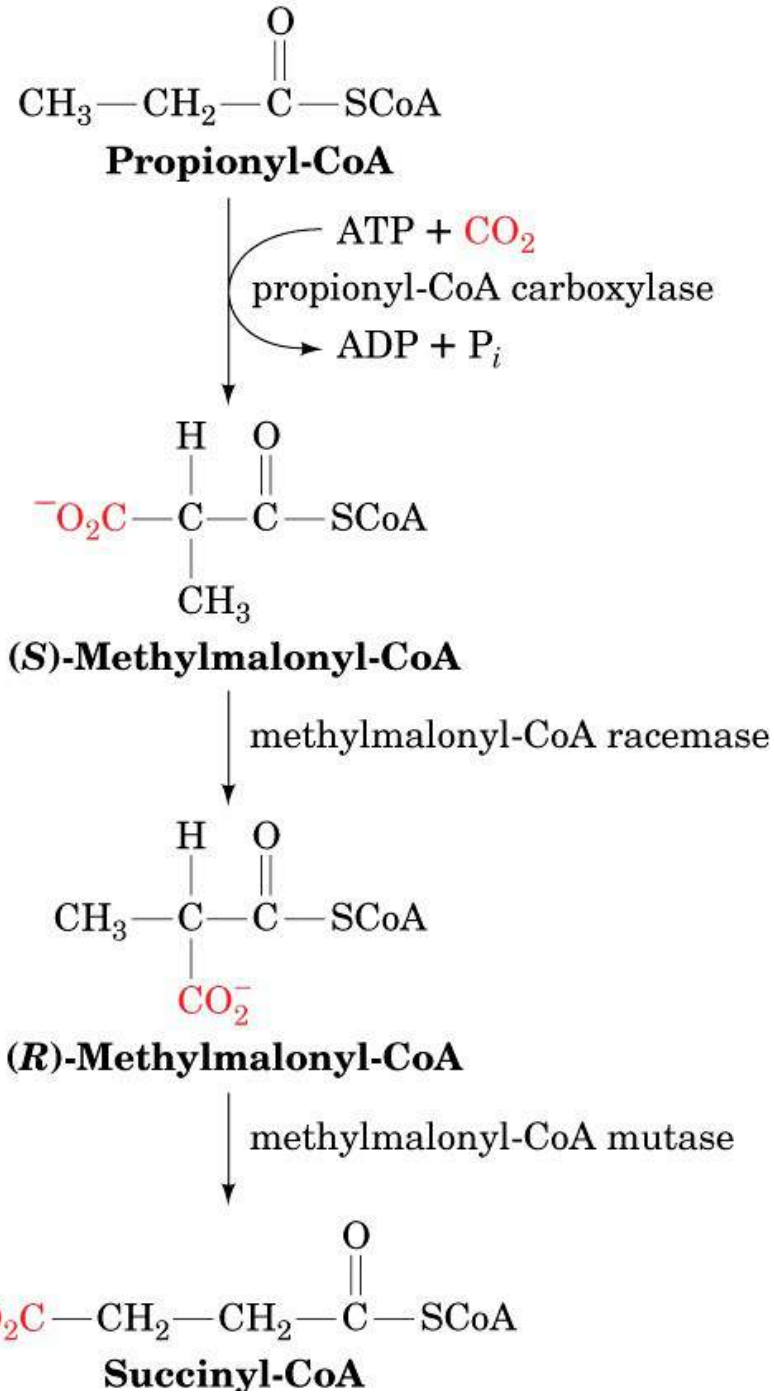
Propionyl-CoA -> succinyl-CoA

3-step reaction:

1) Propionyl-CoA carboxylase, tetrameric enzyme with biotin as prosthetic group, C3->C4

2) Methylmalonyl-CoA racemase

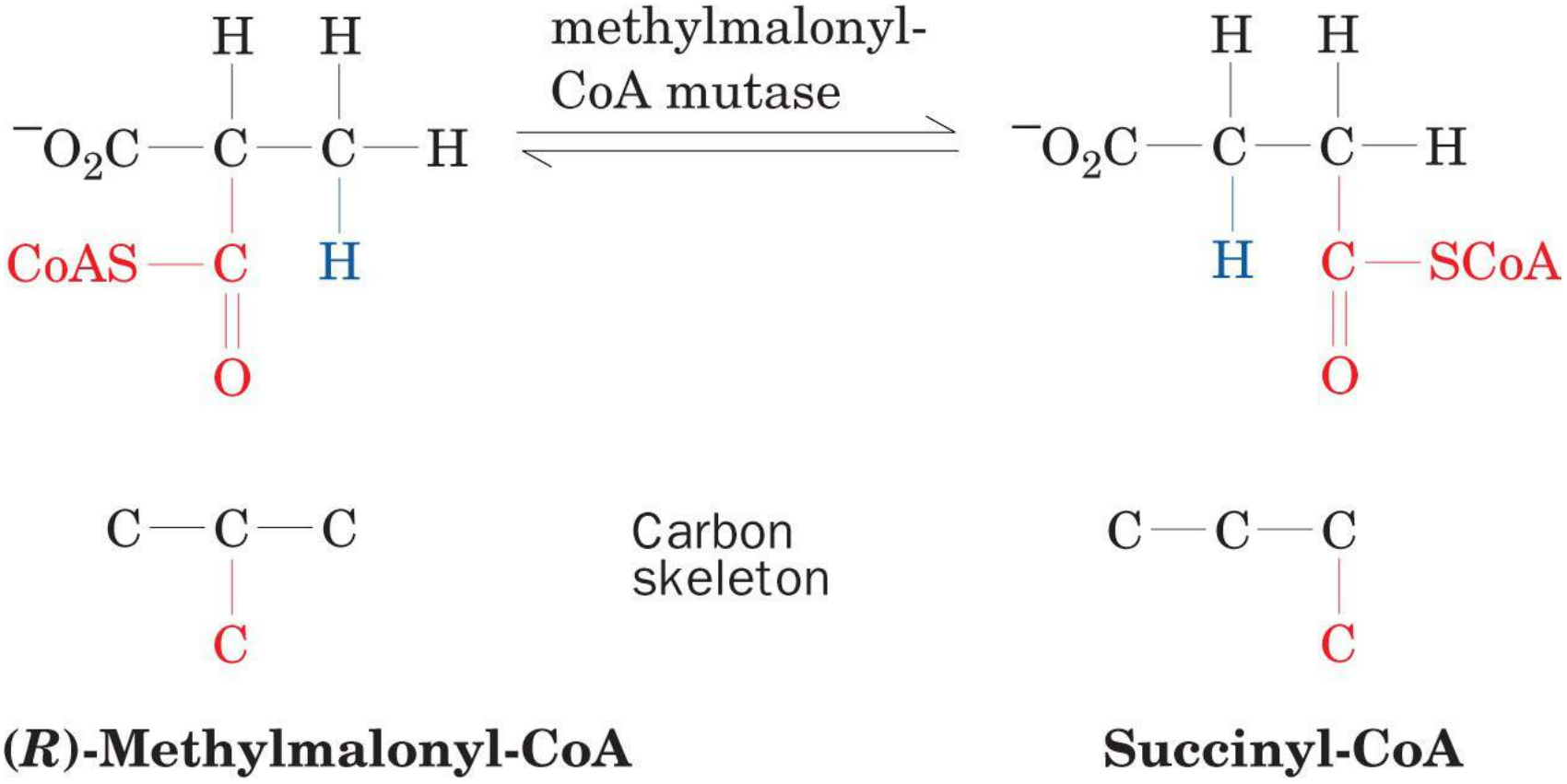
3) Methylmalonyl-CoA mutase, B12 containing (cobalamin)



The rearrangement catalyzed by methylmalonyl-CoA mutase

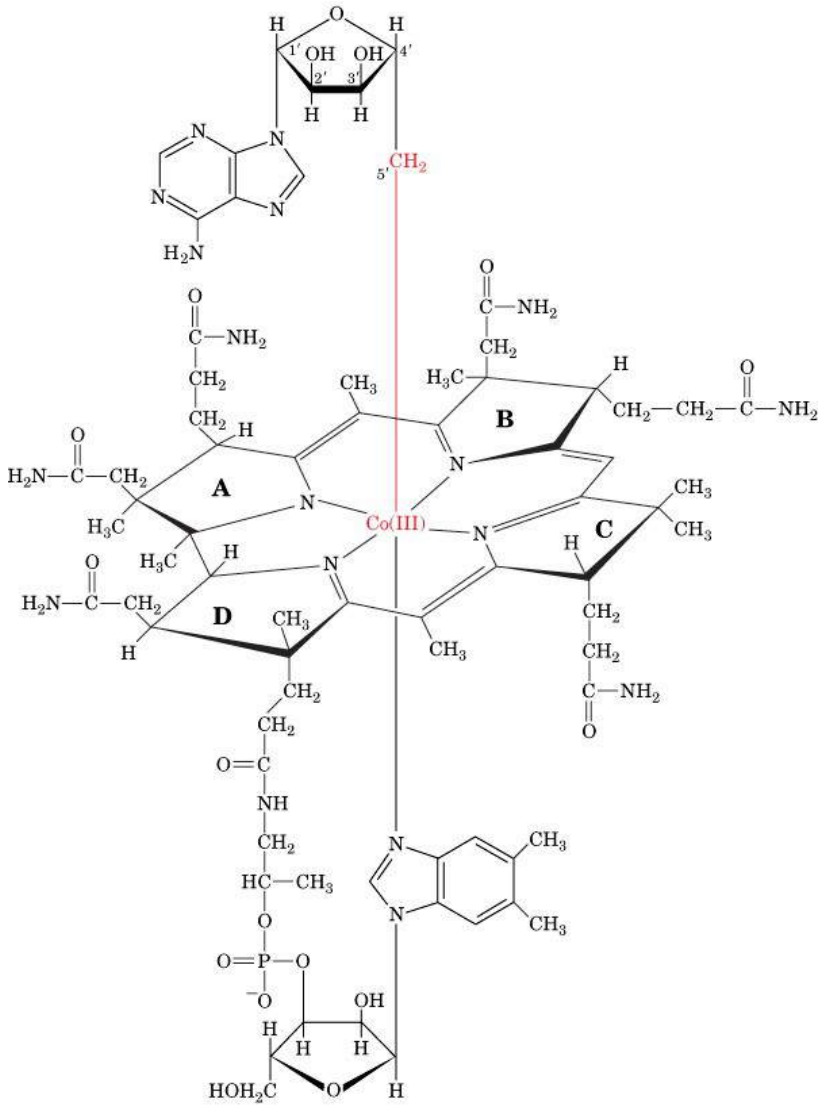
Vit B12-dependent (cobalamin)

Highly stereospecific (R-methylmalonyl-CoA) -> racemase



Coenzyme B_{12}
5'-deoxyadenosylcobalamin

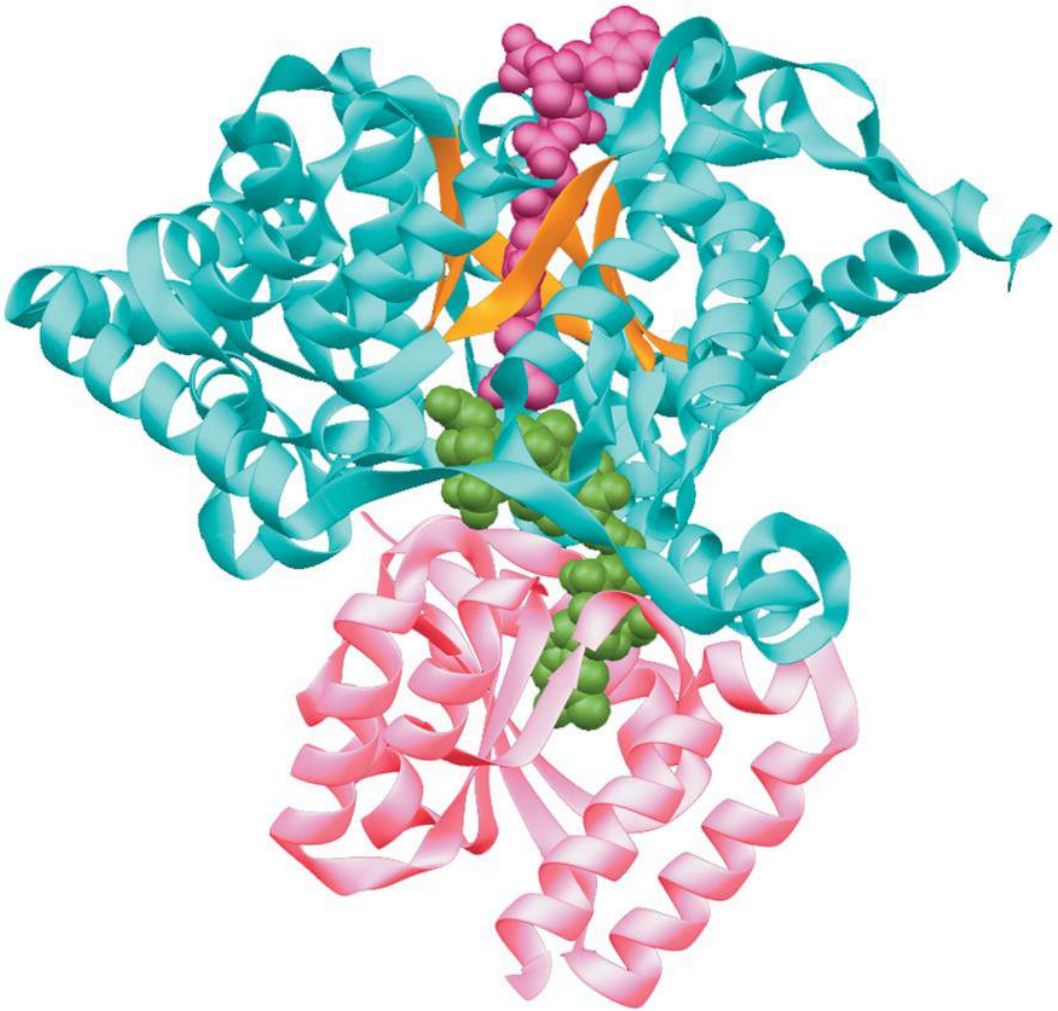
1. Heme-like corrin ring
2. 4 pyrrol N coordinate 6 fold coordinated **Co**
3. 5,6 coordination by dimethylbenzimidazole and deoxyadenosyl (C-Co bond !)
4. In carbon-carbon rearrangements
5. Methyl group transfer
6. About 12 known B12-dependent enzymes
7. **Only 2 in mammals**
   a. **Methylmalonyl mutase, homolytic cleavage, free radical mechanism**
   b. **Methionine synthase**
8. B12 acts as a reversible free radical generator, hydrogen rearrangement or methyl group transfer by homolytic cleavage

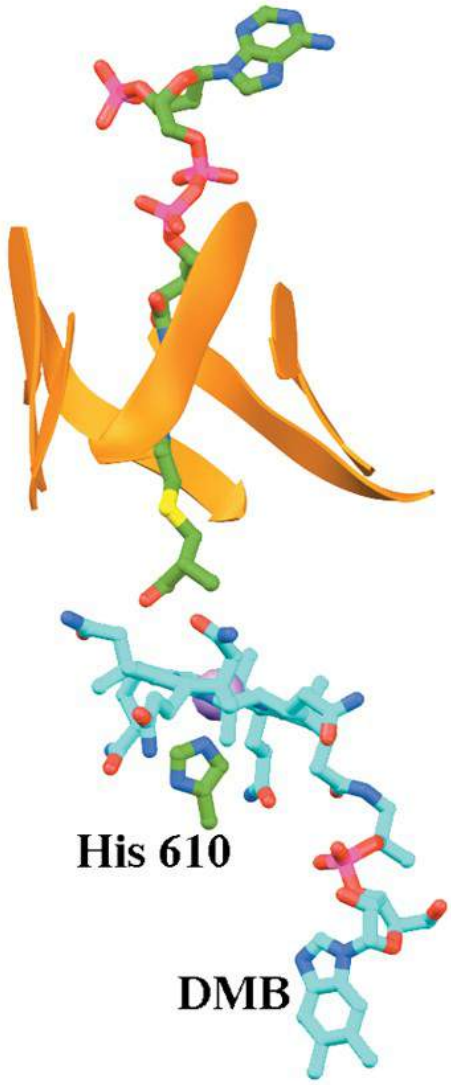


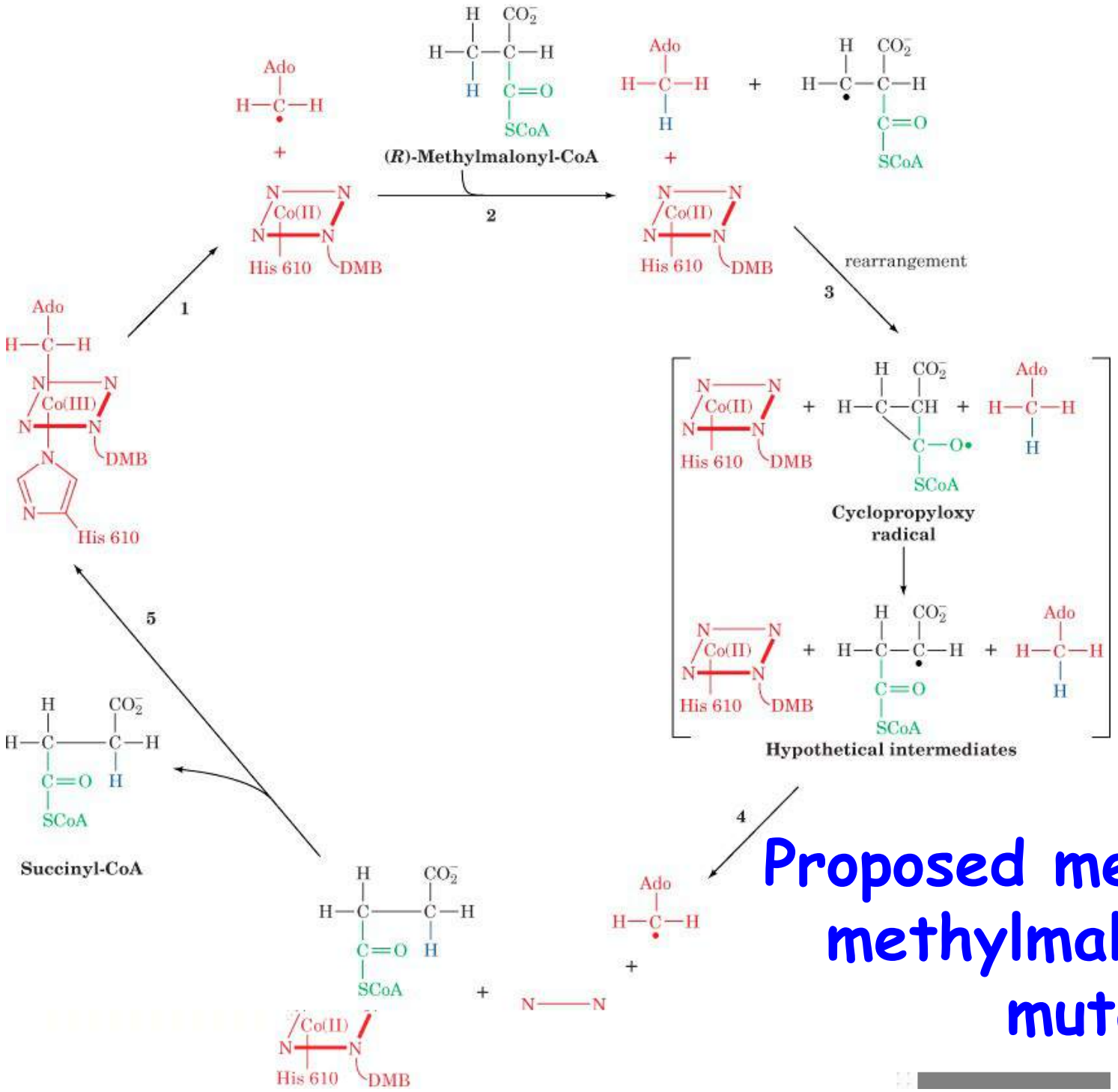
5′-Deoxyadenosylcobalamin (coenzyme B_{12})

X-Ray structure of *P. shermanii* methylmalonyl-CoA mutase in complex with 2-carboxypropyl-CoA and AdoCbl

α/β-barrel class of enzymes







Proposed mechanism of methylmalonyl-CoA mutase

Vit B12 deficiency

Pernicious anemia

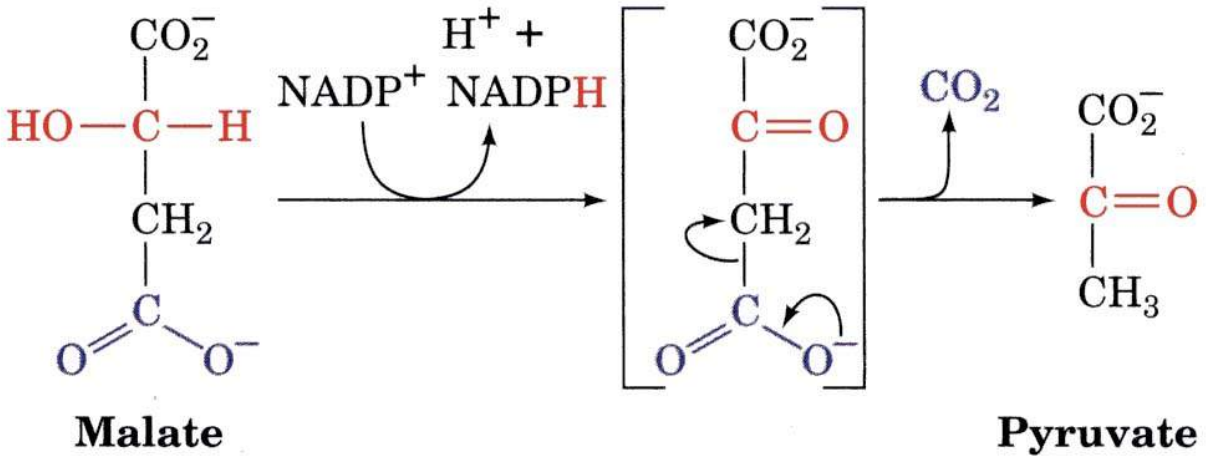
- in elderly
- decreased number of red blood cells
- treated by daily consumption of raw liver (1926) -> (1948)
- only few bacteria synthesize B12, plants and mammals not
- human obtain it from meat
- Vit. B12 is specifically bound in intestine by **intrinsic factor**
- complex absorbed in intestinal mucosa -> blood
- bound to **transcobalamins** in blood for uptake by tissue
- not usually a dietary disease but result from insufficient secretion of **intrinsic factor**

The fate of Succinyl-CoA

1) Succinyl-CoA is not consumed in TCA cycle but has a catalytic function

2) To consume it, it must first be converted to pyruvate or acetyl-CoA

- Conversion to malate (TCA)
- Export of malate to cytosol, if conc. are high
- Conversion to pyruvate by malic enzyme



Malate **Pyruvate**

F) Peroxisomal β oxidation

- β-oxidation occurs both in mitochondria and in peroxisomes
- *Peroxisomes:* Shortening of very-long chain fatty acids (VLCFA) for subsequent transport and oxidation in mitochondria
- **ALD protein** to transport VLCFA into peroxisomes, no carnitine required, VLCFA-CoA synthetase
- *X-adrenoleukodystrophy caused by defects in ALD,* lethal in young boys, 13% reduced efficiency of lignoceric acid (C24:0) to lignoceryl-CoA conversion
- first step in perox. oxid. **Acyl-CoA oxidase** generates H_2O_2 (peroxide) -> name ! Catalase
- carnitine for transport of chain shortened FAs out of peroxisomes and into mito.

Peroxisomal β-oxidation

First step:

Fatty acyl-CoA + O_2 -> enoyl-CoA + H_2O_2

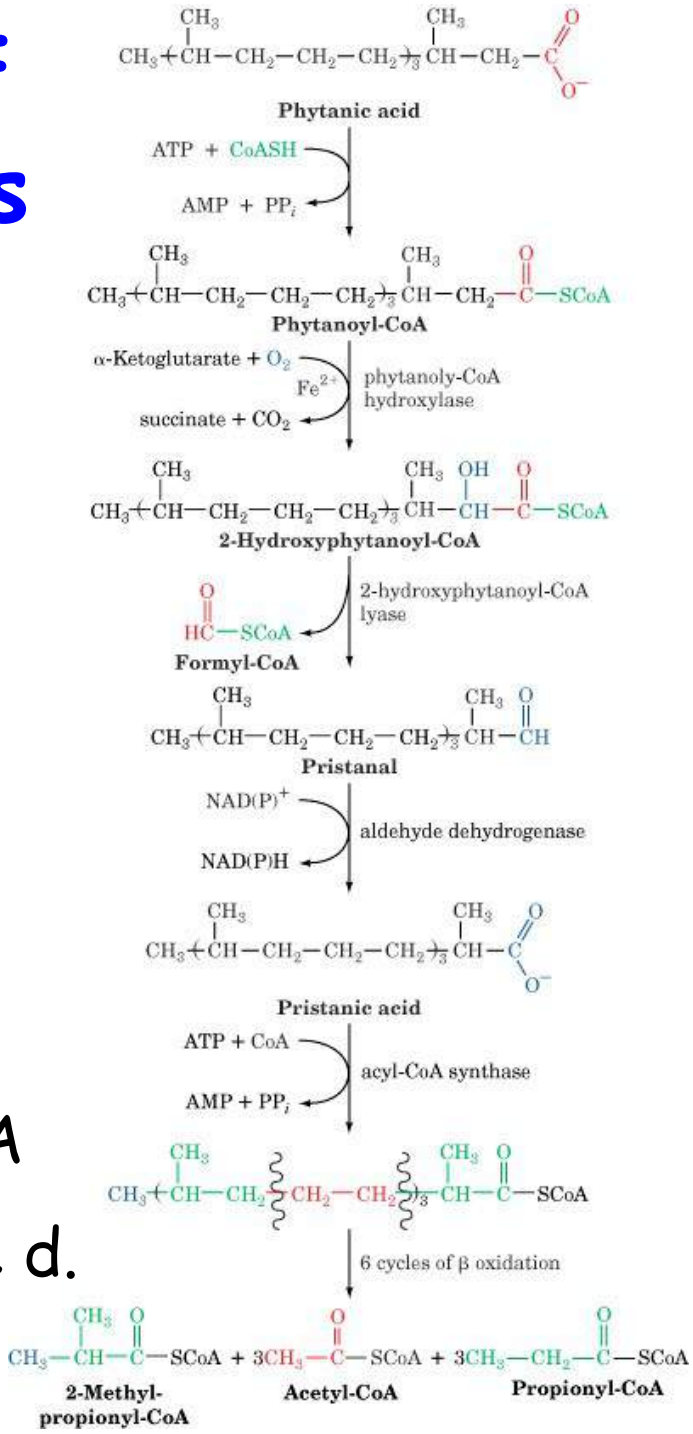
catalyzed by acyl-CoA oxidase

FAD dependent but direct transfer of electrons to O_2 -> H_2O_2

Pathway of α oxidation of branched chain fatty acids

- β-oxidation is blocked by methyl group at Cβ

- Phytanic acid, breakdown product of Chlorophyll's phytyl side chain
- Degraded by α-oxidation
- generates formyl-CoA
- and propionyl-CoA
- C-end will give 2-methyl-propionyl-CoA
- Refsum disease/phytanic acid storage d.
- omega oxidation in the ER, Cyt P450

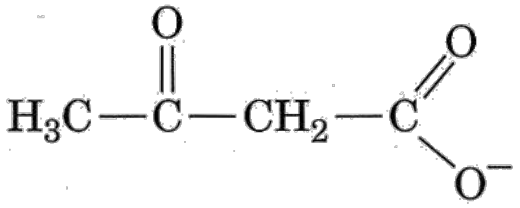


3) Ketone bodies

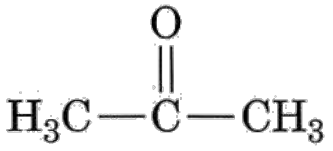
- Fate of acetyl-CoA generated by β-oxidation:

  1. TCA cycle

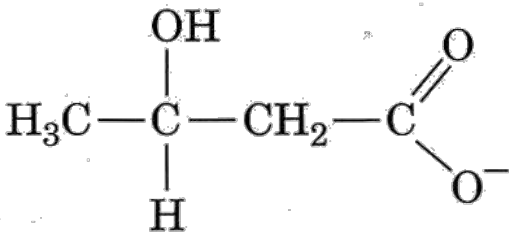
  2. Ketogenesis in liver mitochondria



Acetoacetate



Acetone



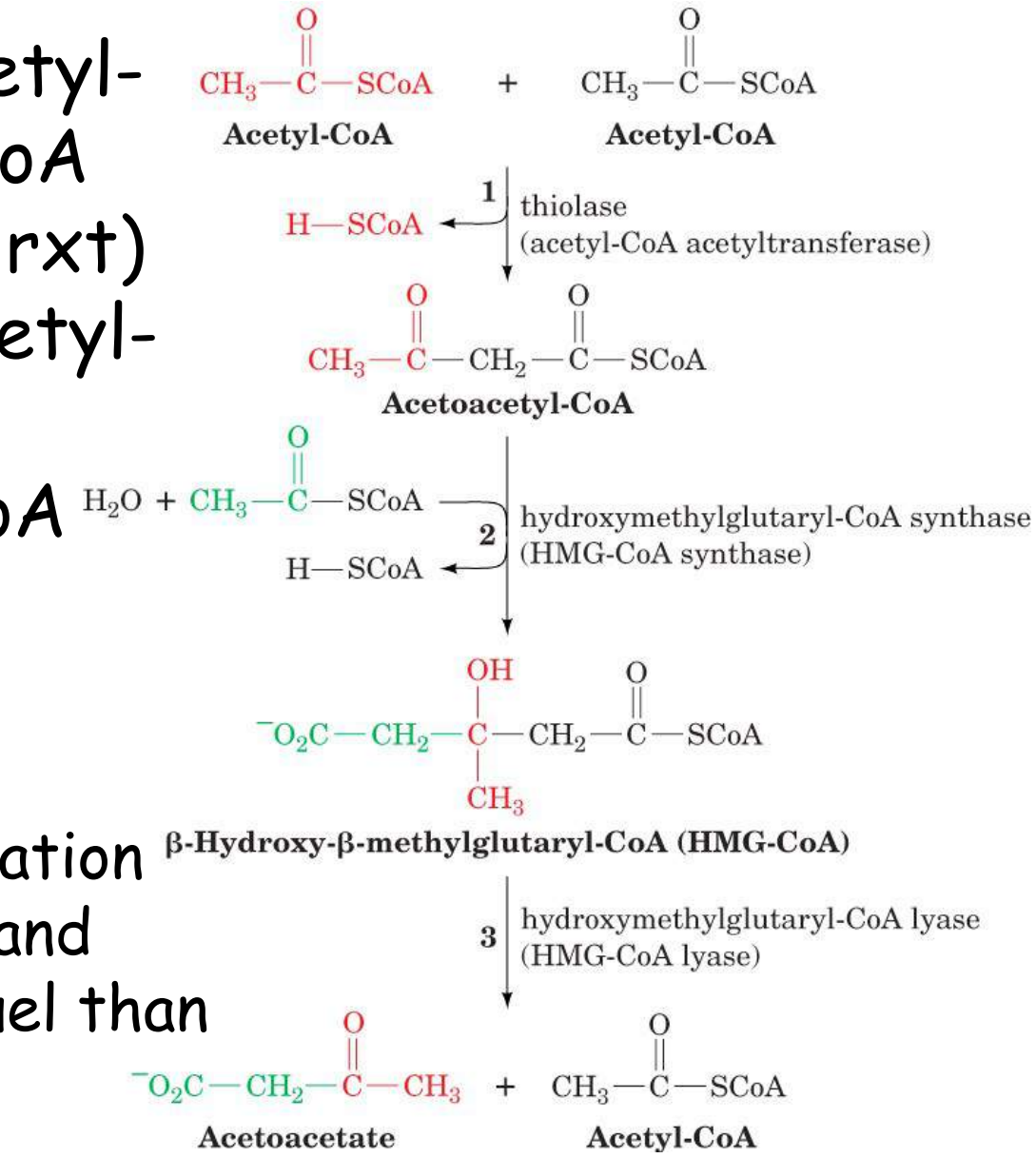
D-β-Hydroxybutyrate

- Keton bodies, fuel for peripheral tissue (brain !)
- where they are again converted into acetyl-CoA
- water soluble equivalent of fatty acids

Ketogenesis

3 step reaction:

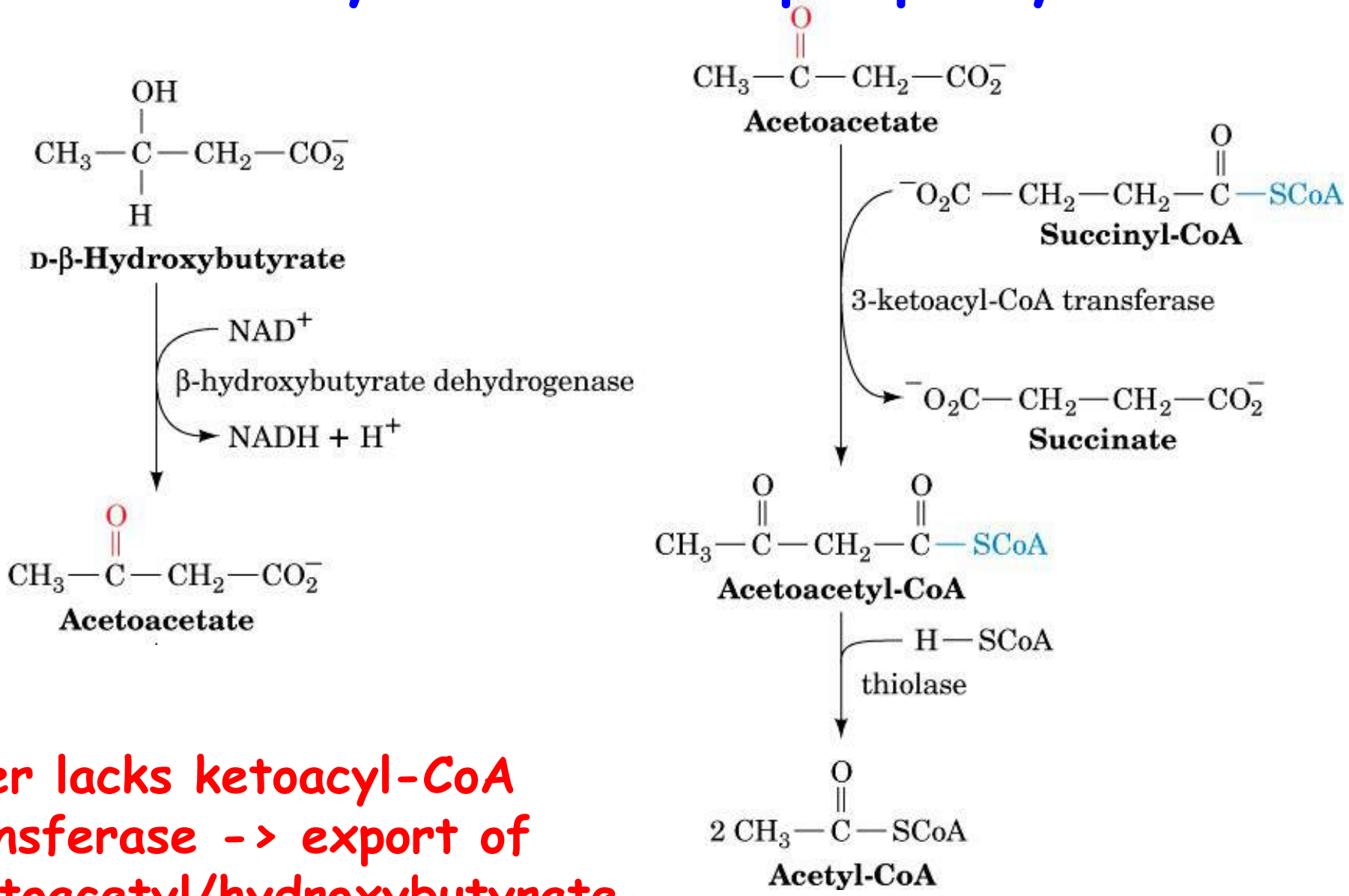
1. Condesation of 2 acetyl-CoA -> acetoacetyl-CoA (reversal of thiolase rxt)
2. Addition of third acetyl-CoA
3. Cleavage by HMG-CoA lyase



Ketosis:

Spontaneous decarboxylation of acetoacetate to CO_2 and acetone breath (more fuel than used)

The metabolic conversion of ketone bodies to acetyl-CoA in the periphery



Liver lacks ketoacyl-CoA transferase -> export of acetoacetyl/hydroxybutyrate

4) Fatty acid Synthesis

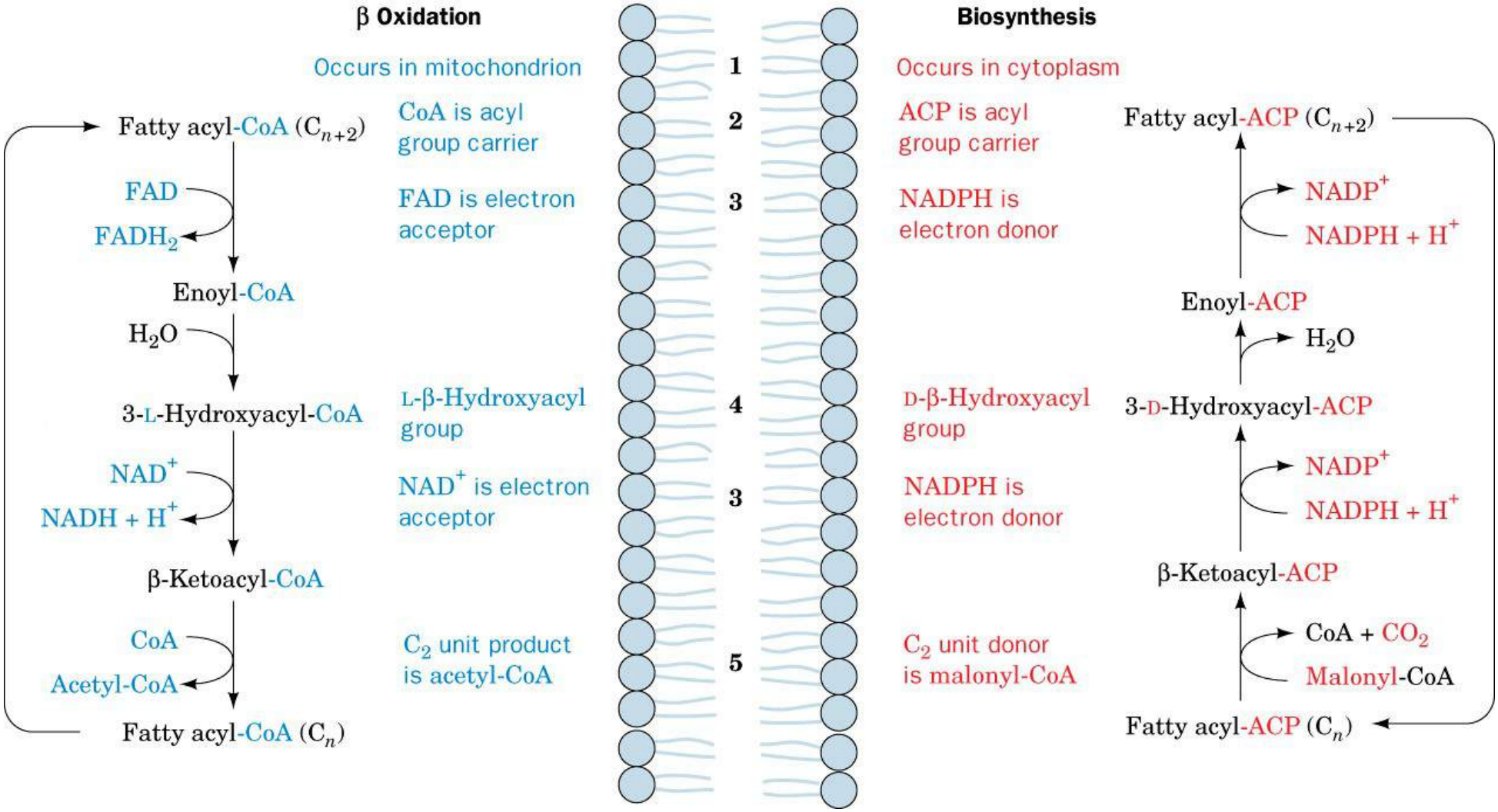
Synthesis of FA through condensation of C2 (C3-CO_2) units -> reversal of β-oxidation

Cytosolic, NADPH <-> mitochondrial, FAD, NAD
Difference in stereochemistry
C3 unit for growth (malonyl-CoA) <-> C2 for oxidation (acetyl-CoA)

Growing chain esterified to acyl-carrier protein (ACP)
Esterified to phosphopantetheine group as in CoA which itself is bound to a Ser on ACP

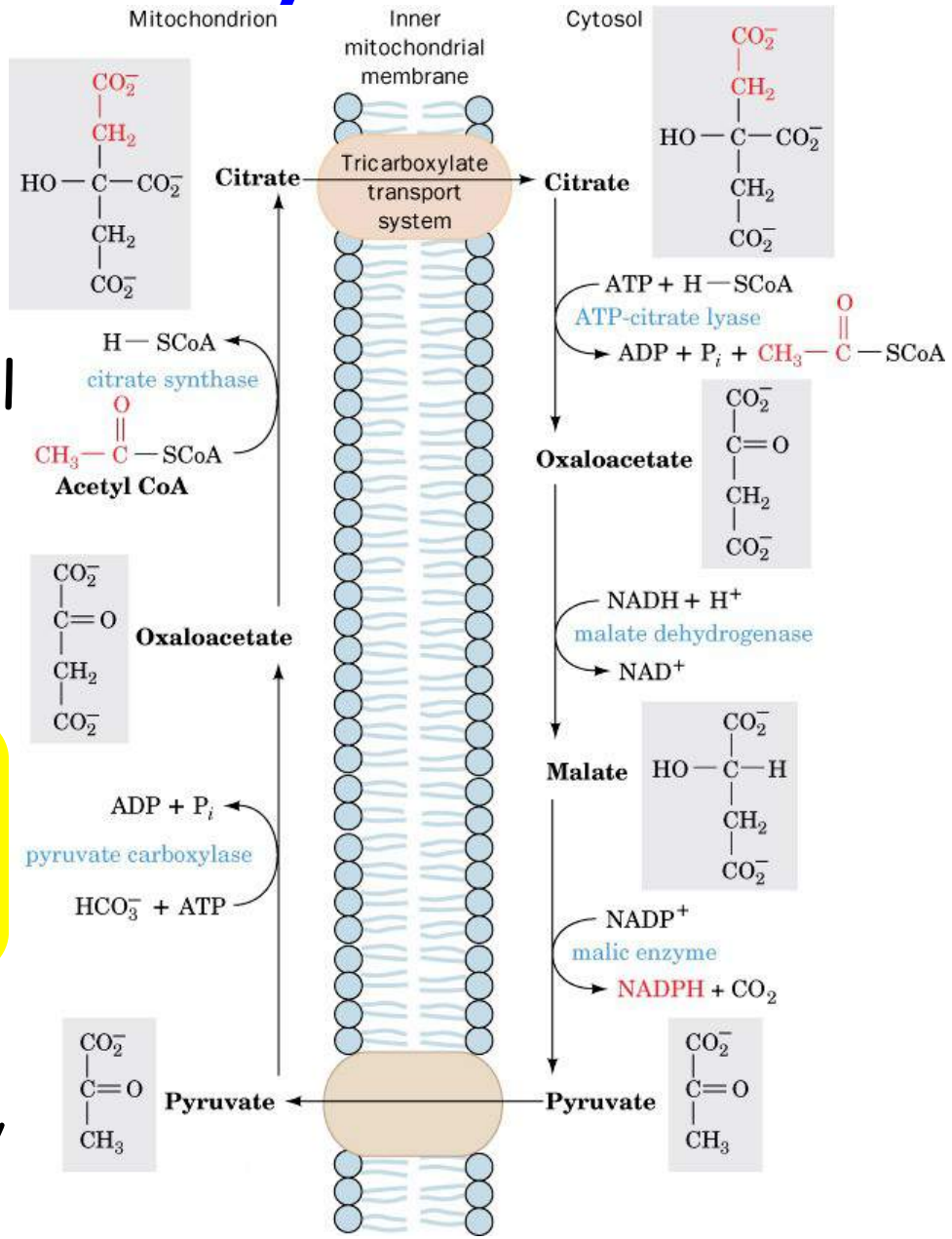
ACP synthase transfers phosphopantetheine to apo-ACP to form a holo-ACP

A comparison of fatty acid β oxidation and fatty acid biosynthesis



A) Mitochondrial acetyl-CoA must be transported into cytosol

- Acetyl-CoA: produced by pyruvate dehydrogenase, β-oxidation in mitochondria
- Acetyl-CoA enters the cytosol in form of citrate via the tricarboxylate transporter
- In the cytosol:
- Citrate + CoA +ATP <-> acetyl-CoA + OXA + ADP + Pi (cytrate lyase)
- citrate export balanced by anion import (malate, pyruvate, or P_i)



B) Acetyl-CoA carboxylase produces malonyl-CoA

- Catalyzes first and **committed** step of FA synthesis
- Biotin-dependent (see propionyl-CoA carboxylase)
- Stimulated by citrate !
- Hormonally regulated: Glucagon -> cAMP up -> PKA -> ACC is phosphorylated (inactivated)
  -> activated by insulin
- Mammals two isoforms:

  α-ACC, adipose tissue

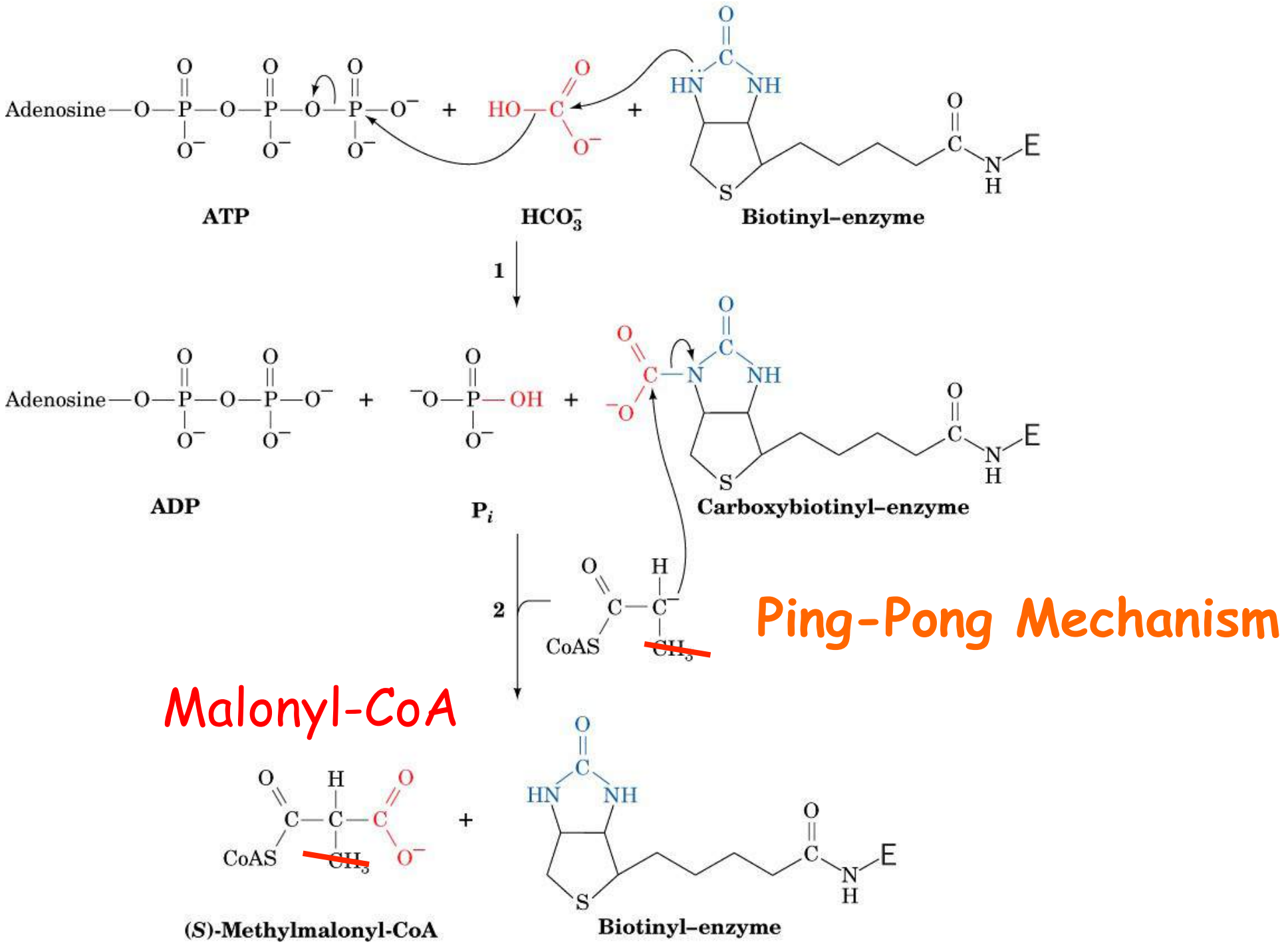
  β-ACC, tissue that beta-oxidize FA, heart muscle, regulates β-ox. as malonyl-CoA inhibits CPT-I

Biotin-dependent carboxylation reactions

1) **Acetyl-CoA carboxylase -> malonyl-CoA**
   (fatty acid synthesis)
2) **Propionyl-CoA carboxylase -> methylmalonyl-CoA**
   (β-oxidations of odd chain fatty acids)
3) **Pyruvate carboxylase -> oxalacetate**
   (TCA cycle, gluconeogenesis)

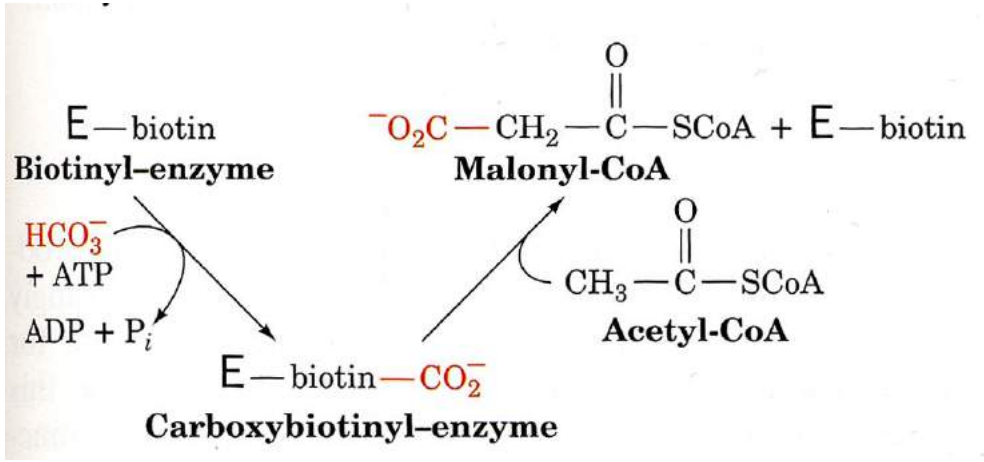
Always:

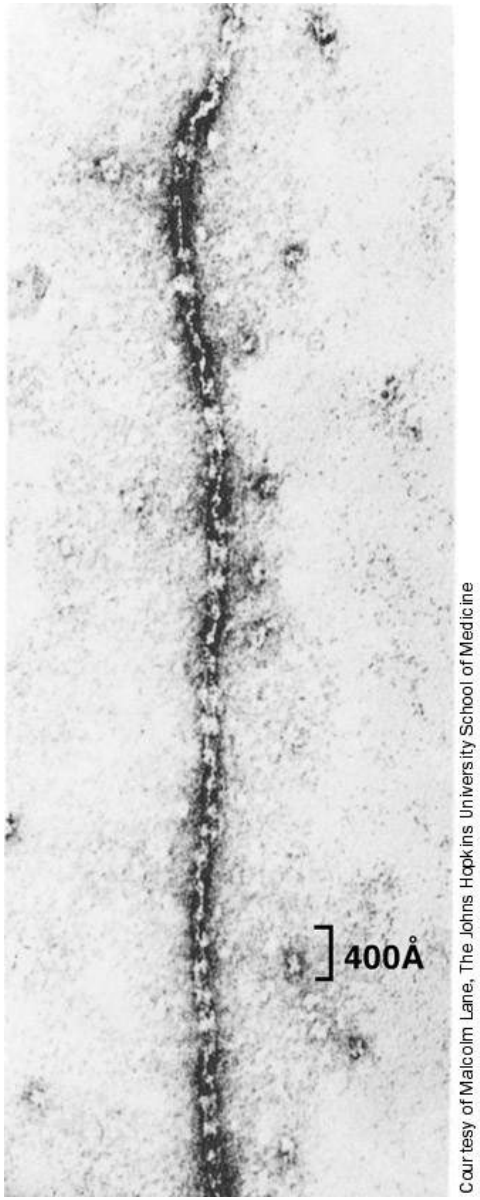
1) Carboxylation of biotin by bicarbonate, ATP requiring
2) Stereospecific transfer of carboxyl group


ATP
HCO_3^-
Biotinyl–enzyme
1
ADP
P_i
Carboxybiotinyl–enzyme
2
Malonyl-CoA
(S)-Methylmalonyl-CoA
Biotinyl–enzyme
Ping-Pong Mechanism

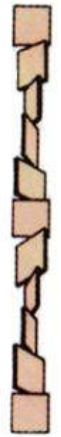
Association of acetyl-CoA carboxylase protomers

- Multifunctional protein in eukaryotes (1 polypeptide chain)
- Composed of 3 proteins in bacteria:
  - Biotin carboxylase
  - Transcarboxylase
  - Biotin carboxyl-carrier
- Polymerizes upon activation



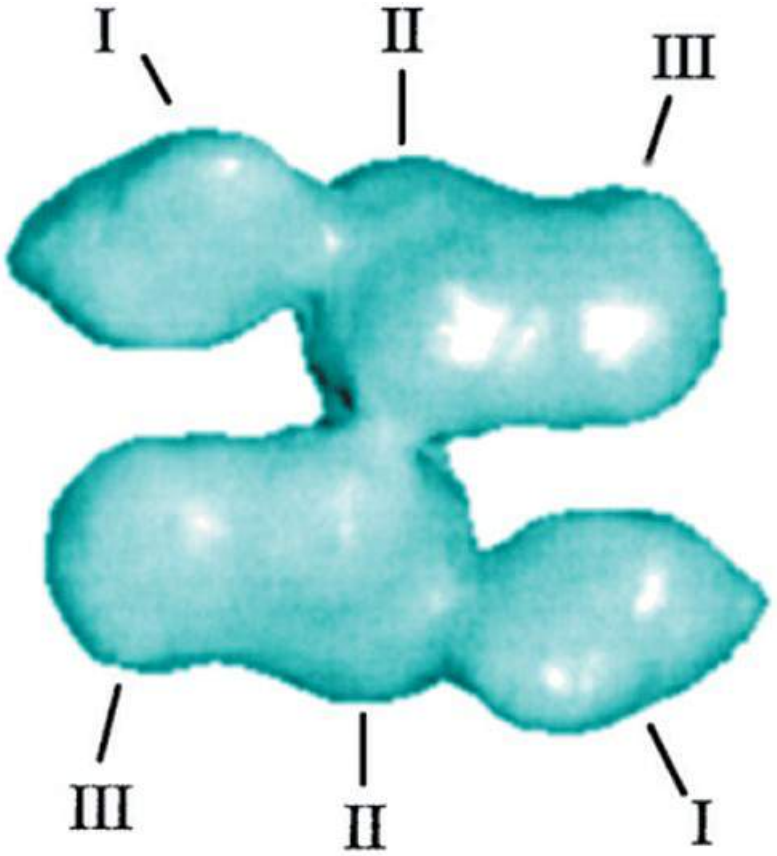


Courtesy of Malcolm Lane, The Johns Hopkins University School of Medicine



C) Fatty acid synthase catalyzes seven reactions

- Synthesis of FA from acetyl-CoA (starter) and malonyl-CoA (elongation) requires 7 enzymatic reactions,
- 7 proteins in E. coli + ACP
- $\alpha_6\beta_6$ complex in yeast (2500 kD)
- homodimer in mammals, 272 kD



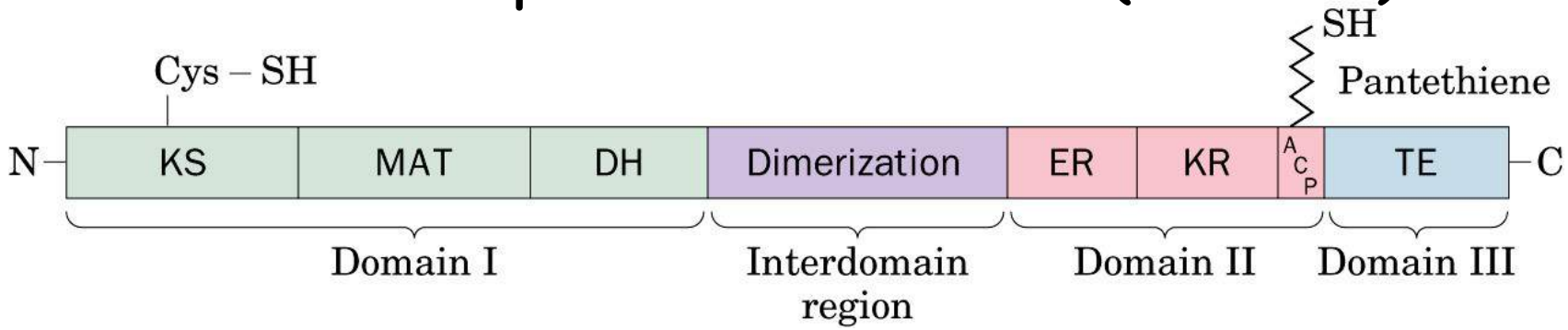
Courtesy of Salih Wakil and Wah Chiu, Baylor College of Medicine

EM-based image of the human FAS dimer as viewed along its 2-fold axis, each monomer has 4 50 Å diameter lobs -> functional domains antiparallel orientation

The animal fatty acid synthase (FAS)

Multifunctional protein with 7 catalytic activities
Head to tail interaction of monomer in the dimer (KS close to ACP)

Two monomers operate in concert (534 kD).



Ketoacyl ACP synthase

β-hydroxyacyl-ACP dehydratase

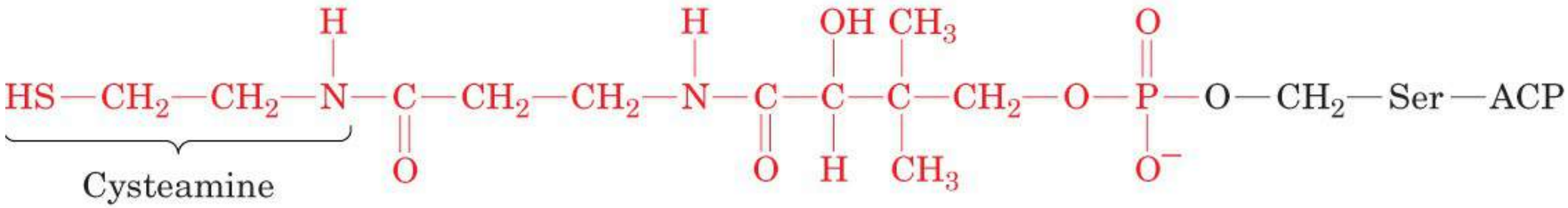
β-ketoacyl-ACP reductase

Malonyl/acetyl-CoA-ACP transacylase

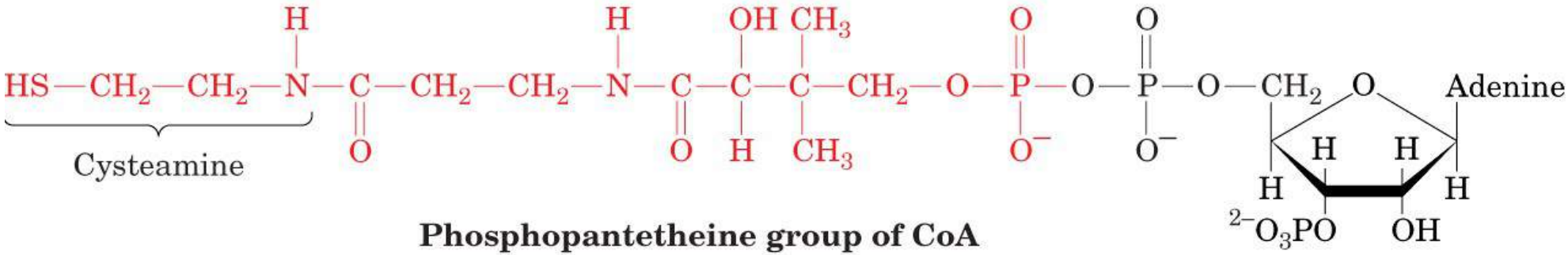
Enoyl-ACP reductase

Palmitoyl thioesterase

The phosphopantetheine group in acyl-carrier protein (ACP) and in CoA



Phosphopantetheine prosthetic group of ACP

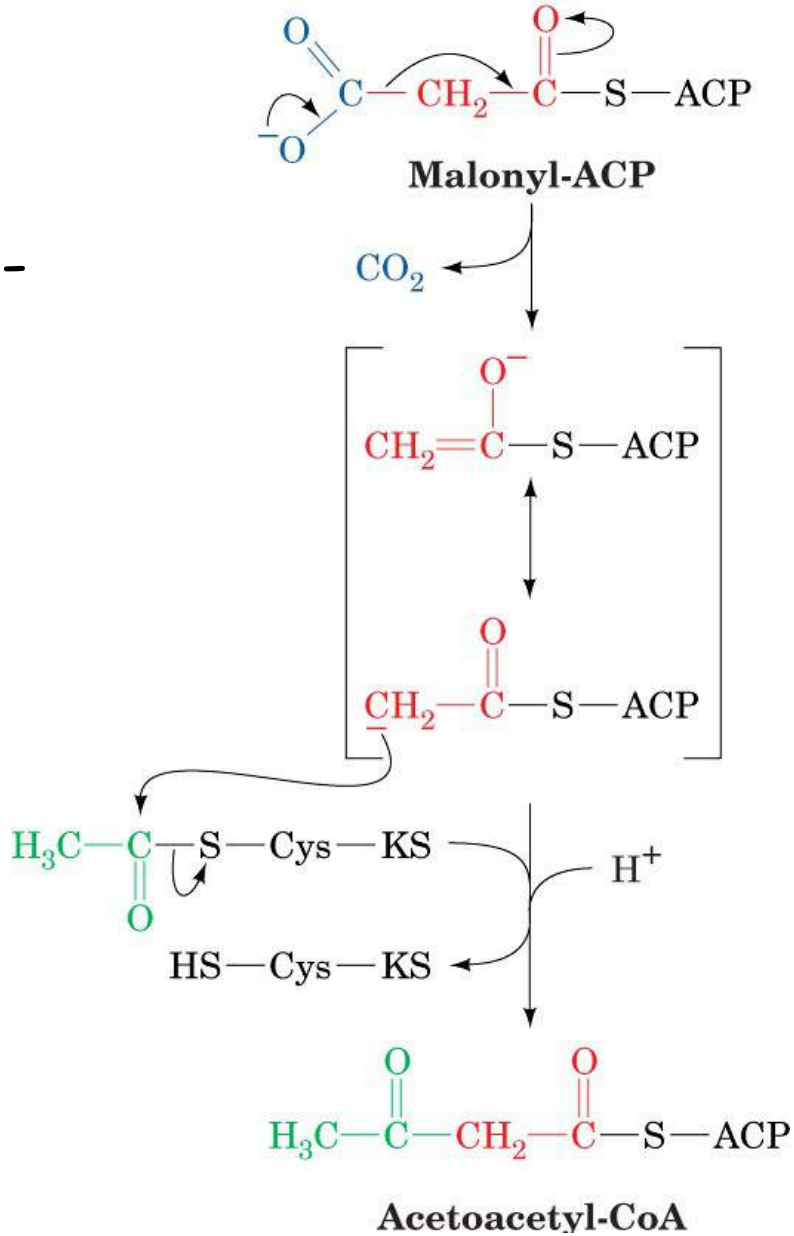


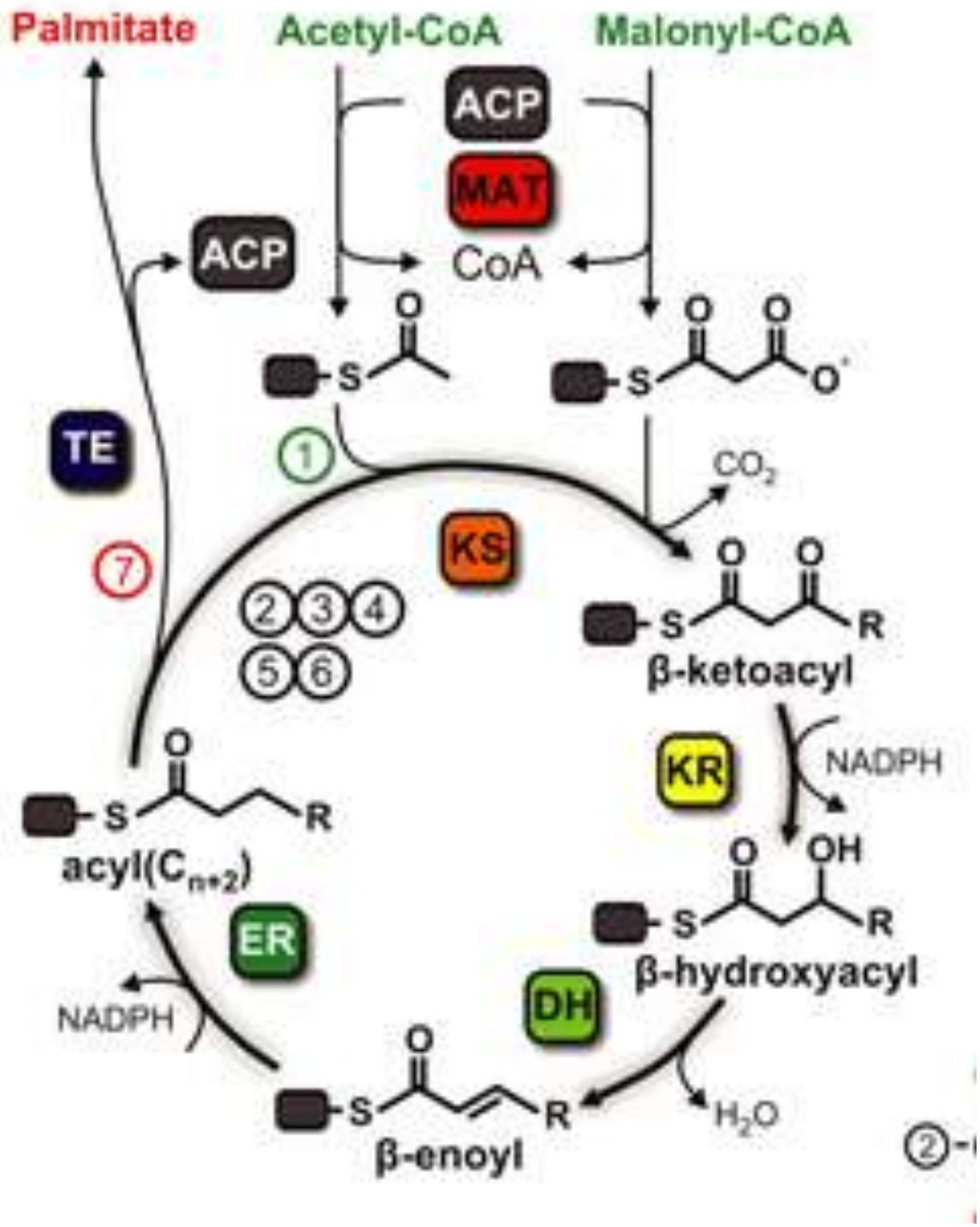
Phosphopantetheine group of CoA

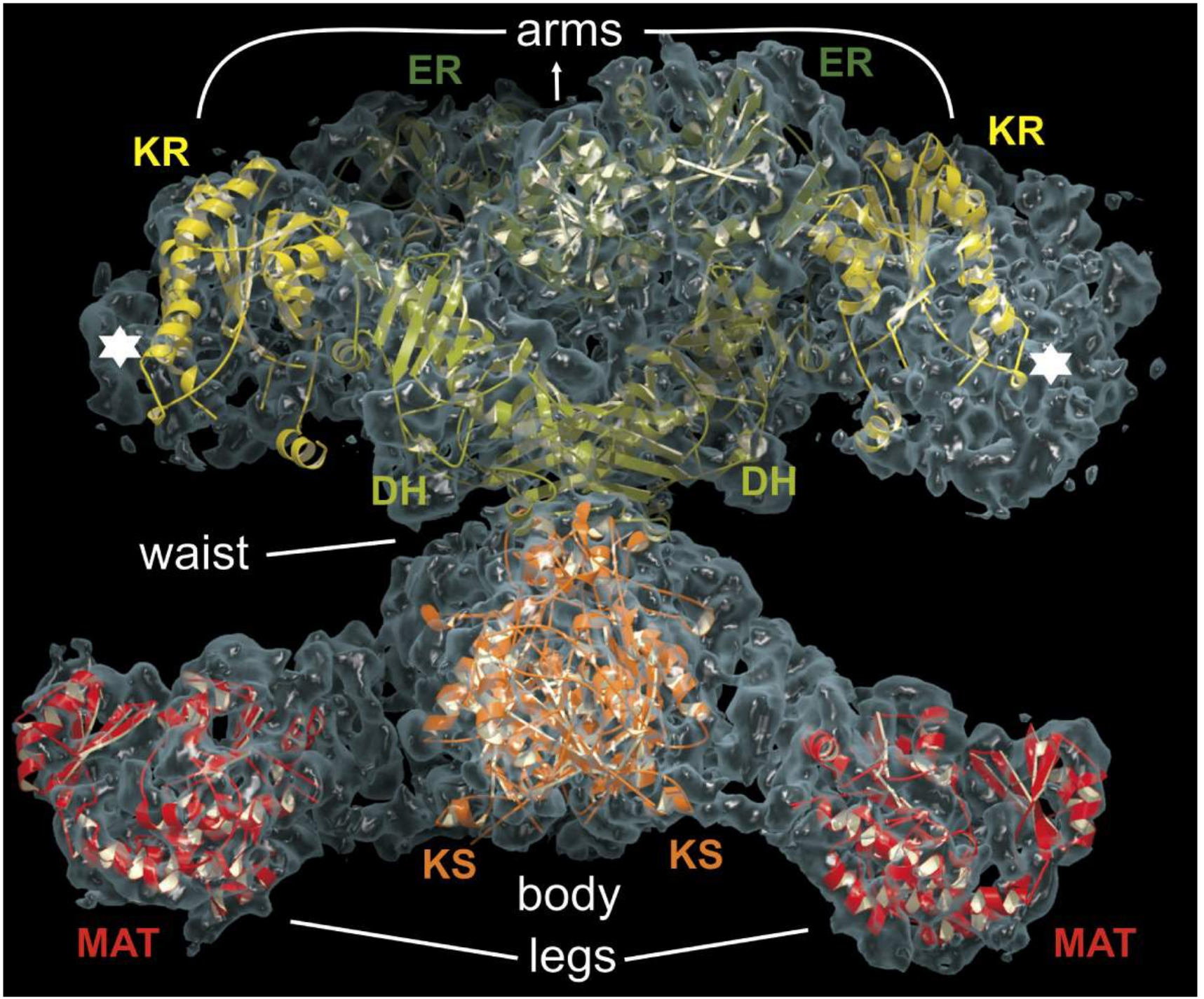
The mechanism of carbon–carbon bond formation in fatty acid biosynthesis

CO_2 that has been incorporated into malonyl-CoA is not found in the final Fatty Acid !

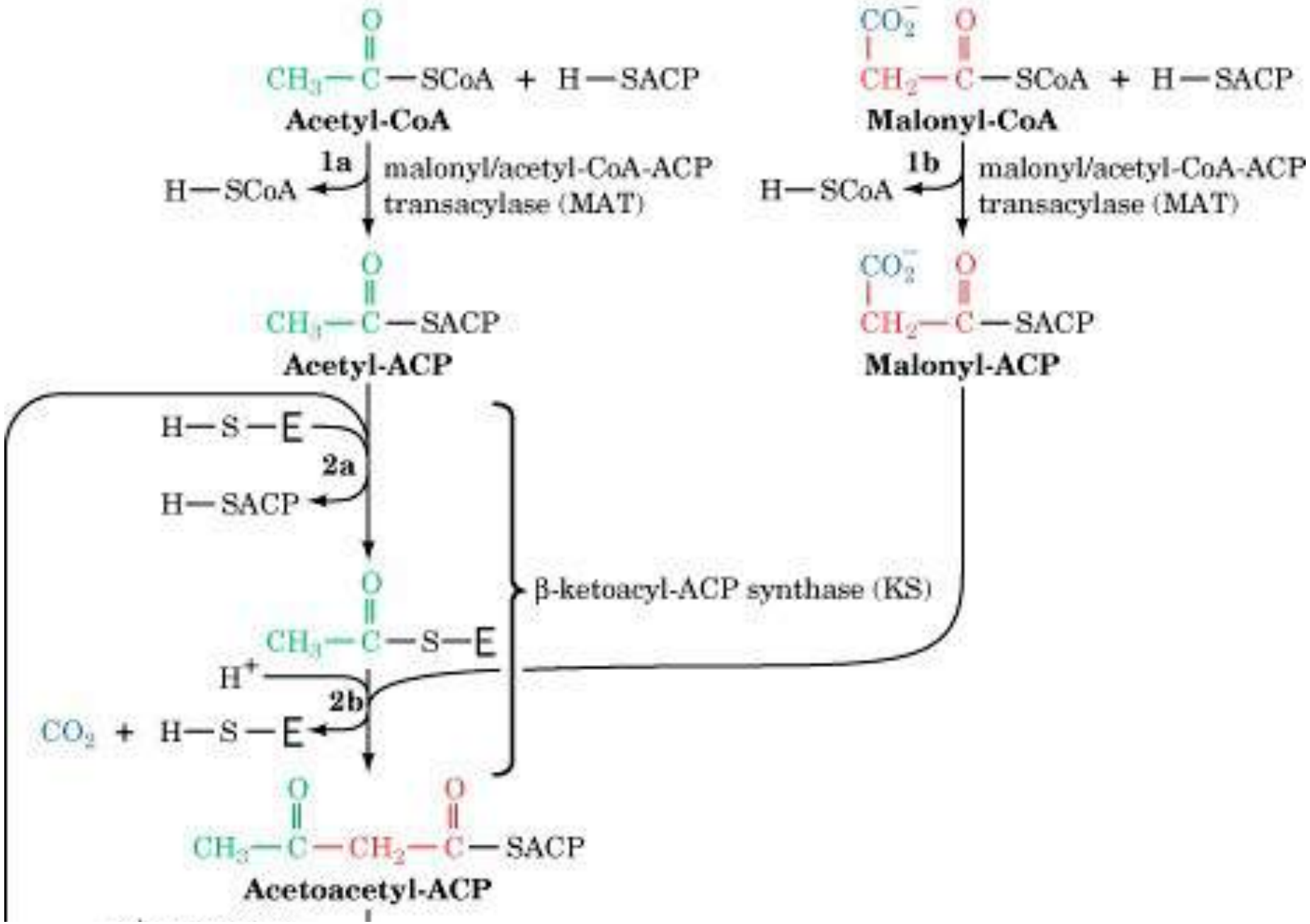
But makes the reaction irreversible !

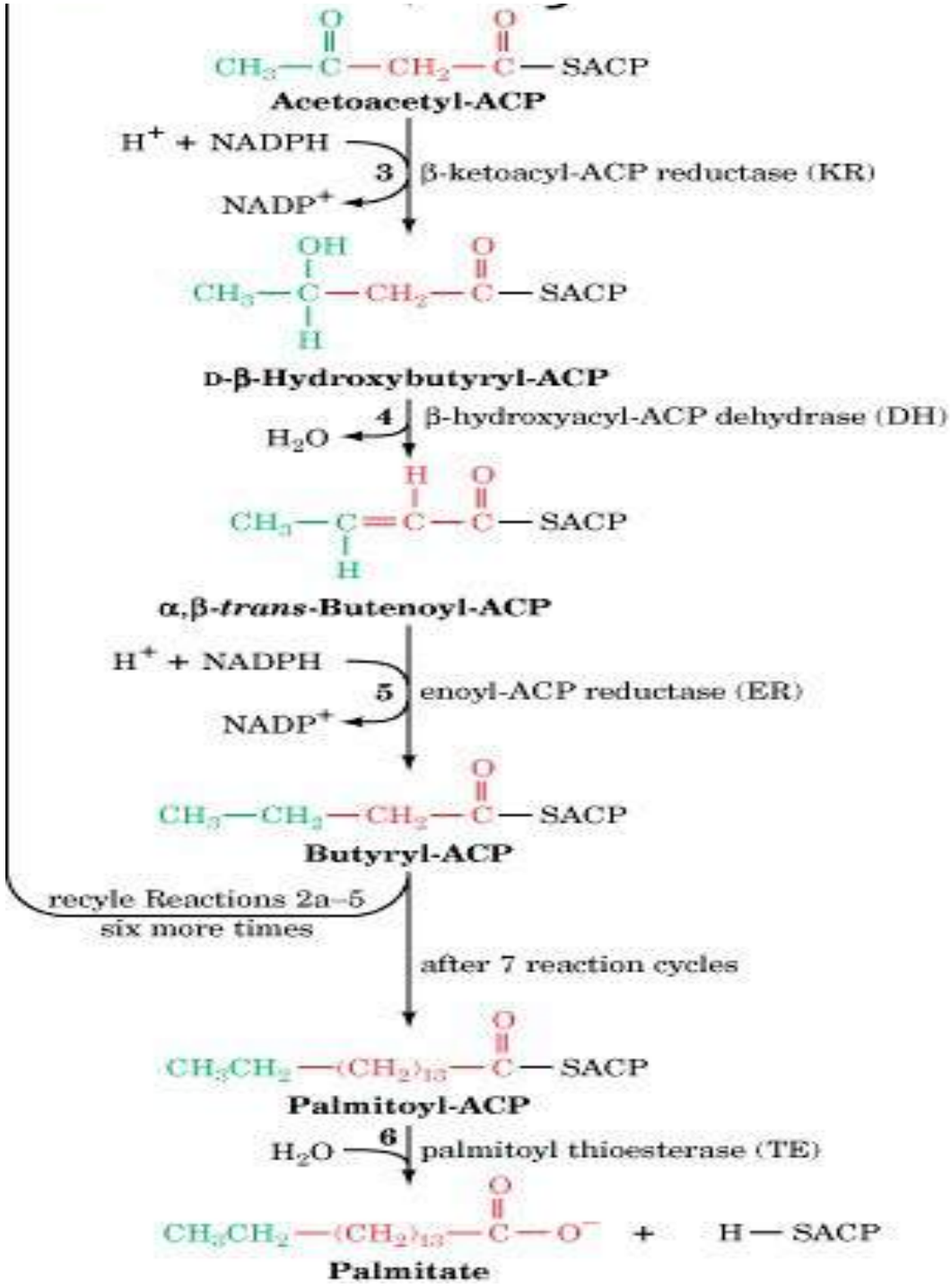


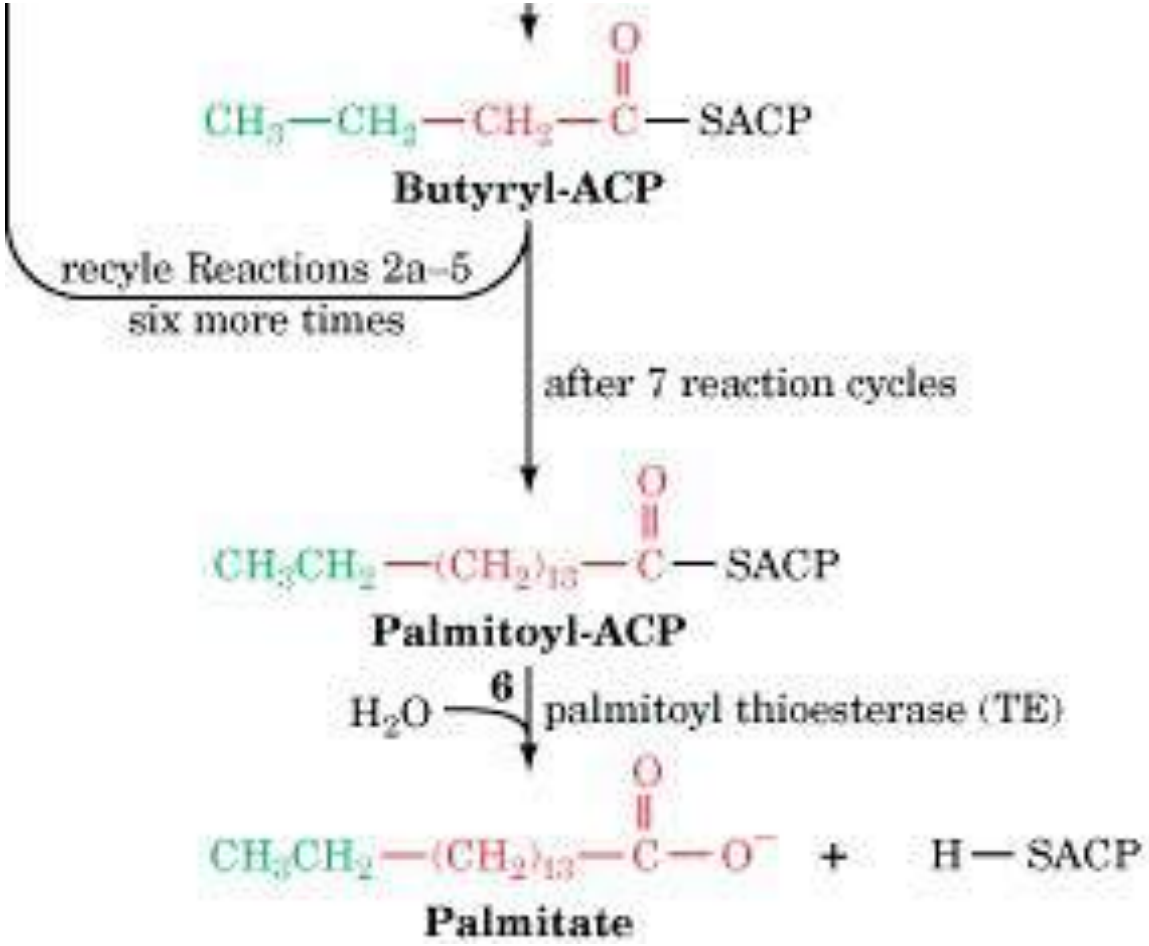

Palmitate
Acetyl-CoA
Malonyl-CoA
ACP
MAT
CoA
ACP
TE
7
1
CO_2
KS
2 3 4
5 6
β-ketoacyl
KR
NADPH
OH
β-hydroxyacyl
DH
H_2O
β-enoyl
ER
NADPH
acyl(C_{n+2})

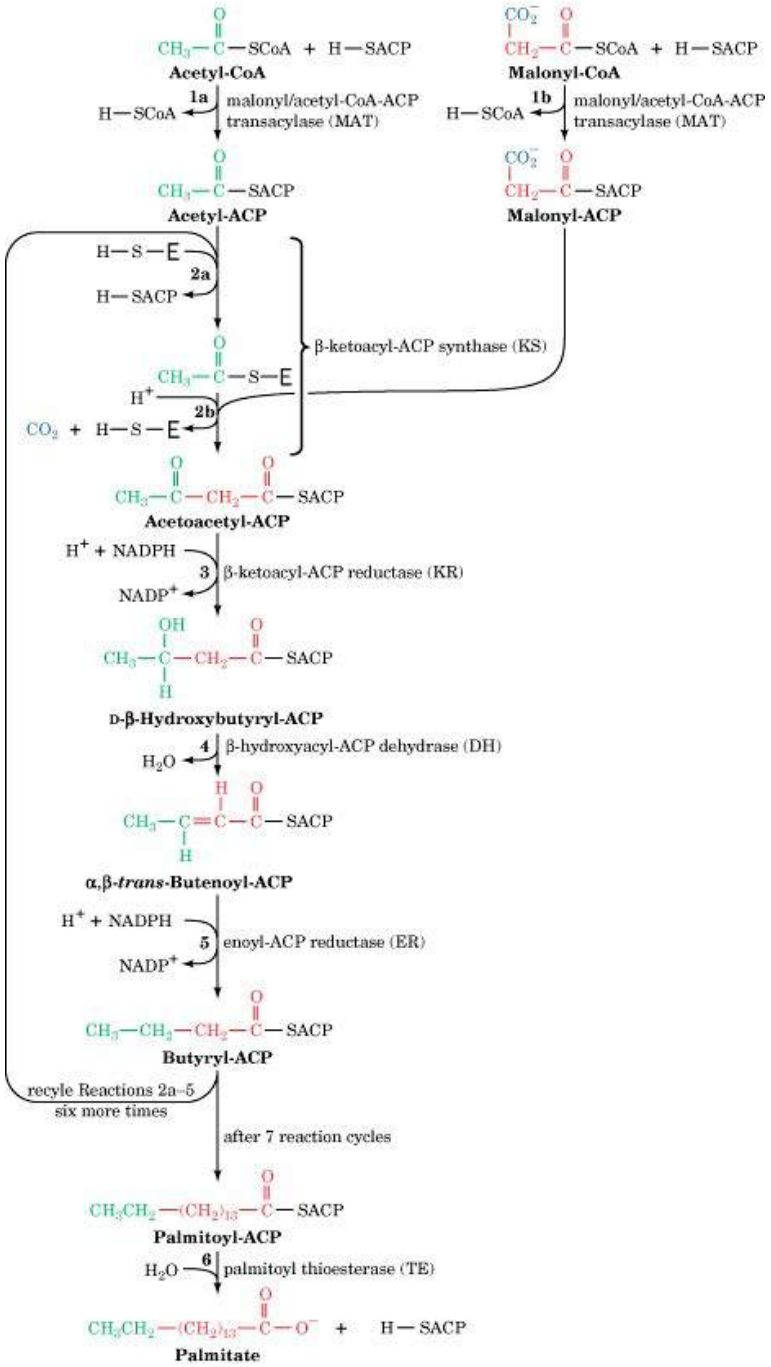


Courtesy of Nenad Ban and Tim Maier, Swiss Federal Institute of Technology


Acetyl-CoA
+ H—SACP
Malonyl-CoA
+ H—SACP
1a
malonyl/acetyl-CoA-ACP
transacylase (MAT)
H—SCoA
1b
malonyl/acetyl-CoA-ACP
transacylase (MAT)
H—SCoA
Acetyl-ACP
Malonyl-ACP
H—S—E
2a
H—SACP
β-ketoacyl-ACP synthase (KS)
H+
2b
+ H—S—E
Acetoacetyl-ACP

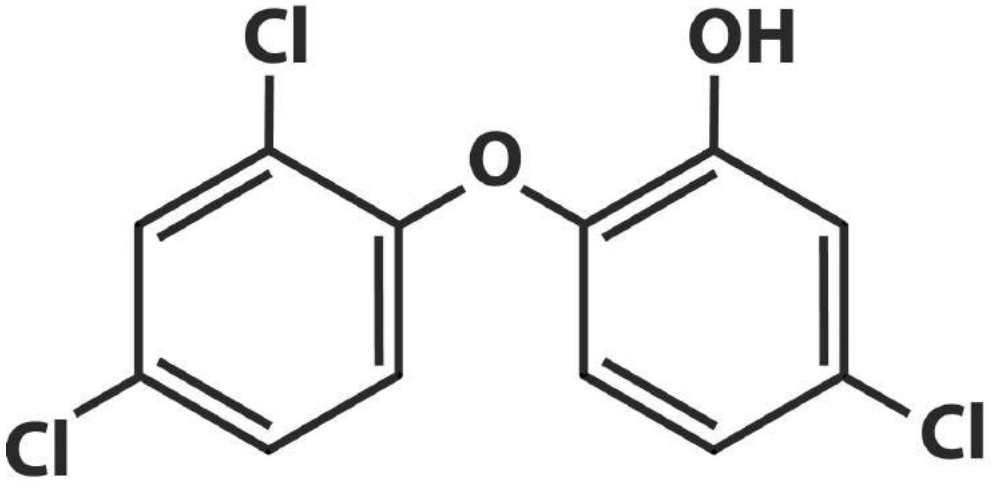

Acetoacetyl-ACP
H+ + NADPH
3
β-ketoacyl-ACP reductase (KR)
NADP+
D-β-Hydroxybutyryl-ACP
4
β-hydroxyacyl-ACP dehydrase (DH)
H2O
α,β-trans-Butenoyl-ACP
H+ + NADPH
5
enoyl-ACP reductase (ER)
NADP+
Butyryl-ACP
recyle Reactions 2a–5
six more times
after 7 reaction cycles
Palmitoyl-ACP
H2O
6
palmitoyl thioesterase (TE)
Palmitate
+
H — SACP


CH3—CH2—CH2—C—SACP
Butyryl-ACP
recyle Reactions 2a–5
six more times
after 7 reaction cycles
CH3CH2—(CH2)13—C—SACP
Palmitoyl-ACP
H2O
6
palmitoyl thioesterase (TE)
CH3CH2—(CH2)13—C—O⁻
+
H—SACP
Palmitate


Acetyl-CoA
Malonyl-CoA
1a
1b
malonyl/acetyl-CoA-ACP transacylase (MAT)
Acetyl-ACP
Malonyl-ACP
2a
2b
β-ketoacyl-ACP synthase (KS)
Acetoacetyl-ACP
3
β-ketoacyl-ACP reductase (KR)
D-β-Hydroxybutyryl-ACP
4
β-hydroxyacyl-ACP dehydrase (DH)
α,β-trans-Butenoyl-ACP
5
enoyl-ACP reductase (ER)
Butyryl-ACP
recyle Reactions 2a–5 six more times
after 7 reaction cycles
Palmitoyl-ACP
6
palmitoyl thioesterase (TE)
Palmitate

Triclosan: An inhibitor of bacterial fatty acid synthesis

- In cosmetics, toothpastes, toys etc
- As antibacterial agent
- *inhibits bacterial enoyl-ACP reductase*
- resistance is developing….

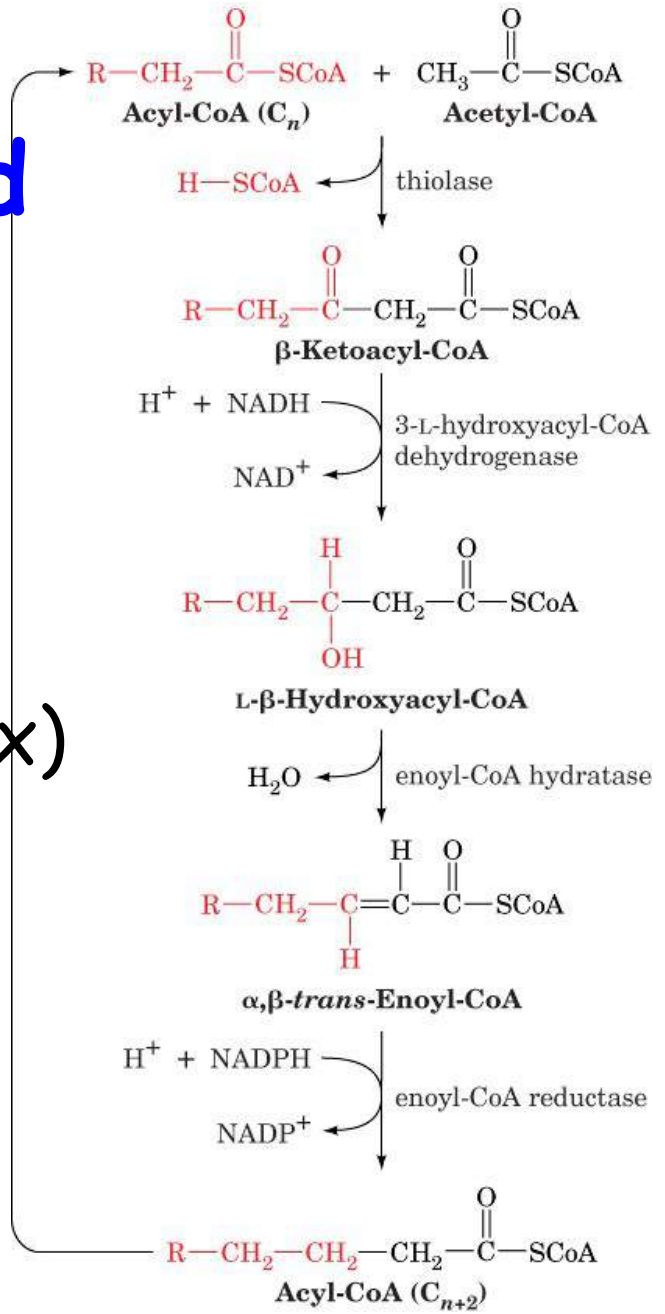


Triclosan

D) Fatty acids may be elongated and desaturated

Elongation at carboxy terminus:

- mitochondria (reversal of β-ox)
- ER (malonyl-CoA)

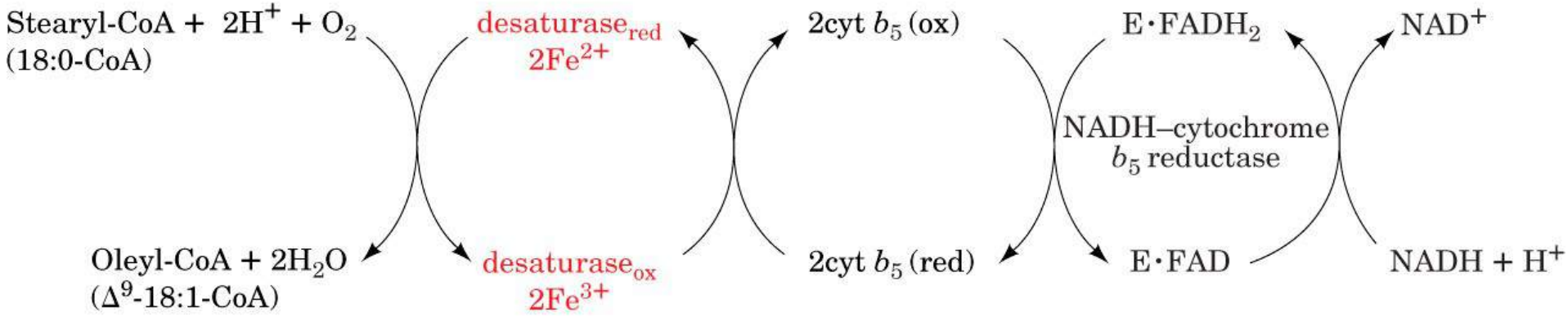


Mitochondrial fatty acid elongation

FA desaturation

Properties:

- Cis, Δ9 first, not conjugated
- membrane-bound, nonheme iron enzymes, cyt b_5-dependent
- mammals front end desaturation (Δ9, 6, 5/4)
- *essential FA, linoleic (C18:2n-6, $\Delta^{9,12}$), linolenic (C18:3n-3, $\Delta^{9,12,15}$)*
- some made by combination of desaturation and elongation
- PUFAs, fish oil, n-3, n-6 (omega)
- vision, cognitive functions



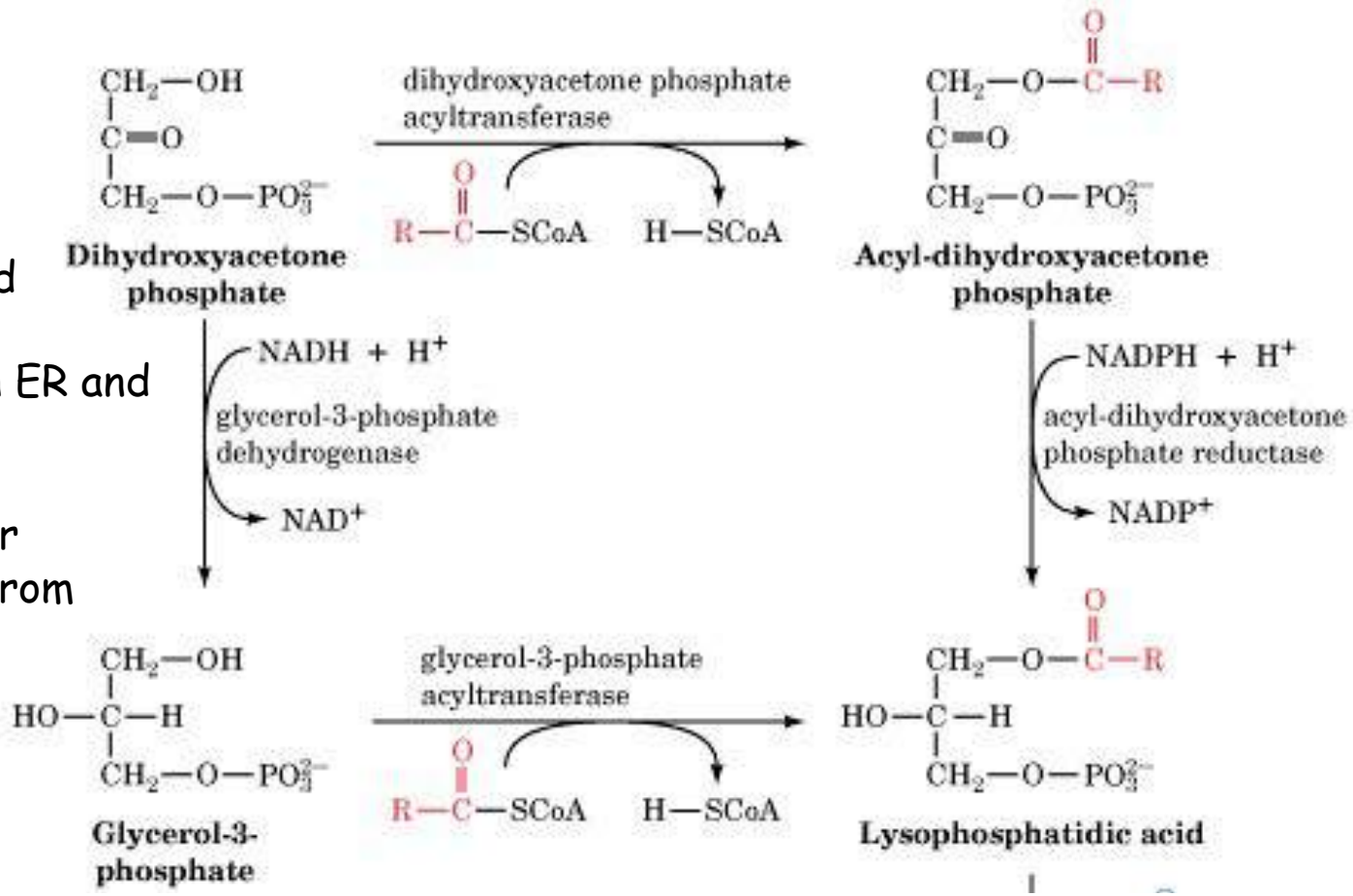
The electron-transfer reactions mediated by the Δ^9-fatty acyl-CoA desaturase complex

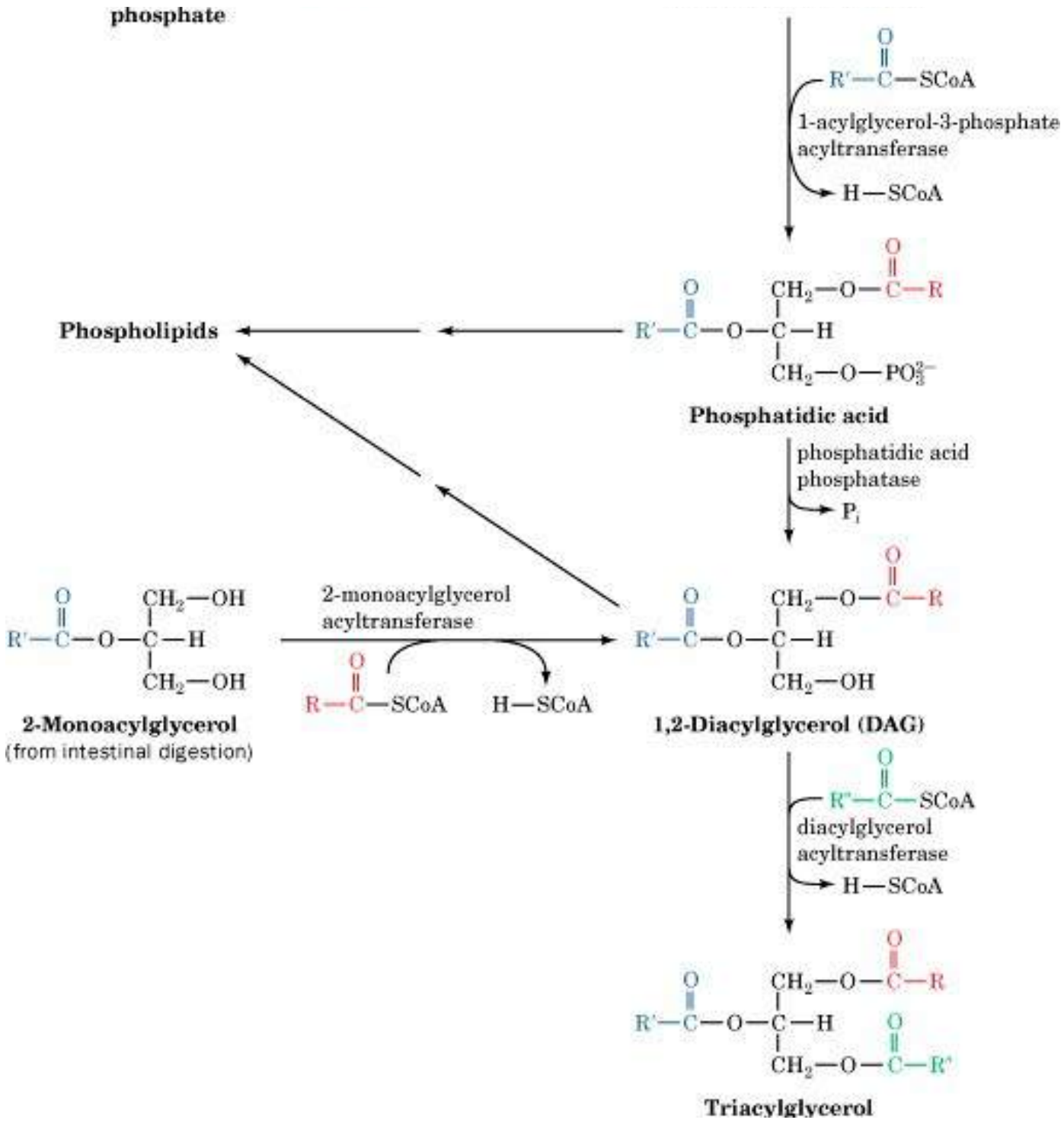
E) Fatty acids are esterified to form triacylglycerol

TAG are synthesized from fatty acyl-CoAs and *glycerol-3-phosphate* or dihydroxyacetone phosphate

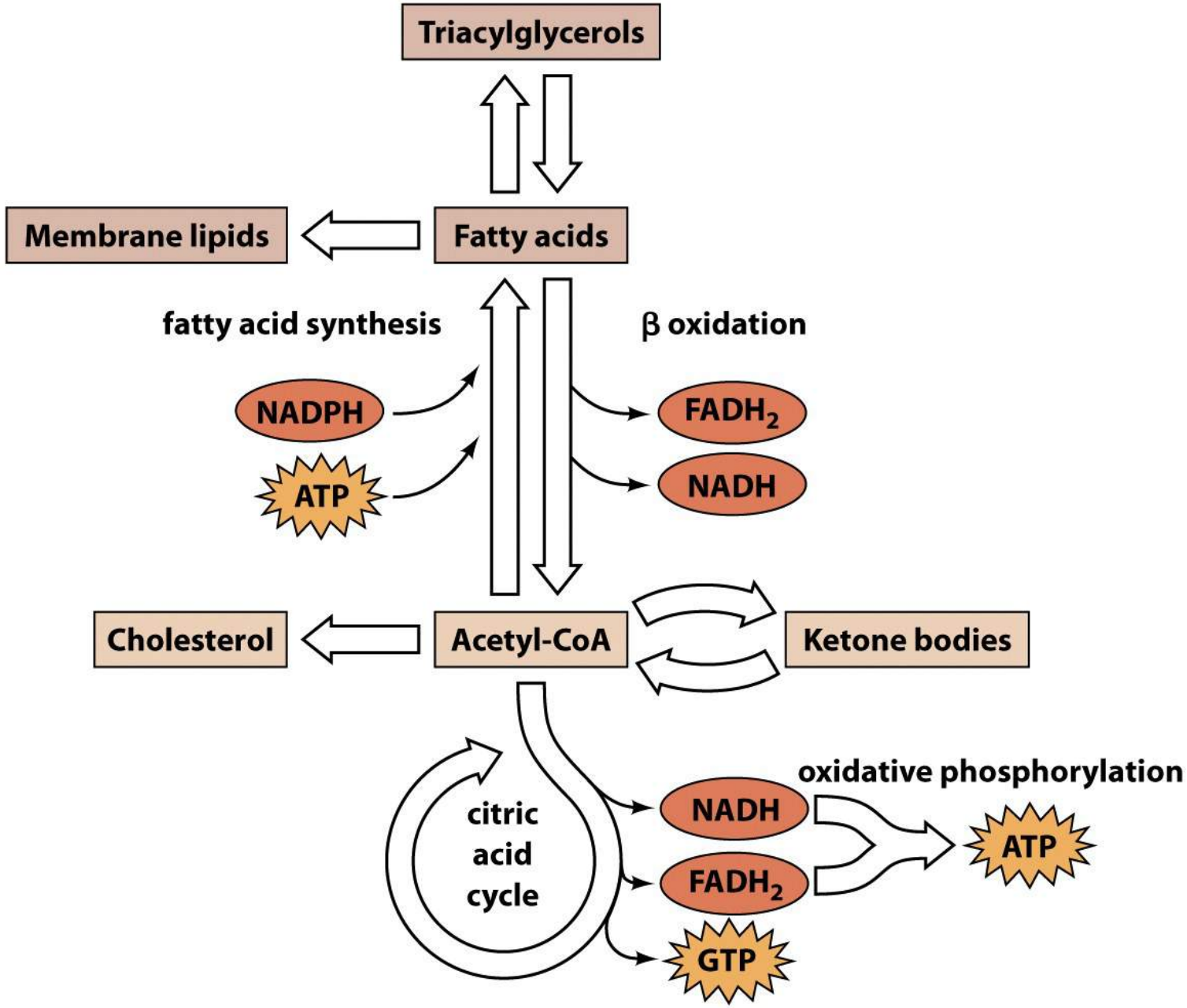
- Glycerol-3-phosphate acyltransferase in ER and mitochondria
- DHP acyltransferase in ER and peroxisomes

Glyceroneogenesis in liver
Partial gluconeogenesis from oxalacetate




phosphate
1-acylglycerol-3-phosphate acyltransferase
H—SCoA
Phospholipids
Phosphatidic acid
phosphatidic acid phosphatase
P_i
2-monoacylglycerol acyltransferase
H—SCoA
2-Monoacylglycerol
(from intestinal digestion)
1,2-Diacylglycerol (DAG)
diacylglycerol acyltransferase
H—SCoA
Triacylglycerol

Summary of lipid metabolism



5) Regulation of fatty acid metabolism

Differences in energy needs:

- between resting and activated muscle 100x
- feed <-> fasting

- Breakdown of glycogen and fatty acids concern the whole organism
- organs and tissues connected by blood stream, coordination

- Blood glucose levels sensed by pancreatic α cells, glucose down -> secrete glucagon -> glycogen degradation,
- β cells, glucose up -> insulin -> glucose uptake, FS synthesis

- These hormones also control fatty acid synthesis <-> β oxidation

Two levels of metabolic control

Short term regulation

regulates catalytic activities of key enzymes in minutes or less:

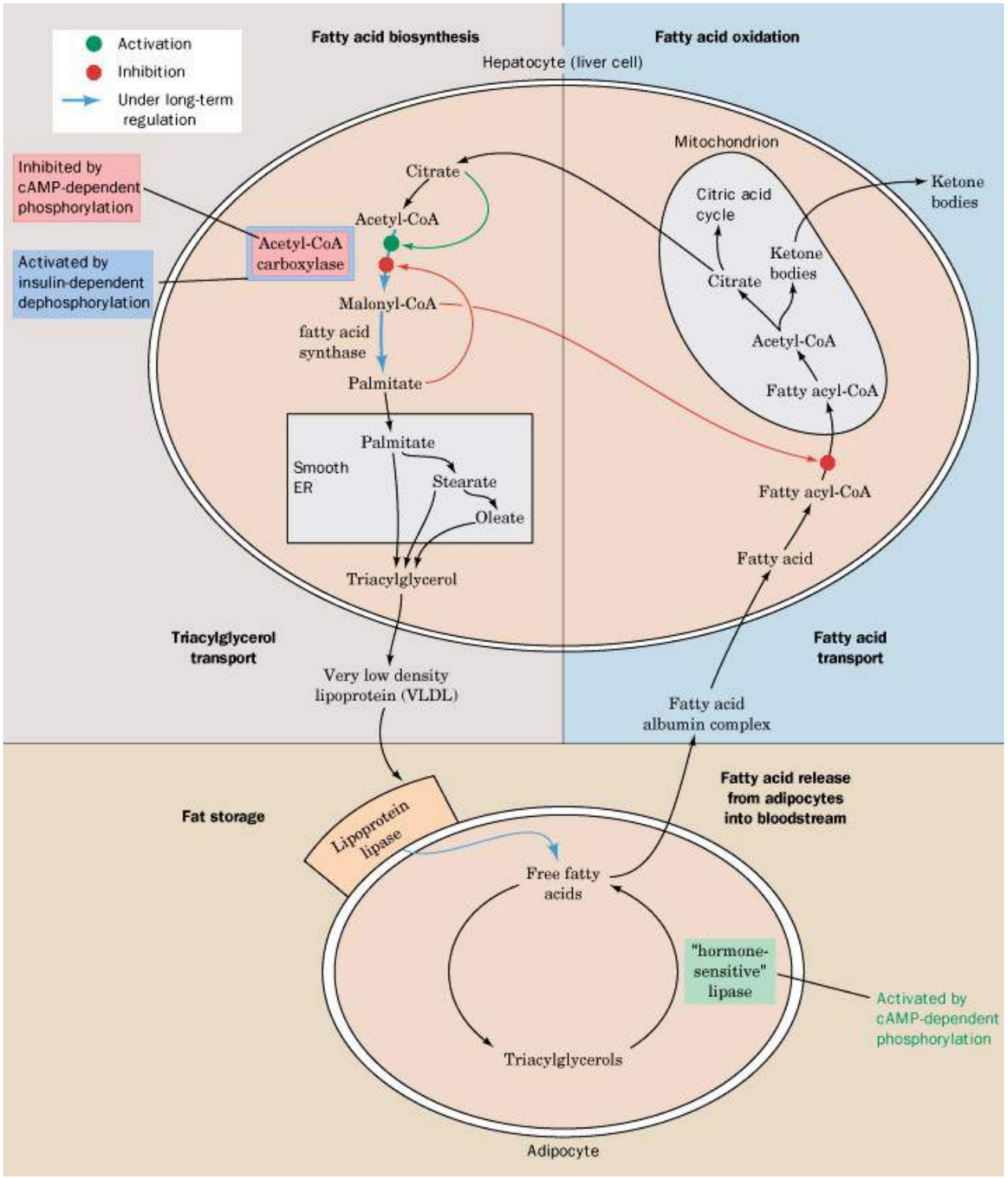
- substrate availability
- allosteric interactions
- Covalent modification

-> ACC (activated by citrate, inhibited by palmitoyl-CoA, inactivated by phosphorylation)

Long term regulation

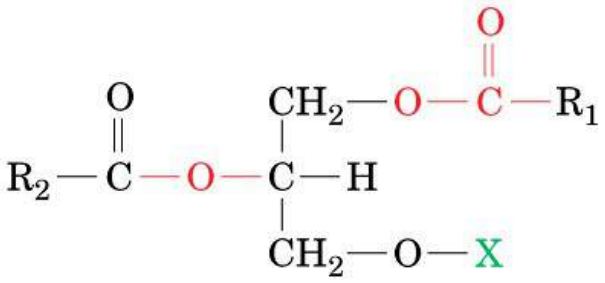
amount of enzyme present, within hours or days

-> ACC

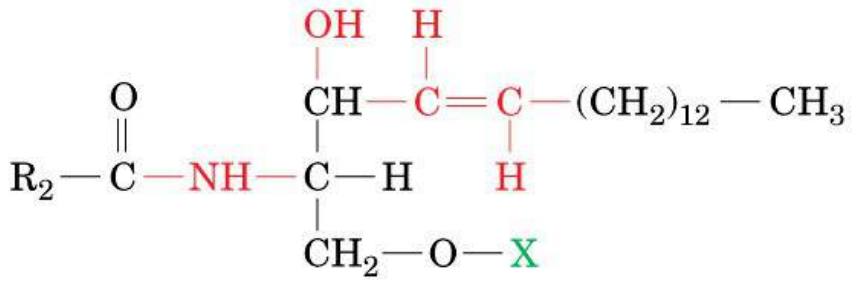

Activation
Inhibition
Under long-term regulation
Fatty acid biosynthesis
Fatty acid oxidation
Hepatocyte (liver cell)
Mitochondrion
Inhibited by cAMP-dependent phosphorylation
Activated by insulin-dependent dephosphorylation
Citrate
Acetyl-CoA
Acetyl-CoA carboxylase
Malonyl-CoA
fatty acid synthase
Palmitate
Palmitate
Smooth ER
Stearate
Oleate
Triacylglycerol
Citric acid cycle
Ketone bodies
Citrate
Ketone bodies
Acetyl-CoA
Fatty acyl-CoA
Fatty acyl-CoA
Fatty acid
Triacylglycerol transport
Fatty acid transport
Very low density lipoprotein (VLDL)
Fatty acid albumin complex
Fat storage
Fatty acid release from adipocytes into bloodstream
Lipoprotein lipase
Free fatty acids
"hormone-sensitive" lipase
Activated by cAMP-dependent phosphorylation
Triacylglycerols
Adipocyte

6) Phospholipid and glycerolipid metabolism:

The glycerolipids and sphingolipids



Glycerolipid



Sphingolipid

X = H — **1,2-Diacylglycerol** — ***N*-Acylsphingosine (ceramide)**

X = Carbohydrate — **Glyceroglycolipid** — **Sphingoglycolipid (glycosphingolipid)**

X = Phosphate ester — **Glycerophospholipid** — **Sphingophospholipid**

Membrane lipids

Amphipathic: hydrophobic tail / hydrophilic head

- glycerol, 1,2-diacyl-sn-glycerol
- N-acylsphingosine (ceramide)
- Head:
  - phosphate ester
  - carbohydrate

- **2 categories of phospholipids:**
  Glycerophospholipids, sphingophospholipids

- **2 categories of glycolipids**
  Glyceroglycolipids, sphingoglycolipids/glycosphingolipids

A) Glycerophospholipids are built from intermediates of Triacylglycerol biosynthesis

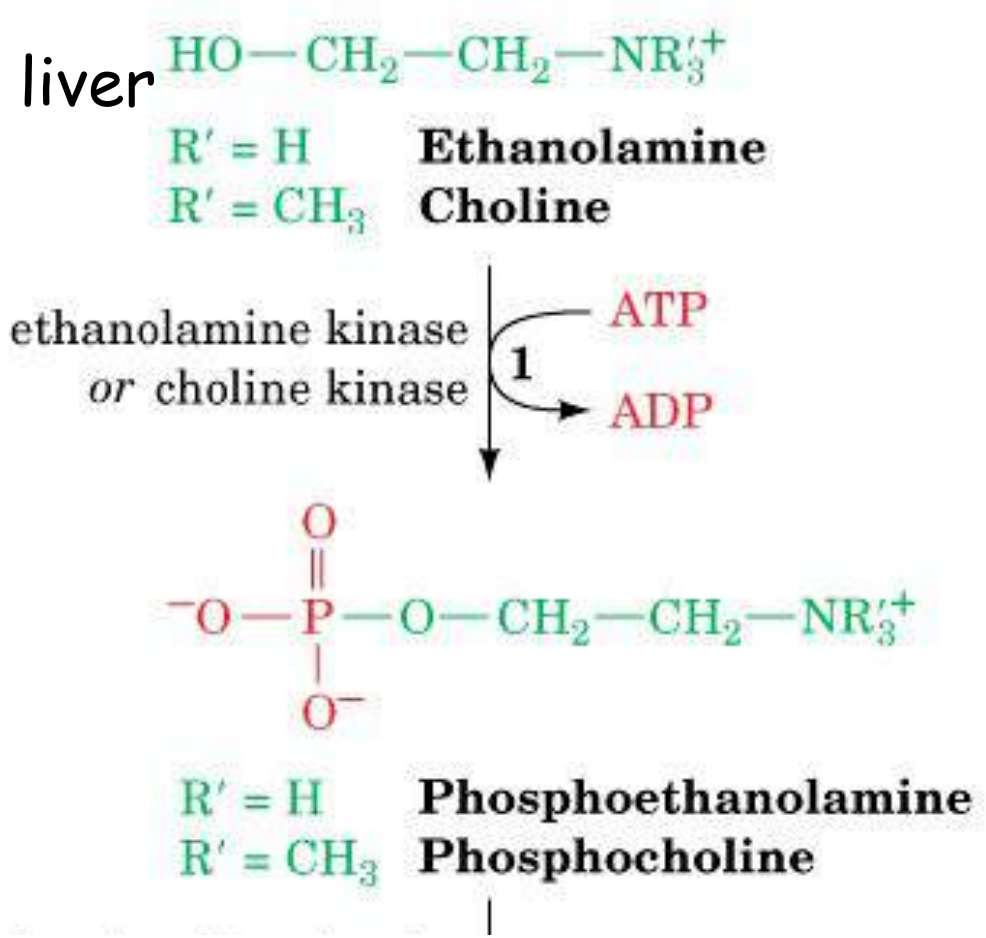
- sn-1: prevalence saturated FA
- sn-2: prevalence unsaturated FA

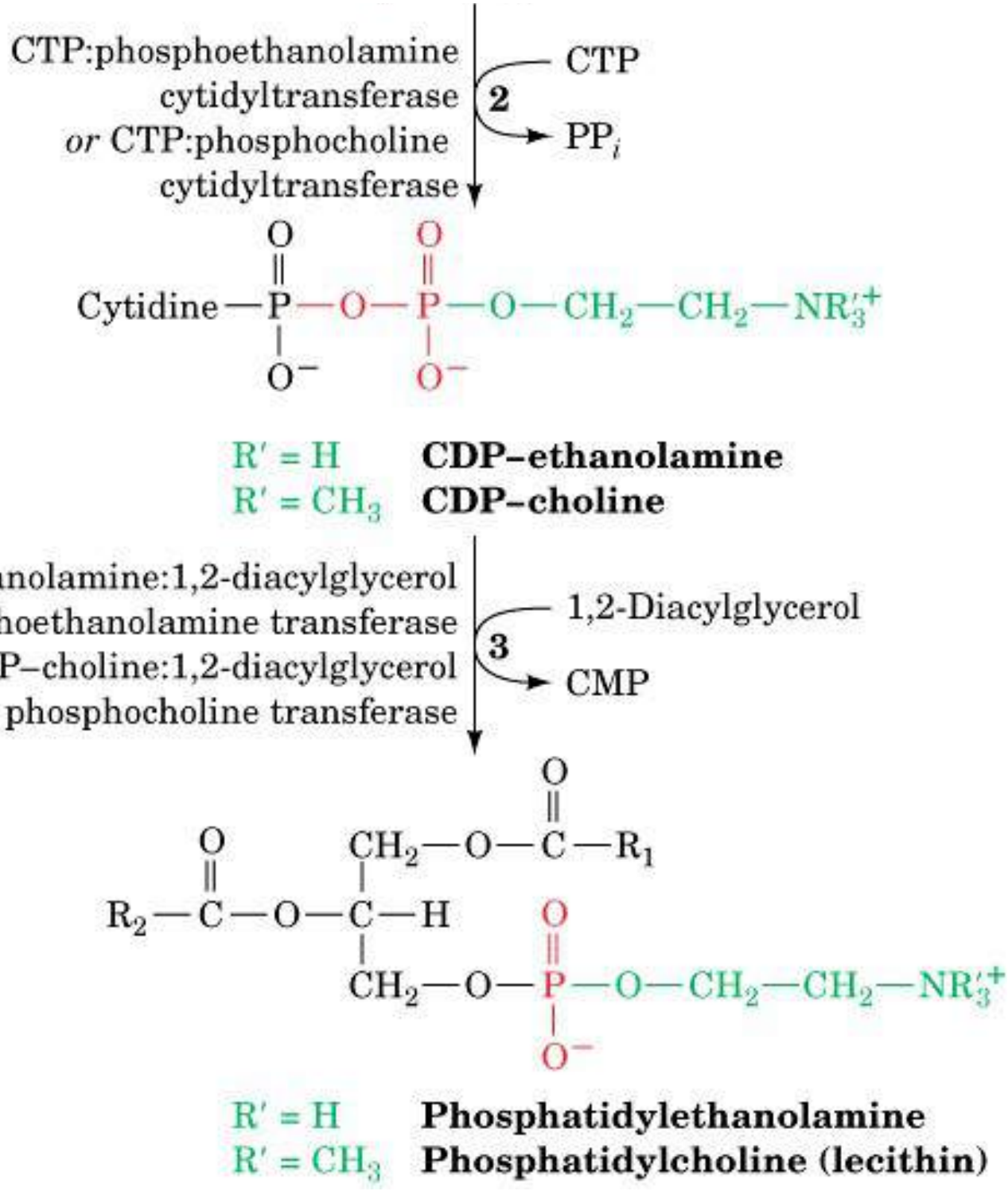
- Biosynthesis of diacylglycerophospholipids
  - from DAG and PA as TAG synthesis

- Head group addition:
  - **PC/PE**
    - P-activated Etn or Cho
    - -> CDP-activated Etn or Chol
    - -> transfer on DAG
  - **PS**, head-group exchange on PE with Serine
  - **PI/PG**, CDP-DAG

The biosynthesis of phosphatidylethanolamine and phosphatidylcholine

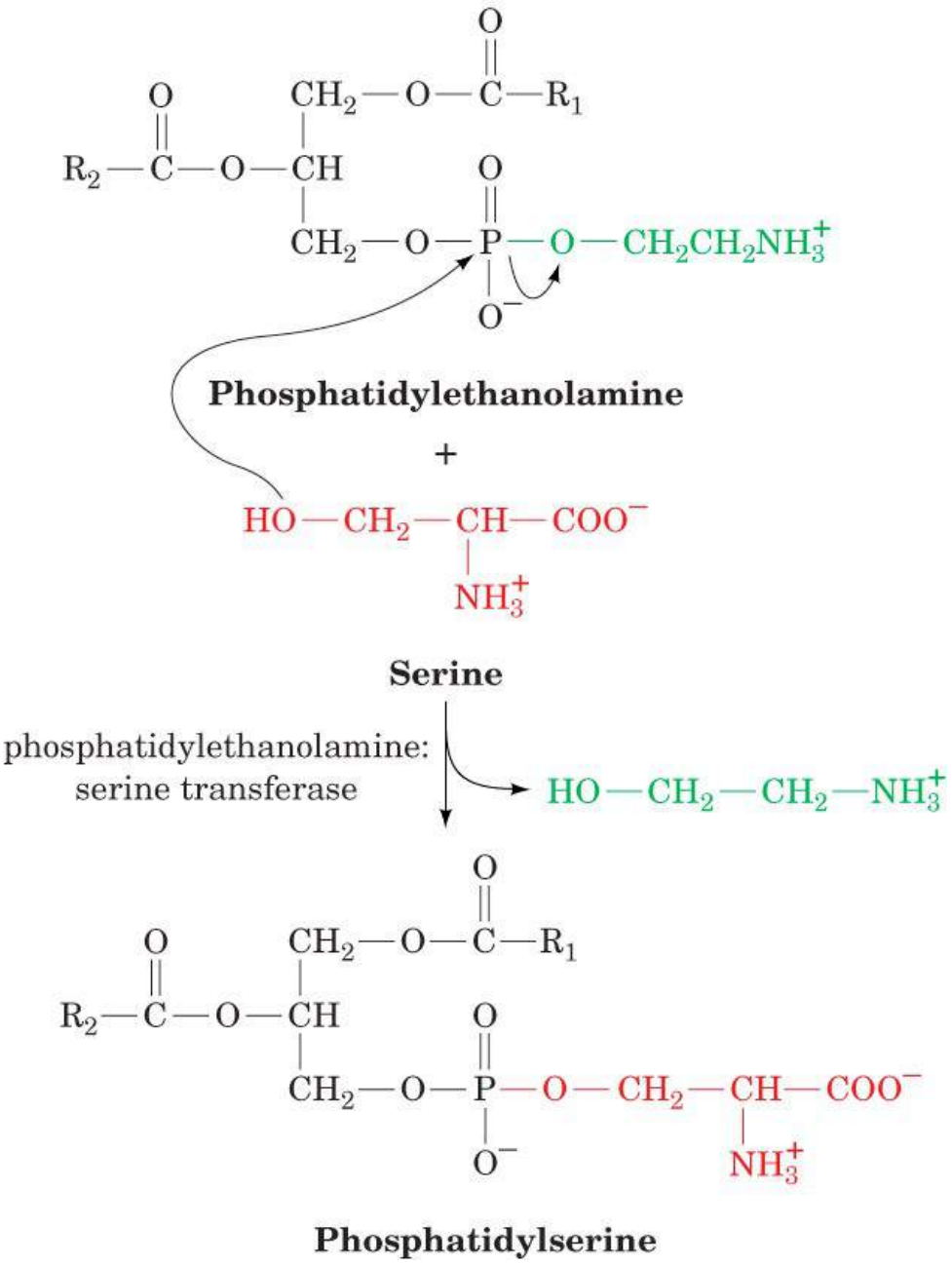
- DAG and CDP-etn or CDP-chol
- methylation pathway in the liver
  PE -> PC, SAM-dependent



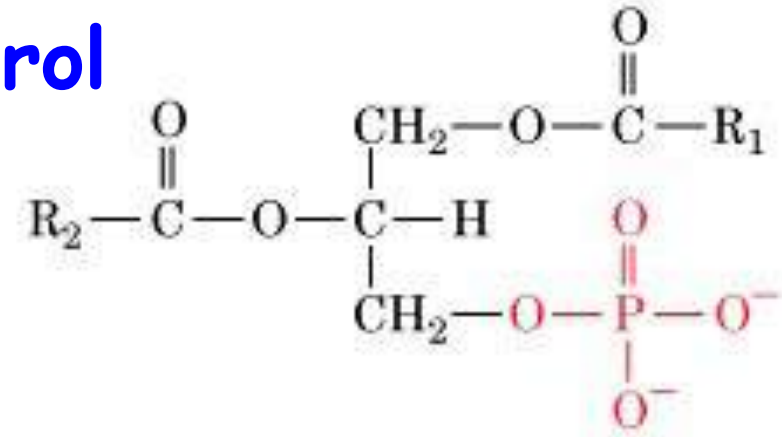

CTP:phosphoethanolamine
cytidyltransferase
or CTP:phosphocholine
cytidyltransferase
2
CTP
PPi
Cytidine
R′ = H
CDP–ethanolamine
R′ = CH3
CDP–choline
CDP–ethanolamine:1,2-diacylglycerol
phosphoethanolamine transferase
or CDP–choline:1,2-diacylglycerol
phosphocholine transferase
3
1,2-Diacylglycerol
CMP
R′ = H
Phosphatidylethanolamine
R′ = CH3
Phosphatidylcholine (lecithin)

Phosphatidylserine synthesis

Head group exchange
on PE with Serine

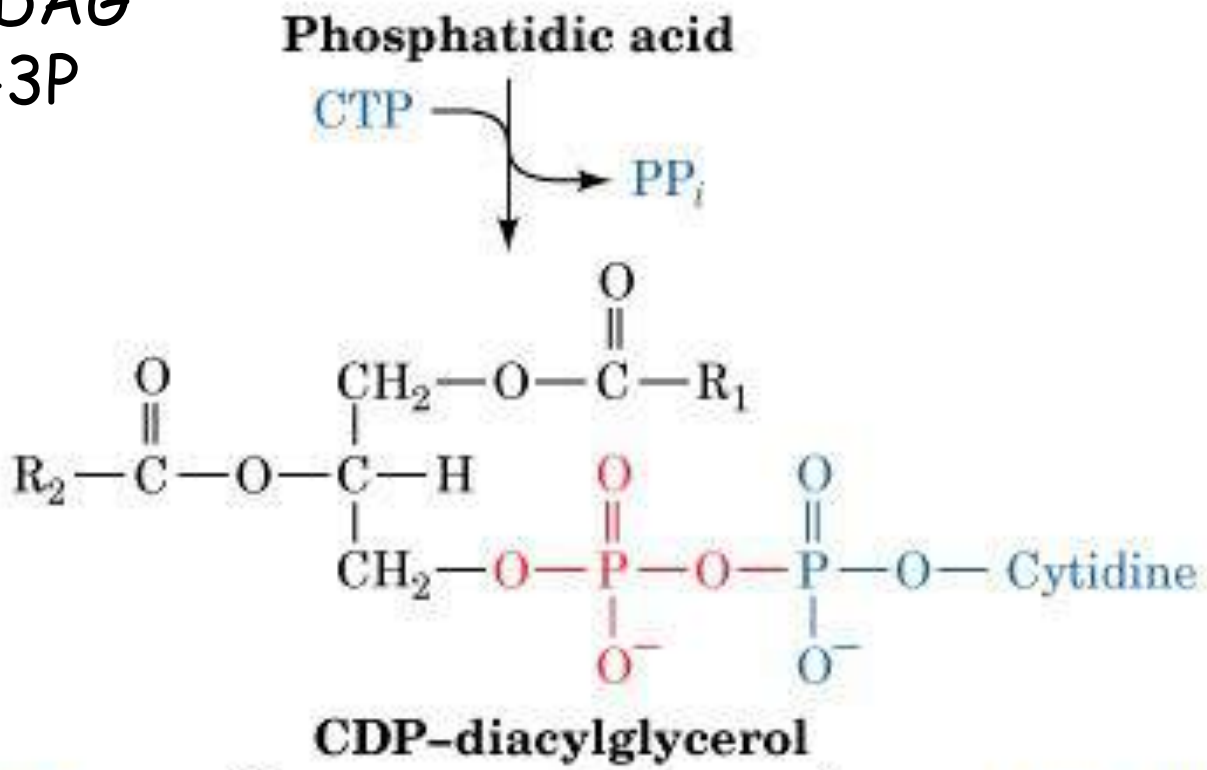


The biosynthesis of phosphatidylinositol and phosphatidylglycerol

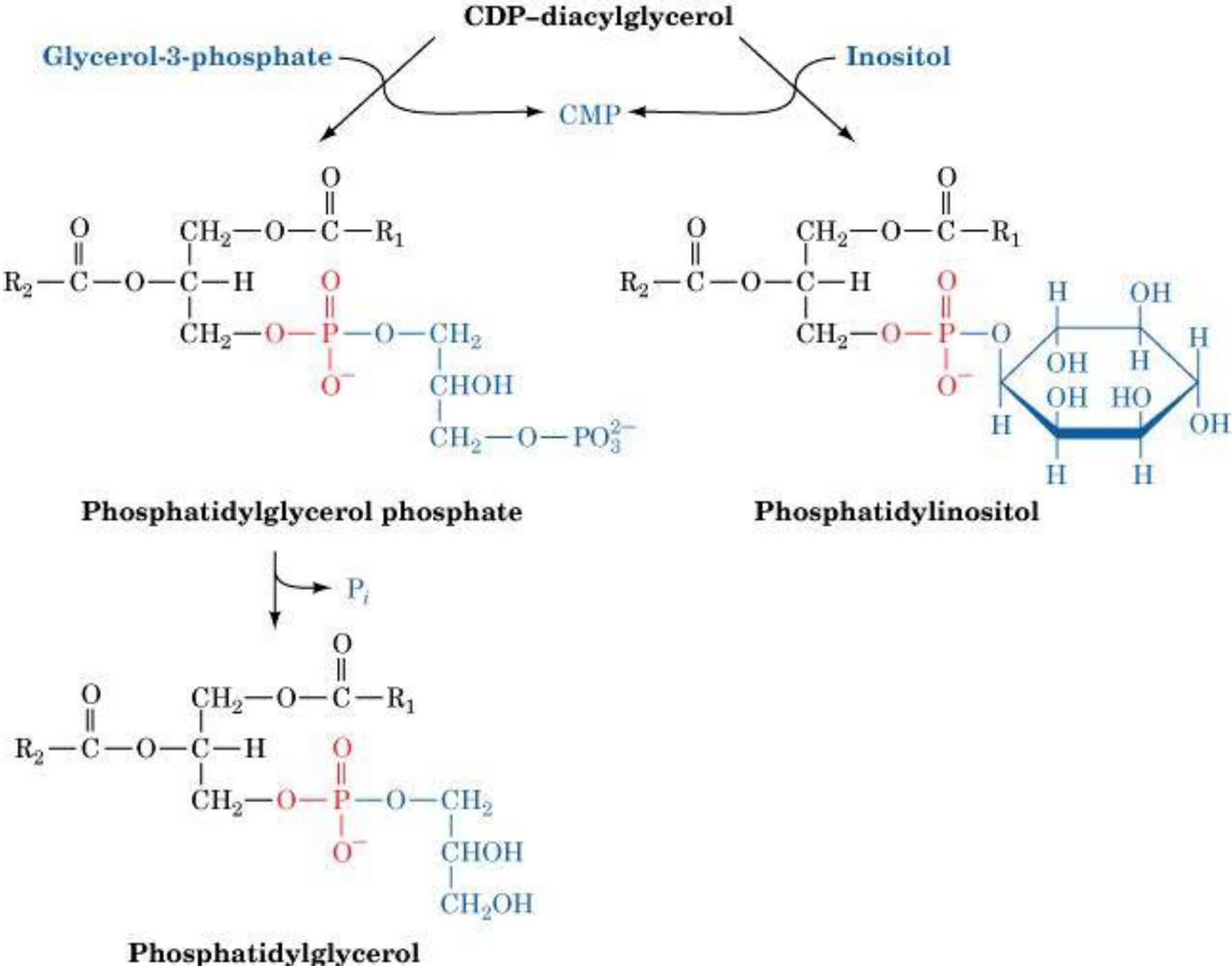


Phosphatidic acid

CDP-DAG activated DAG
+ inositol or glycerol-3P
= PI or PG

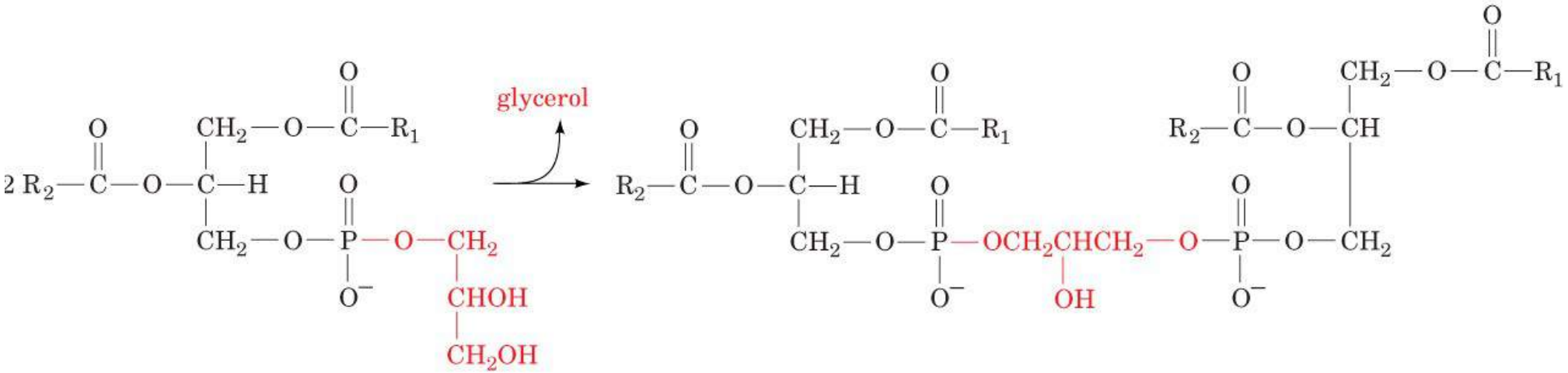


CDP-diacylglycerol


CDP–diacylglycerol
Glycerol-3-phosphate
Inositol
CMP
Phosphatidylglycerol phosphate
Phosphatidylinositol
P_i
Phosphatidylglycerol

The formation of cardiolipin

Mitochondrial phospholipid
2x PG = CL + Glycerol



Phosphatidylglycerol **Cardiolipin**

FA Remodeling

Tissue and cell-type specific introduction of defined FA into lipids

Examples:

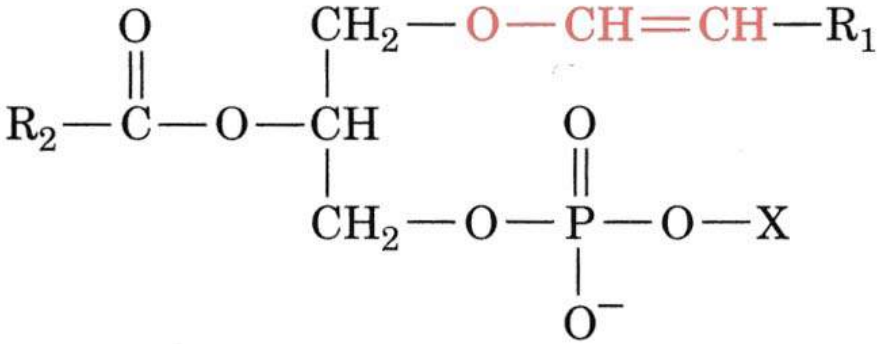
- 80% of brain PI contains C18:0 in sn-1 and C20:4 in sn-2
- 40% of lung PC has C16:0 in both positions, surfactant

Plasmalogens

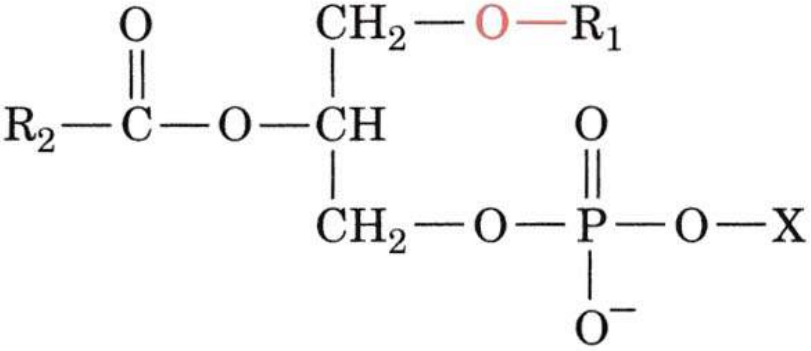
Around 20% of mammalian PLs are plasmalogens

- Nervous tissue
- Mainly PEs

1. Plasmalogens: vinyl ether linkage in C1
2. Alkylacylglycerophospholipids: ether linkage



A plasmalogen



An alkylacyl-glycerophospholipid

B) Sphingolipids

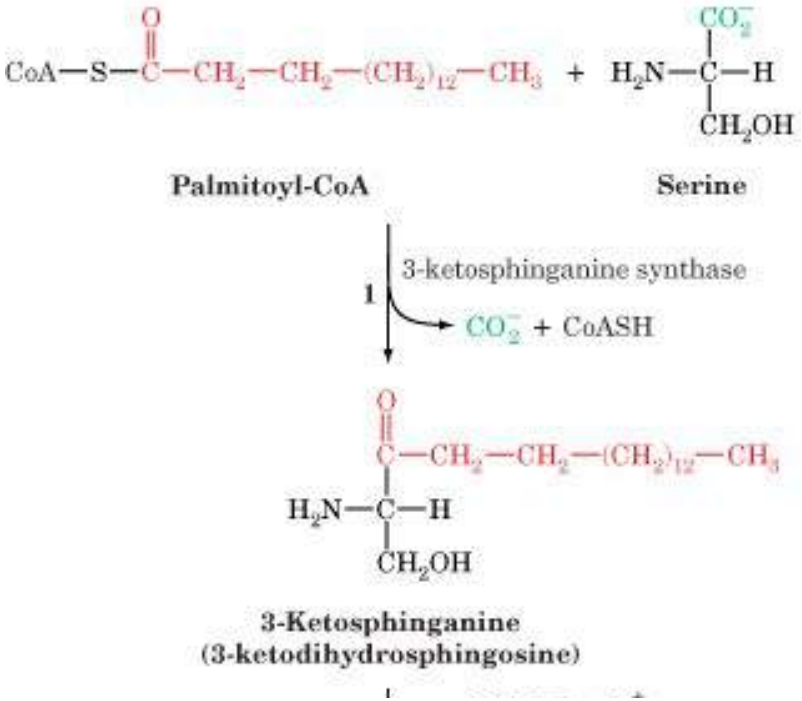
1. Cover the external surface of the plasma membrane, biosynthesis in ER/Golgi lumen

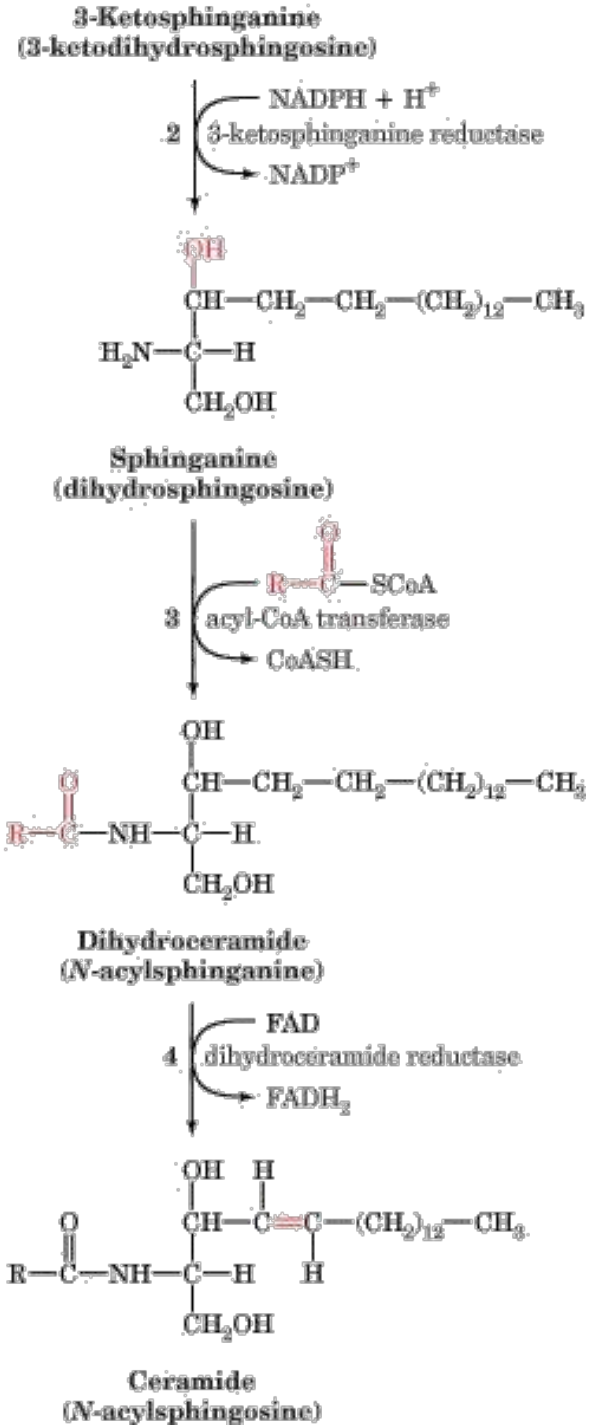
2. **Sphingomyelin** is major phosphosphingolipid, phosphocholine head group, not from CDP-choline but from PC

3. **Sphingoglycolipids**
    1. Cerebrosides, ceramide monosaccharides
    2. Sulfatides, ceramide monosaccharides sulfates
    3. Globosides, neutral ceramide oligosaccharides
    4. Gangliosides, acidic, sialic acid-containing ceramide oligosaccharides

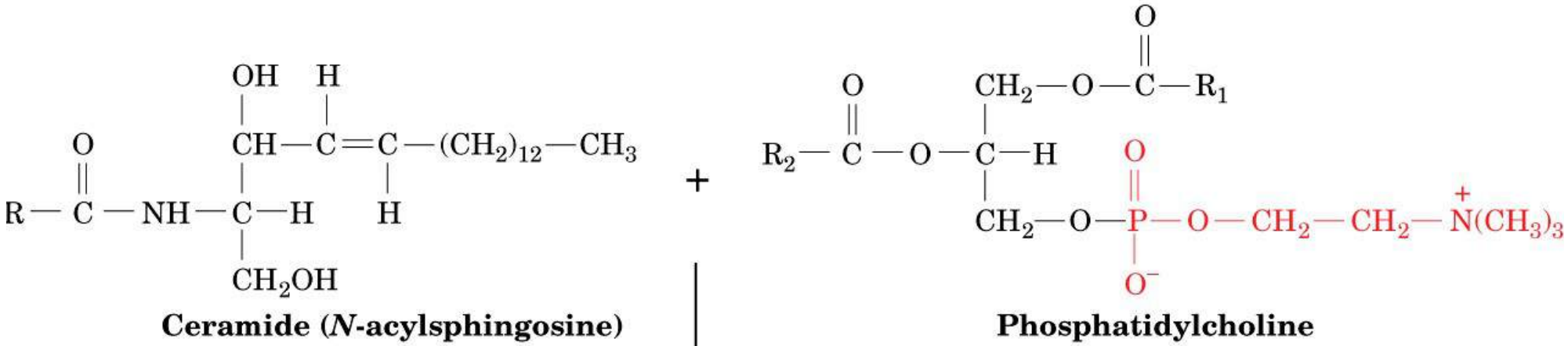
The biosynthesis of ceramide

1) Serine + palmitoyl-CoA = KS
2) Reduction of KS to sphinganine (LCB)
3) LCB + Acyl-CoA = ceramide (DHC)
4) Oxidation of DHC to Cer

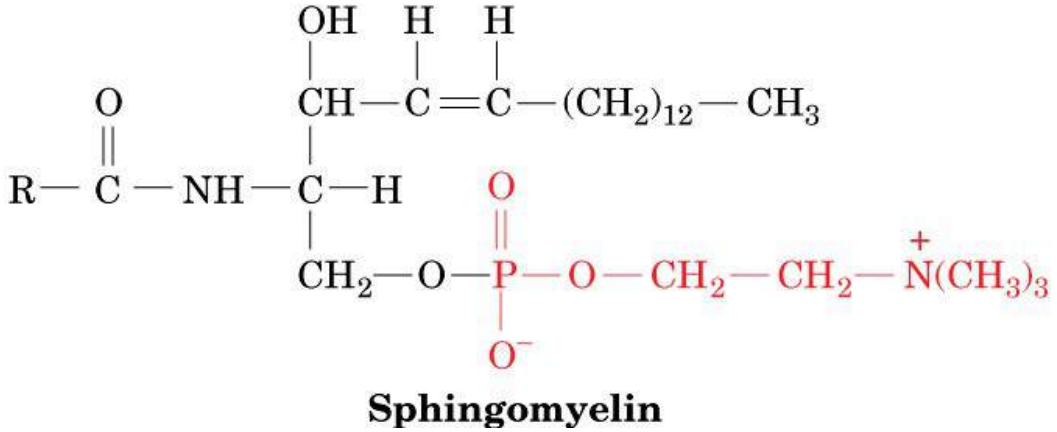




The synthesis of sphingomyelin from *N*-acylsphingosine and phosphatidylcholine



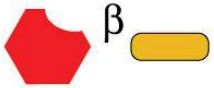
- PC is head-group donor to convert Cer to SM



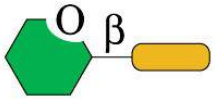
Principal classes of sphingoglycolipids

Cerebrosides

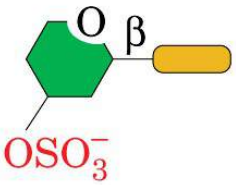
Glucocerebroside



Galactocerebroside



Sulfatide



= glucose

= *N*-acetylgalactosamine

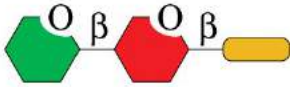
= galactose

= ceramide

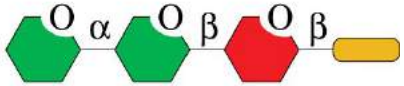
NANA = *N*-acetylneuraminic acid (sialic acid)

Globosides

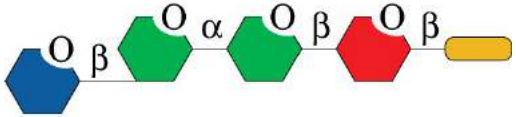
Lactosyl ceramide



Trihexosyl ceramide

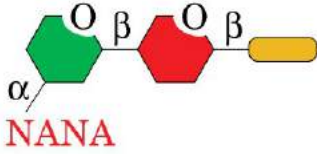


Globoside

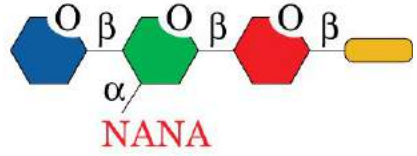


Gangliosides

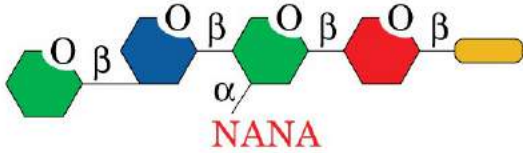
G_{M3}



G_{M2}



G_{M1}



Sphingoglycolipid degradation and lipid storage disease

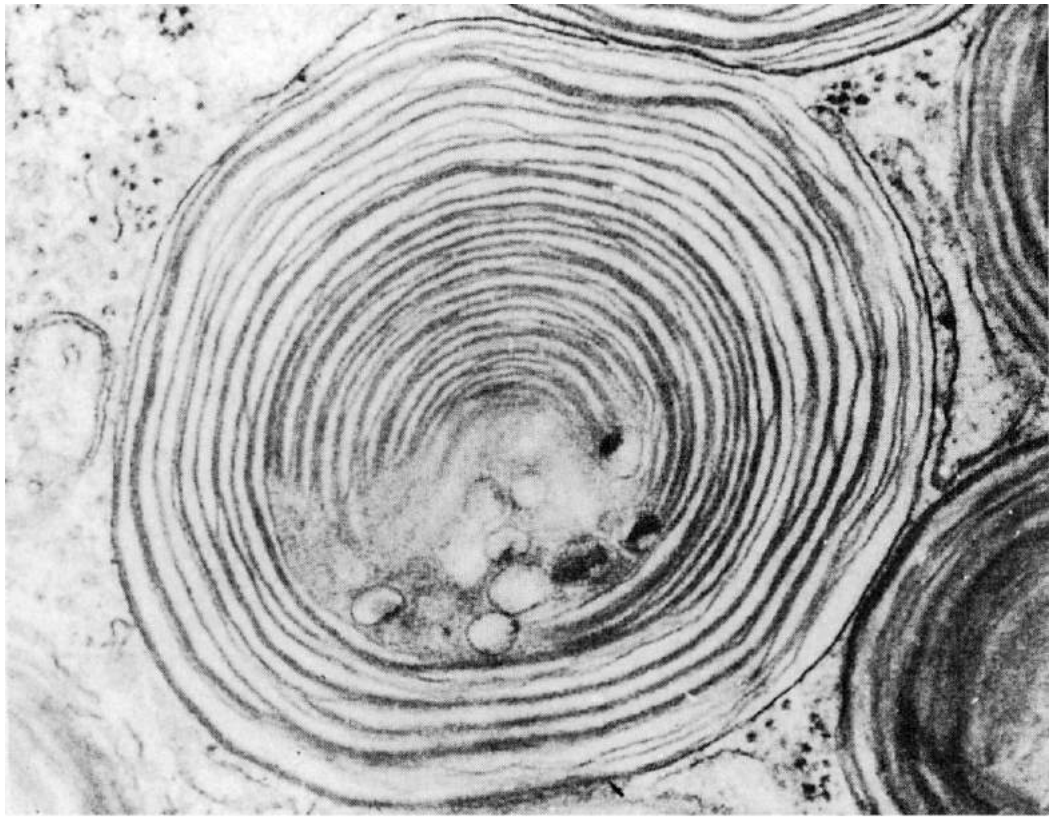
- Degraded in lysosomes by series of enzyme-mediates hydrolytic steps
- Catalyzed at lipid-water interface by soluble enzymes
- Aid of SAPS, sphingolipid activator proteins
- GM_2-activator-GM_2 complex binds hexosaminidase *A* that hydrolyzes N-acetylgalactosamine from GM_2

- Enzymatic defect leads to sphingolipid storage disease, e.g., **Tay-Sachs disease**, deficiency in hexosaminidase *A*, neuronal accumulation of GM_2 as shell like inclusions, In utero diagnosis possible with fluorescent substrate

- Substrate deprivation therapy, inhibition of glucosyl-ceramide synthase

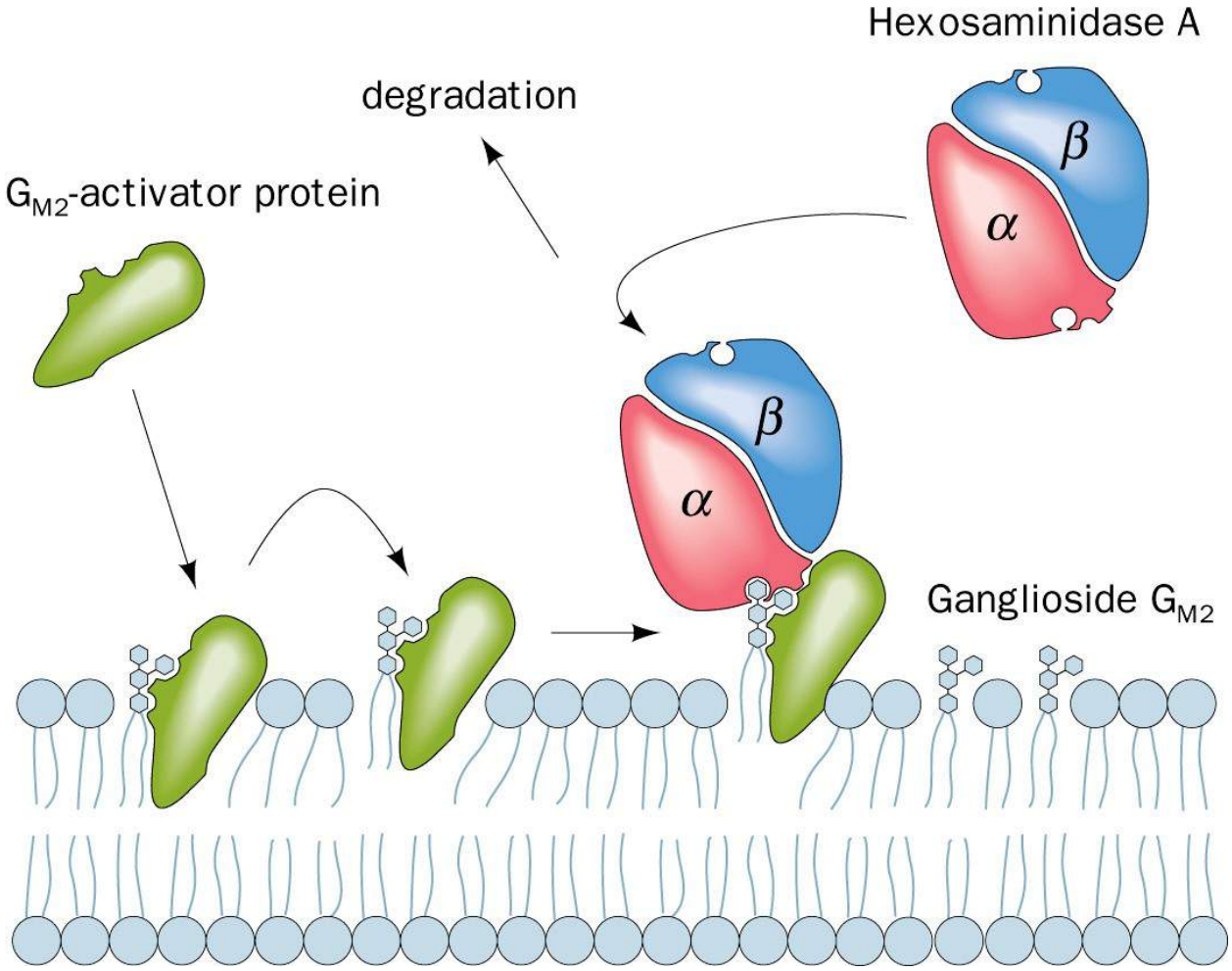
Cytoplasmic membranous body in a neuron affected by Tay–Sachs disease

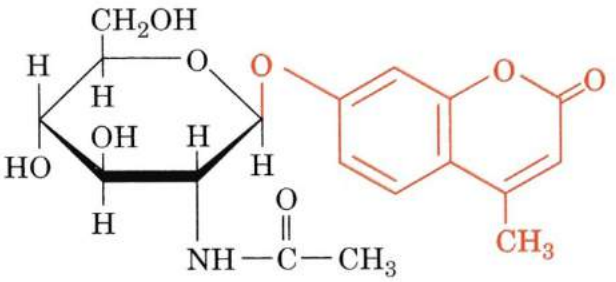
Most common SL storage disease
Hexosaminidase deficiency
Cytoplasmic membrane bodies in neurons



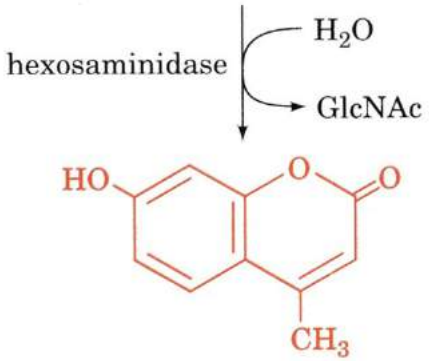
Courtesy of John S. O'Brien, University of California at San Diego Medical School

Model for G_{M2}-activator protein–stimulated hydrolysis of ganglioside G_{M2} by hexosaminidase



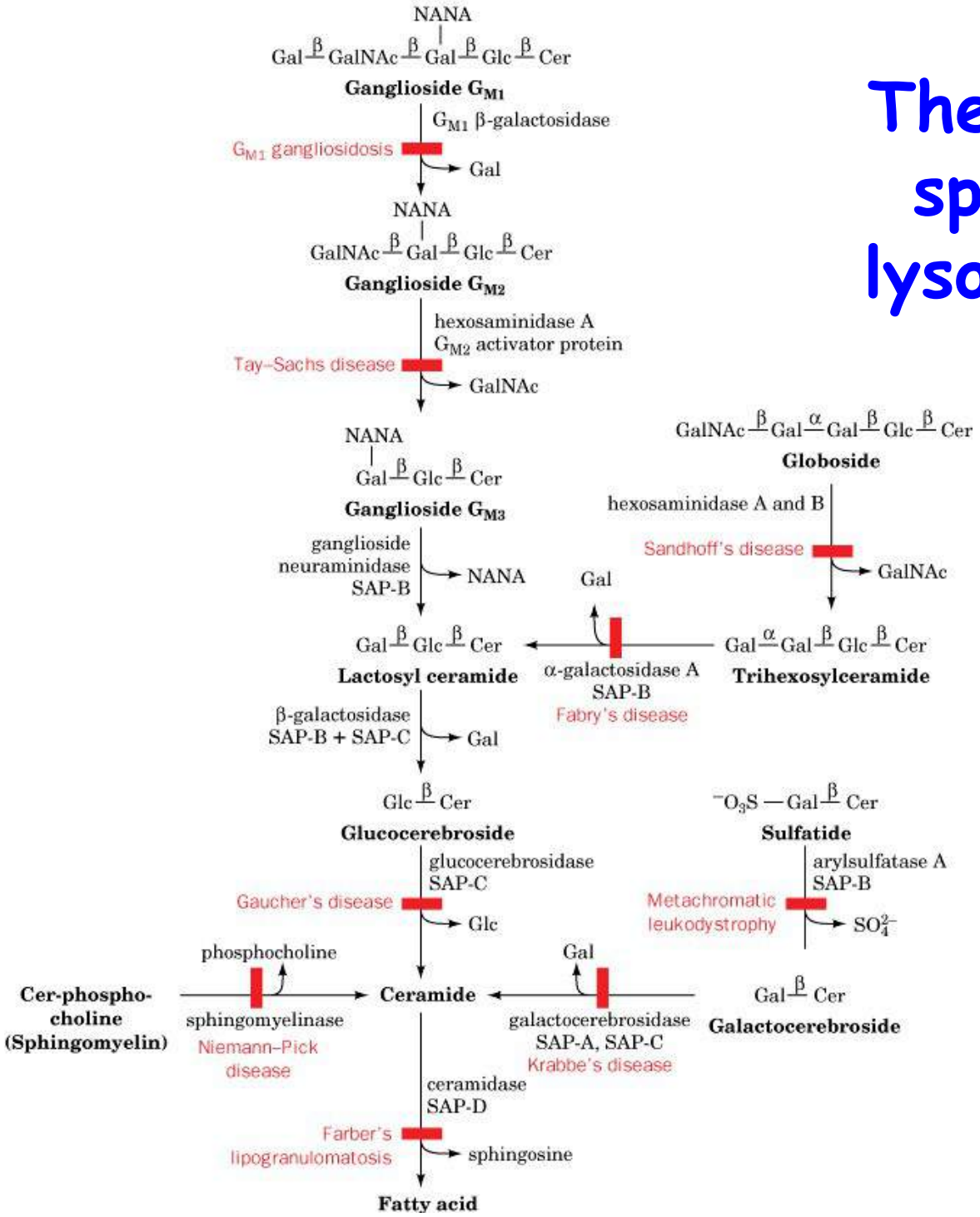


4-Methylumbelliferyl-β-D-*N*-acetylglucosamine



4-Methylumbelliferone

The breakdown of sphingolipids by lysosomal enzymes



Sphingolipid Storage Diseases

Disease	Enzyme Deficiency	Principal Storage Substance	Major Symptoms
G_{M1} Gangliosidosis	G_{M1} β-galactosidase	Ganglioside G_{M1}	Mental retardation, liver enlargement, skeletal involvement, death by age 2
Tay–Sachs disease	Hexosaminidase A	Ganglioside G_{M2}	Mental retardation, blindness, death by age 3
Fabry's disease	α-Galactosidase A	Trihexosylceramide	Skin rash, kidney failure, pain in lower extremities
Sandhoff's disease	Hexosaminidases A and B	Ganglioside G_{M2} and globoside	Similar to Tay–Sachs disease but more rapidly progressing
Gaucher's disease	Glucocerebrosidase	Glucocerebroside	Liver and spleen enlargement, erosion of long bones, mental retardation in infantile form only
Niemann–Pick disease	Sphingomyelinase	Sphingomyelin	Liver and spleen enlargement, mental retardation
Farber's lipogranulomatosis	Ceramidase	Ceramide	Painful and progressively deformed joints, skin nodules, death within a few years
Krabbe's disease	Galactocerebrosidase	Deacylated galactocerebroside	Loss of myelin, mental retardation, death by age 2
Metachromatic leukodistrophy (Sulfatide lipidosis)	Arylsulfatase A	Sulfatide	Mental retardation, death in first decade

C) C20 fatty acids are the precursors of Prostaglandins (PGs)

- 1930, Ulf von Euler: human semen extract stimulates uterus contraction and lower blood pressure
- Thought to originate in prostata -> name
- mid 50s, isolated from body fluids in ether extract (PGE)
- Made by all cells except RBC

Eicosanoid metabolism: Prostaglandins, prostacyclins, thromboxanes, leukotriens, and lipoxins

- Collectively: **eicosanoids**, C20 compounds
  - profound physiological effects at very low conc.
  - hormone-like but paracrine
  - bind to G-coupled receptors, affect cAMP
  - signal as hormones do
  - arachidonic acid C20:4

- What you inhibit by **aspirin** !!
  NSAIDs, nonsteroidal anti-inflammatory drugs

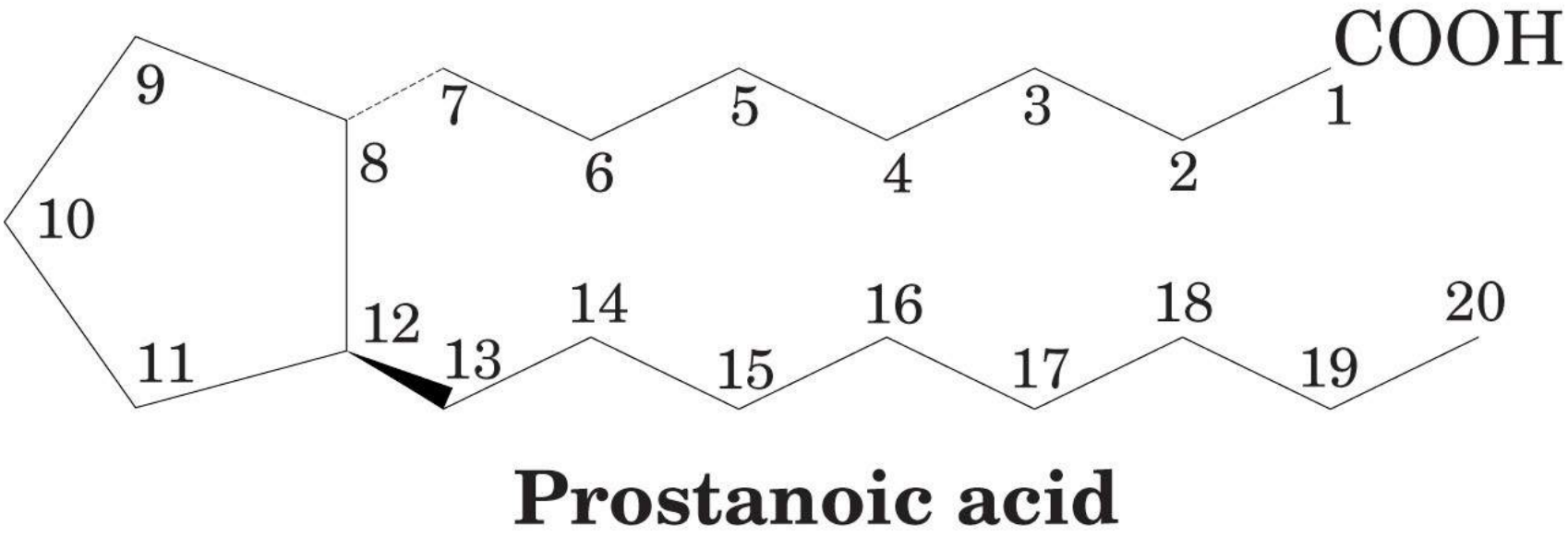
- Whose action you indirectly inhibit by **cortisol** !!

Eicosanoids

Mediate:

1) inflammation
2) production of pain and fever
3) regulate blood pressure
4) induction of blood clotting
5) reproductive functions
6) sleep/wake cycle
7) Egress of T lymphocytes

Prostaglandin structures. (*a*) The carbon skeleton of prostanoic acid, the prostaglandin parent compound

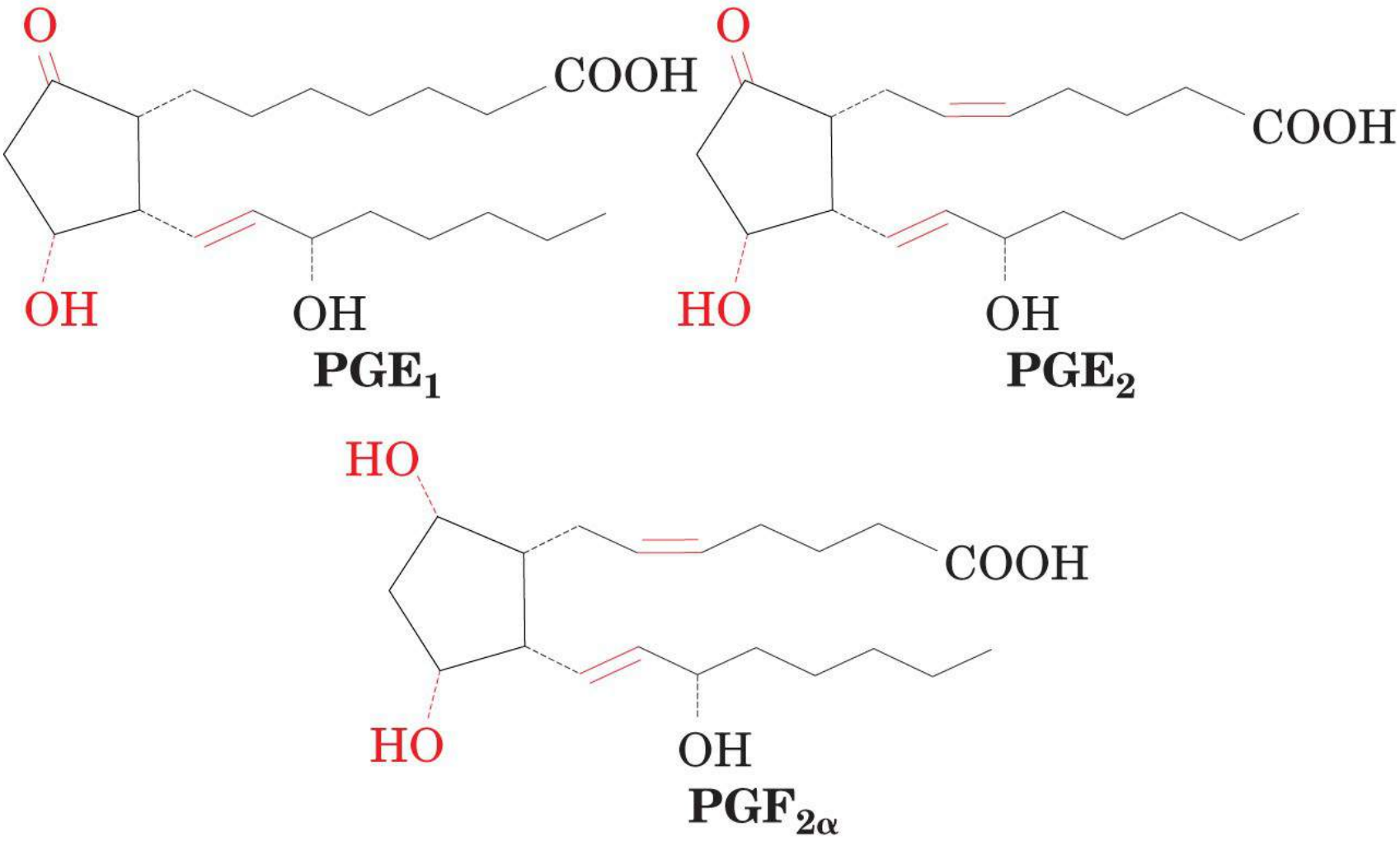


Prostanoic acid

Cyclopentane ring

Synthesized from arachidonic acid, C20:4, Δ5,8,11,14 (ω-6 FA)

Prostaglandin structures. (*c*) Structures of prostaglandins E_1, E_2, and $F_{2\alpha}$ (the first prostaglandins to be identified)



Arachidonic acid is the precursor to PGs

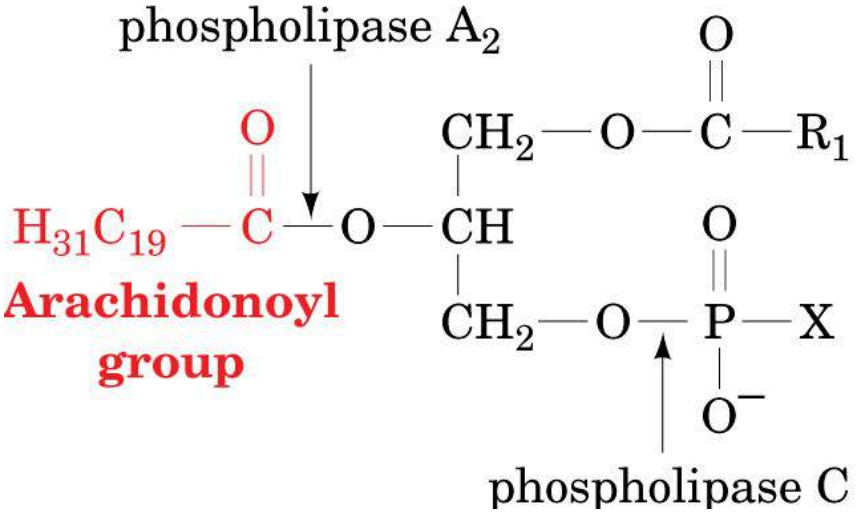
- Arachidonic acid: C20:4, n-6, Δ5,8,11,14

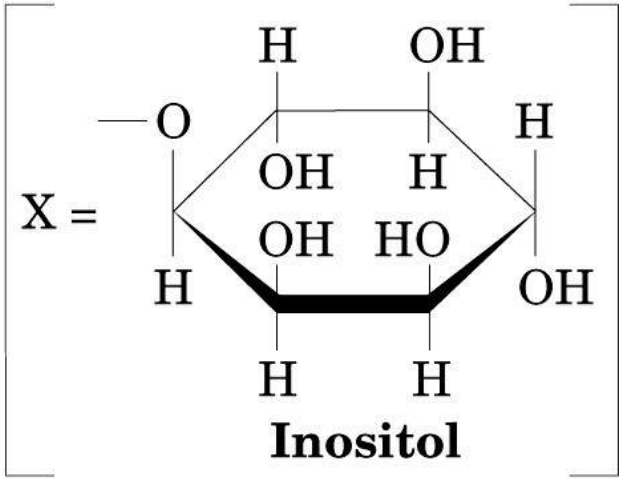
- AA is synthesized from the essential linoleic acid, C18:3, Δ6,9,12 by elongation and desaturation

- AA is phospholipid bound (sn2, PI) and released upon stimuli
  by: **1) phospholipase A2**
  2) phospholipase C -> DAG + P-Ins ->
  PA (DAG kinase) -> AA (PLA2)
  3) DAG hydrolysis by DAG lipase

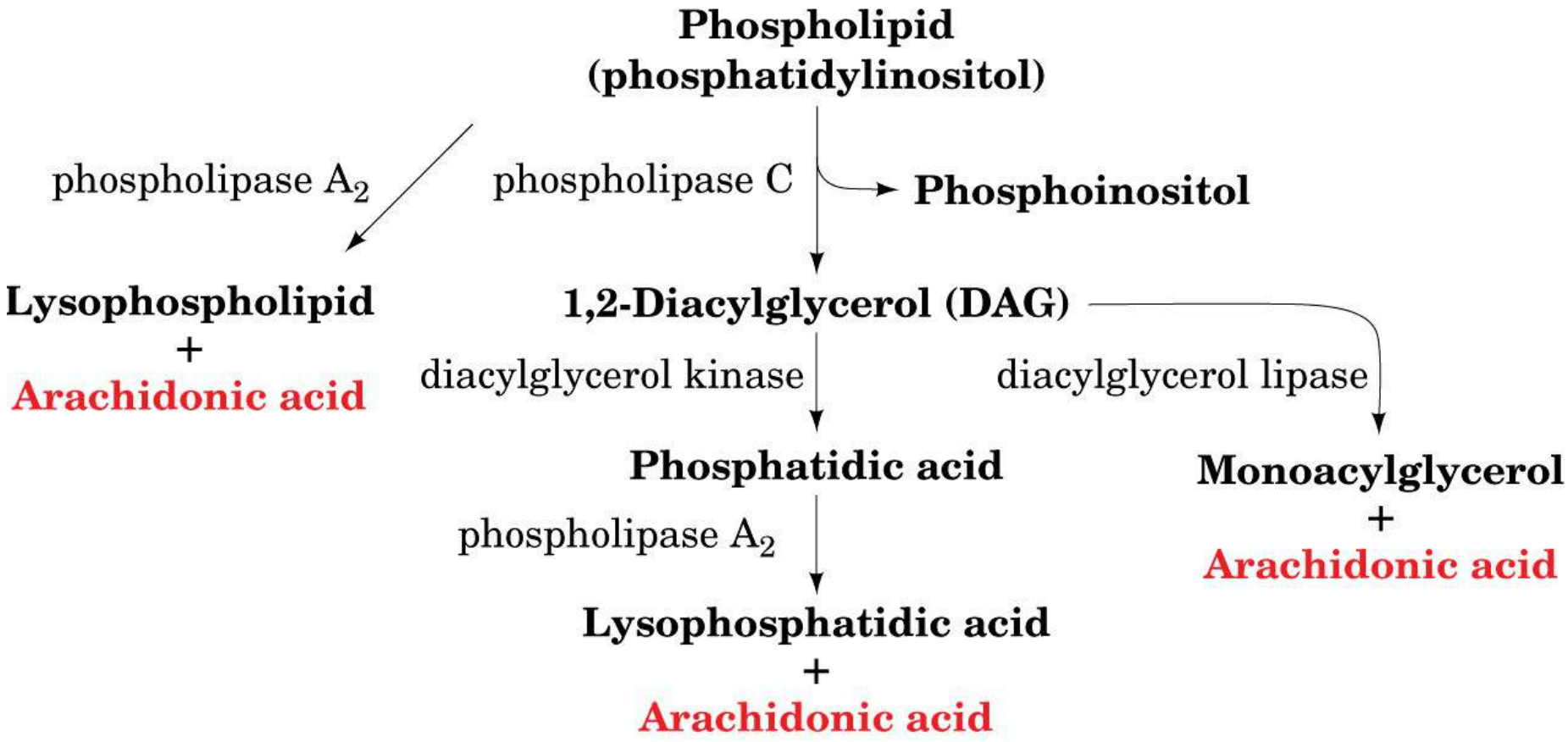
- **Corticosteroids indirectly inhibit PG signaling !!**
  anti-inflammatory

Release of arachidonic acid by phospholipid hydrolysis

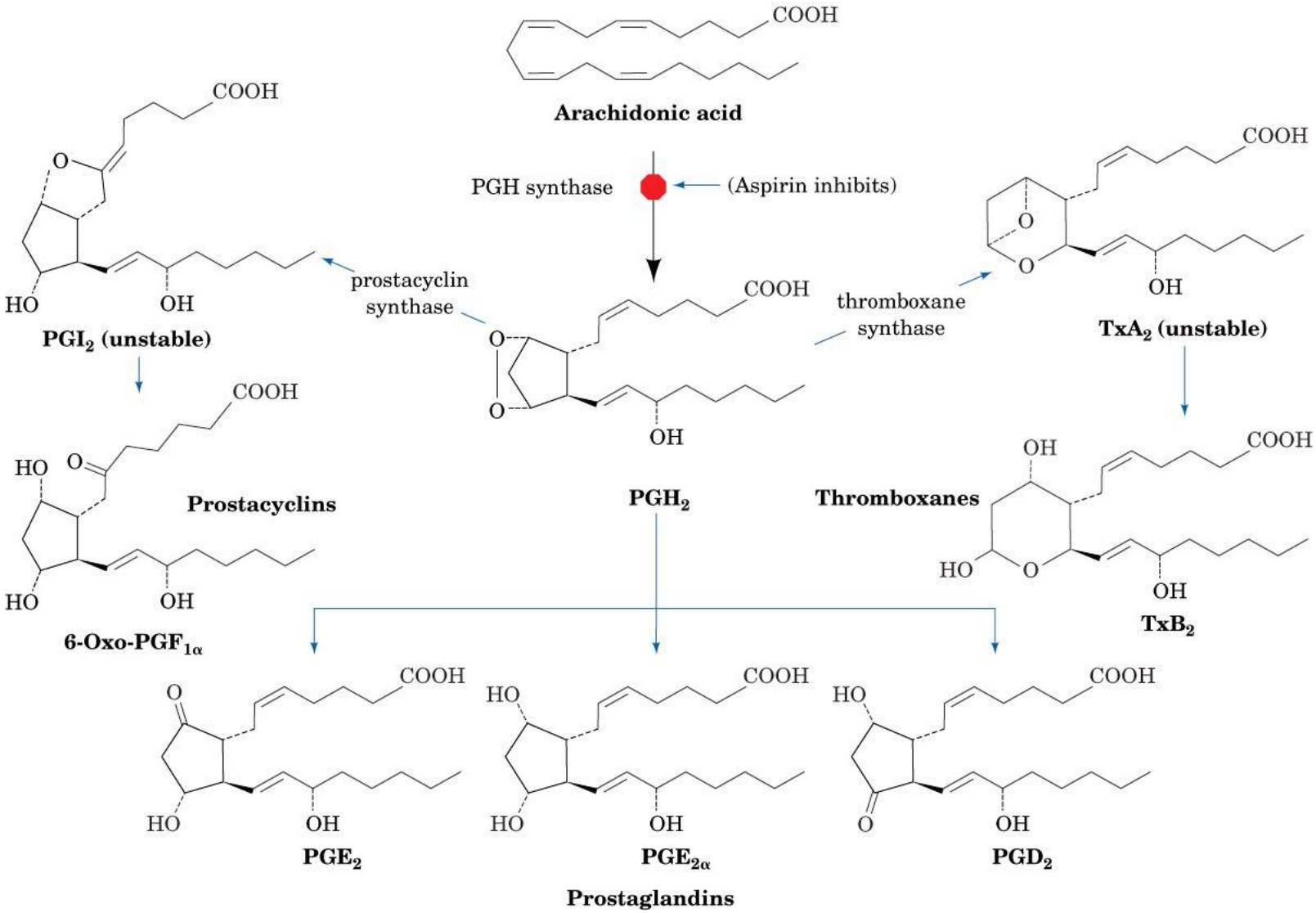




Pathways of arachidonic acid liberation from phospholipids

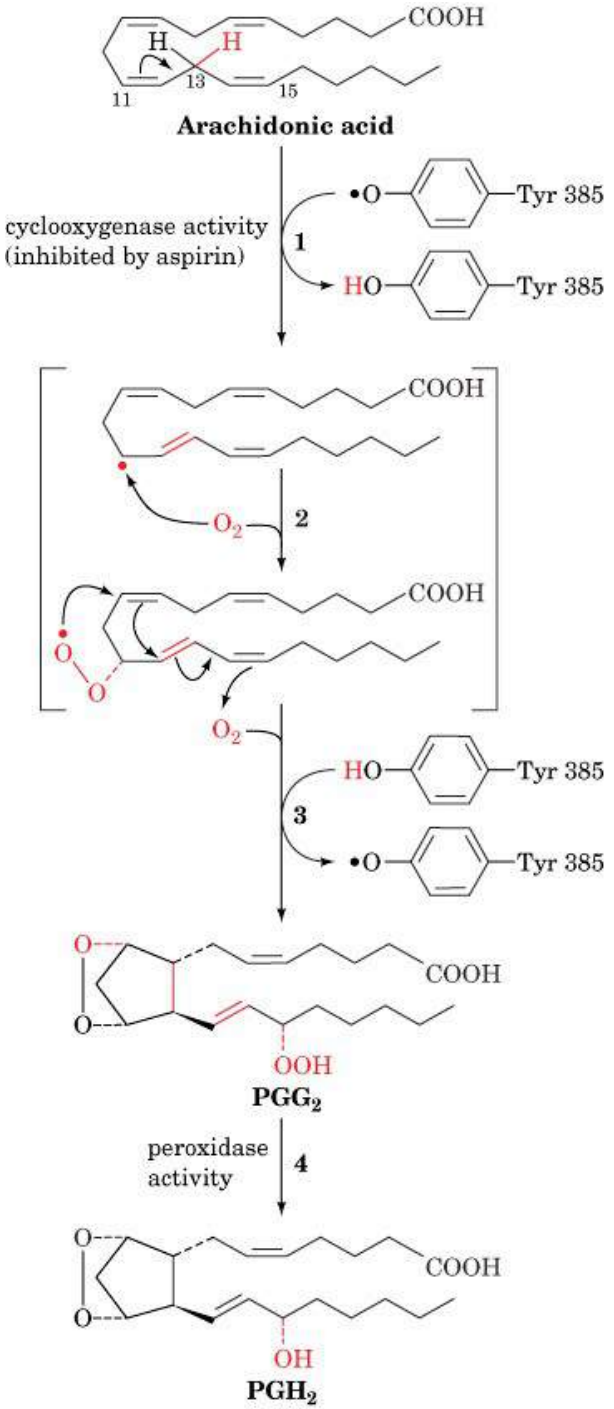


The cyclic pathway of arachidonic acid metabolism



The reactions catalyzed by PGH synthase (PGHS)

- **PGHS** catalyzes first step in the cyclic pathway
- cycloogynase (COX) + peroxidase activity
- heme activates Tyr radical
- Target of aspirin
- Monotopic membrane protein (see squalene-hopene cyclase)



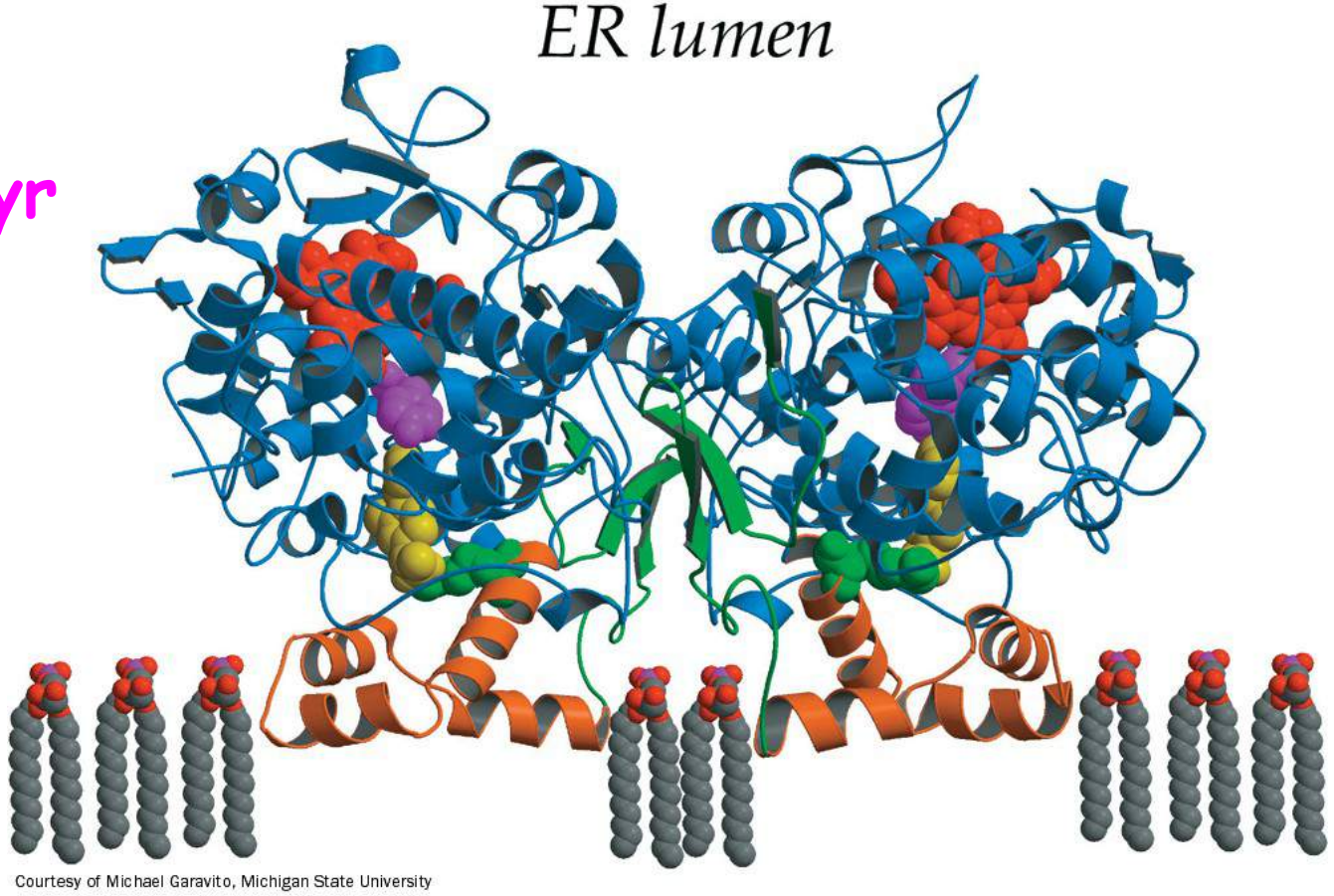
X-Ray structure of PGH synthase (PGHS) from sheep seminal vesicles in complex with the NSAID flurbiprofen

Homodimeric monotopic ER membrane protein

Heme

Fluriprofen

Active side Tyr

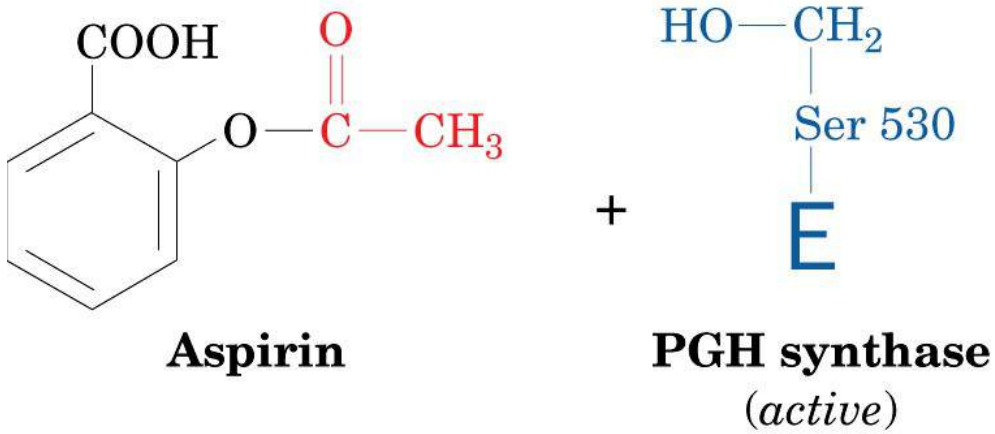


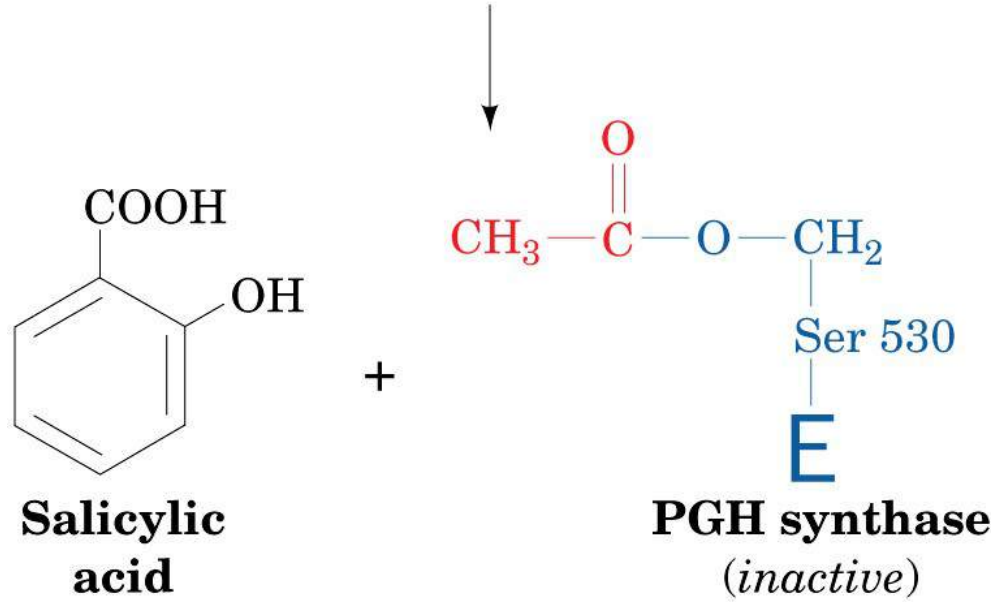
Courtesy of Michael Garavito, Michigan State University

ASPIRIN

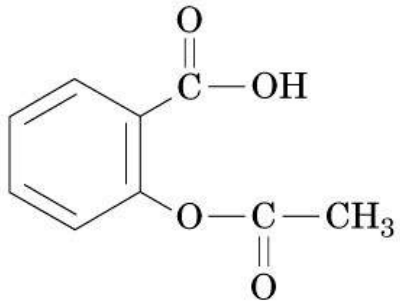
- Acetylsalicylic acid
- Inhibits cyclooxygenase activity of PGHS
- Acetylates Ser 530
- Flurbiprofen blocks channel
- Low dose of aspirin reduce heart-attack risk, inhibits platelet aggregation (enucleated cells, 10 days lifetime, cannot resynthesize enzyme

Inactivation of PGH synthase by aspirin

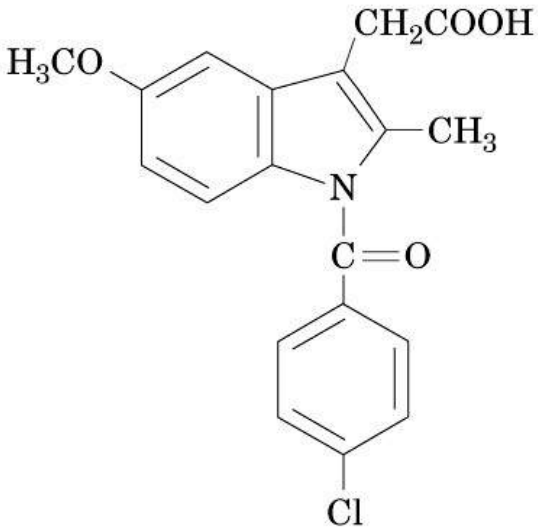




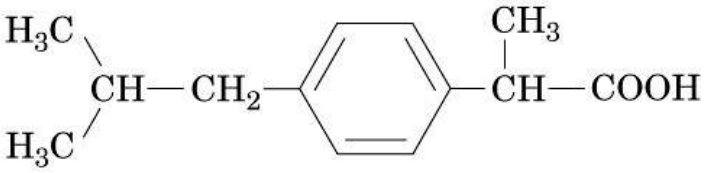
Some nonsteroidal anti-inflammatory drugs (NSAIDs)



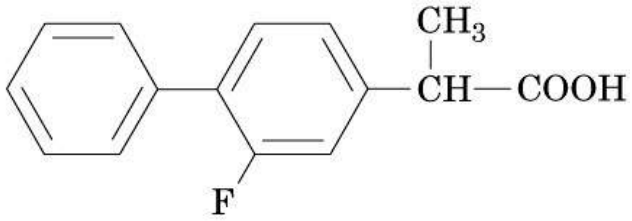
Aspirin
(acetylsalicylic acid)



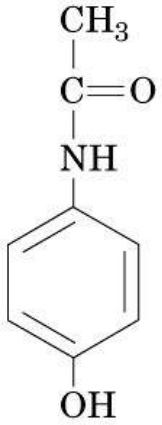
Indomethacin



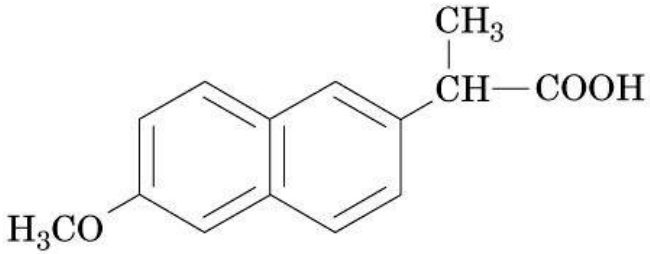
Ibuprofen



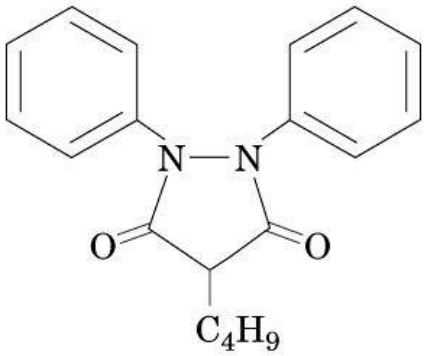
Flurbiprofen



Acetaminophen



Naproxen



Phenylbutazone

Vioxx

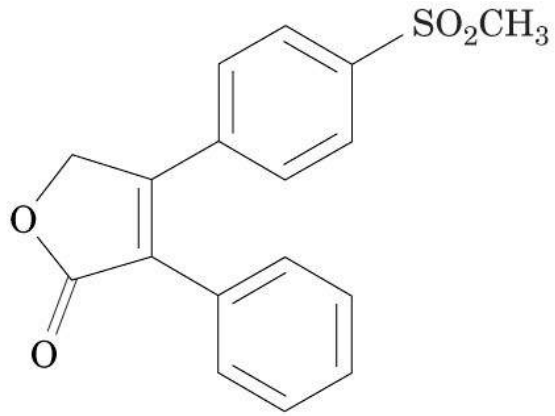
- 2 PGH synthase isoforms, **COX-1**, **COX-2**
- **COX-1** is constitutively expressed in most tissues, including the gastrointestinal mucosa
- **COX-2** only in certain tissues expressed in response to inflammatory stimuli

Aspirin can induce gastrointestinal ulceration

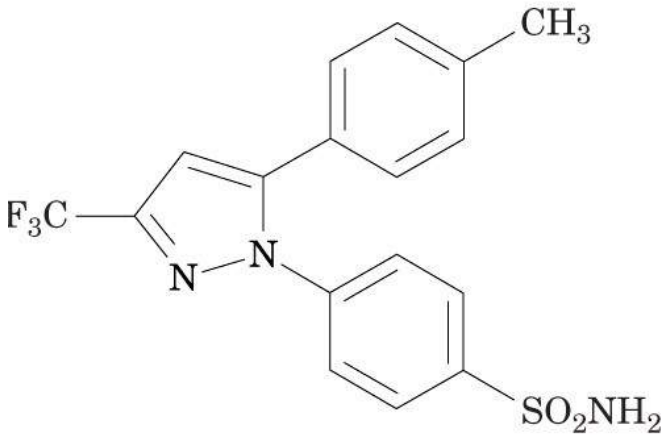
⇒ Search for selective **COX-2** inhibitors (**coxibs**) for long-term treatment, i.e. arthritis

COX-3 may be the target of acetaminophen, widely used analgesic/antipyretic drug -> treat pain & fever

COX-2 inhibitors



Rofecoxib (Vioxx)



Celecoxib (Celebrex)

09. November 2007, 15:33

Merck zahlt Vioxx-Opfern 4,85 Milliarden Dollar

Der US-Pharmakonzern Merck hat sich im Rechtsstreit um das 2004 vom Markt genommene Schmerzmittel Vioxx mit einem Grossteil der Kläger auf eine Entschädigung geeinigt.

Merck legt einen Fonds über 4,85 Milliarden Dollar auf. Damit seien 95 Prozent aller Klagen gegen Merck geregelt, erklärte das Unternehmen in Whitehouse Station im US-Bundesstaat New Jersey. Die Einigung mit den Klägern bedeute aber kein Eingeständnis von Schuld, betonte Merck. Die jeweiligen Ansprüche müssten allerdings individuell geltend gemacht und bewertet werden. Die Summe werde von Merck noch im laufenden vierten Geschäftsquartal als Belastung verbucht. «Dies ist eine gute und verantwortungsvolle Einigung», erklärte Merck-Chef Richard Clarck. Analysten hatten erwartet, dass eine Einigung Merck bis zu 50 Milliarden Dollar kosten könnte, nachdem Merck einen ersten Einzelprozess verloren hatte.

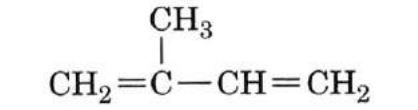
27'000 Fälle

ESKIMOS

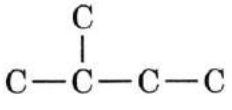
- Low risk of cardiovascular disease despite the fact that they eat a lot of fat, why?
- Are healthy because they eat fish, PUFAs, n-3, n-6
- Reduce cholesterol, leukotriene and PG levels

7) Cholesterol metabolism

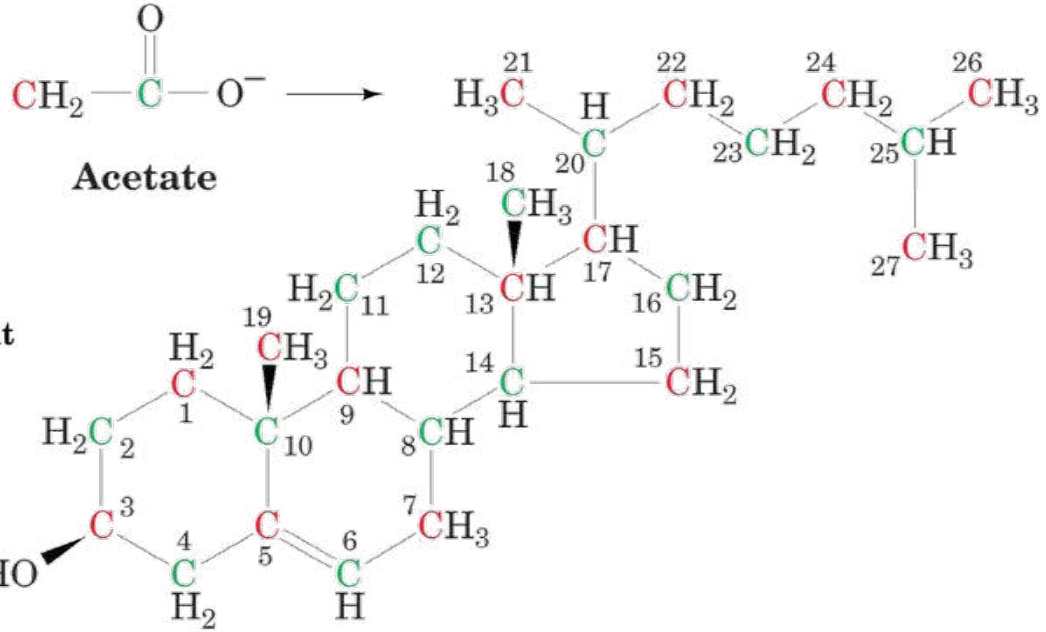
- Vital constituent of cell membranes
- precursor to:
  - steroids
  - bile salts
- Cardiovascular disease, delicate balance !



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



An isoprene unit

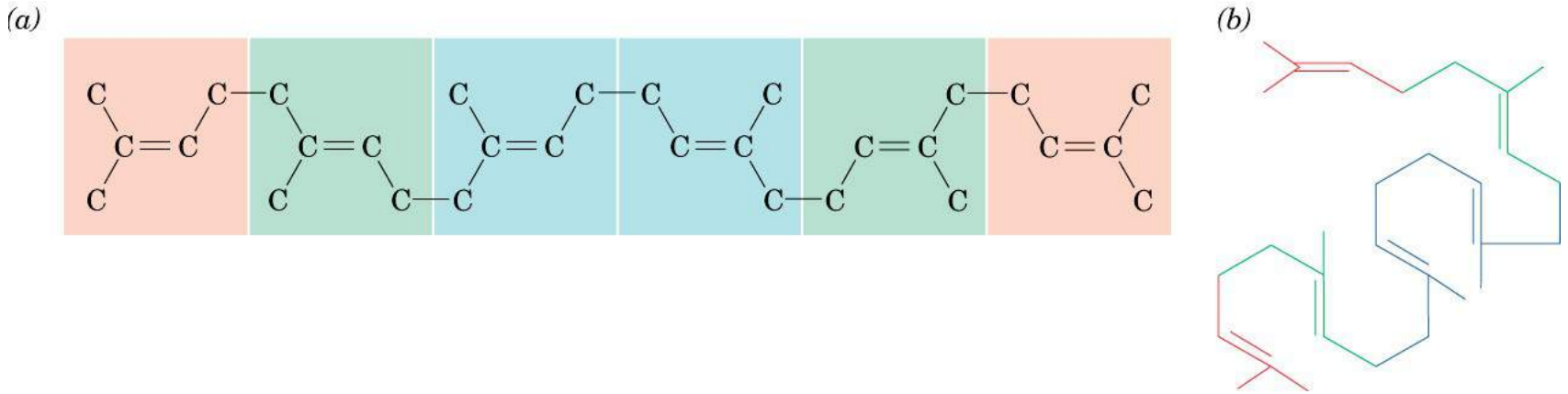


Acetate

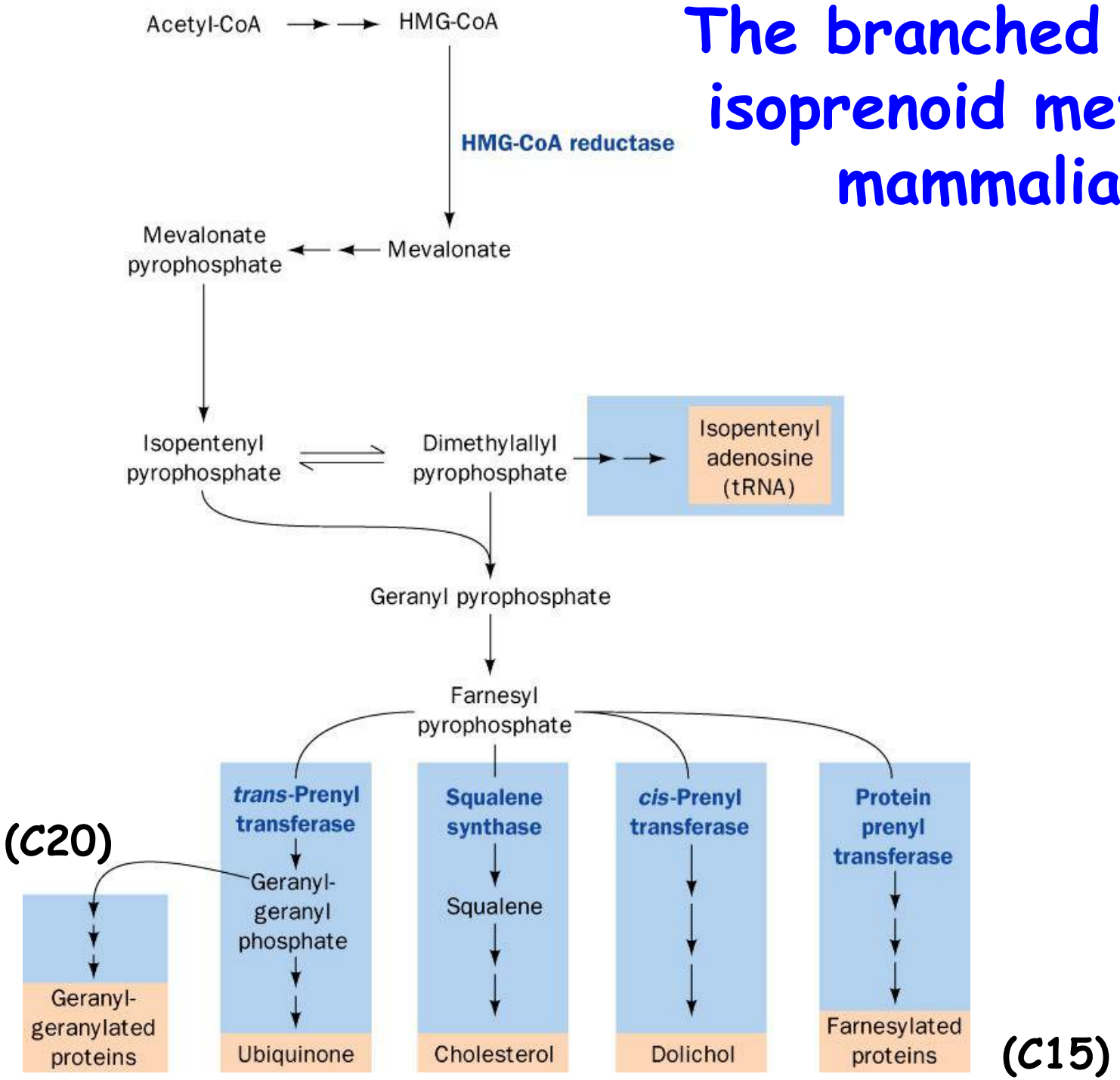
All of cholesterol's carbon atoms are derived from **acetyl-CoA**

Cholesterol is made by cyclization of squalene

Squalene from 6 isopren units (C30), polyisopren
Part of a branched pathway that uses isoprens



The branched pathway of isoprenoid metabolism in mammalian cells



C5

C10

C15

(C20)

(C15)

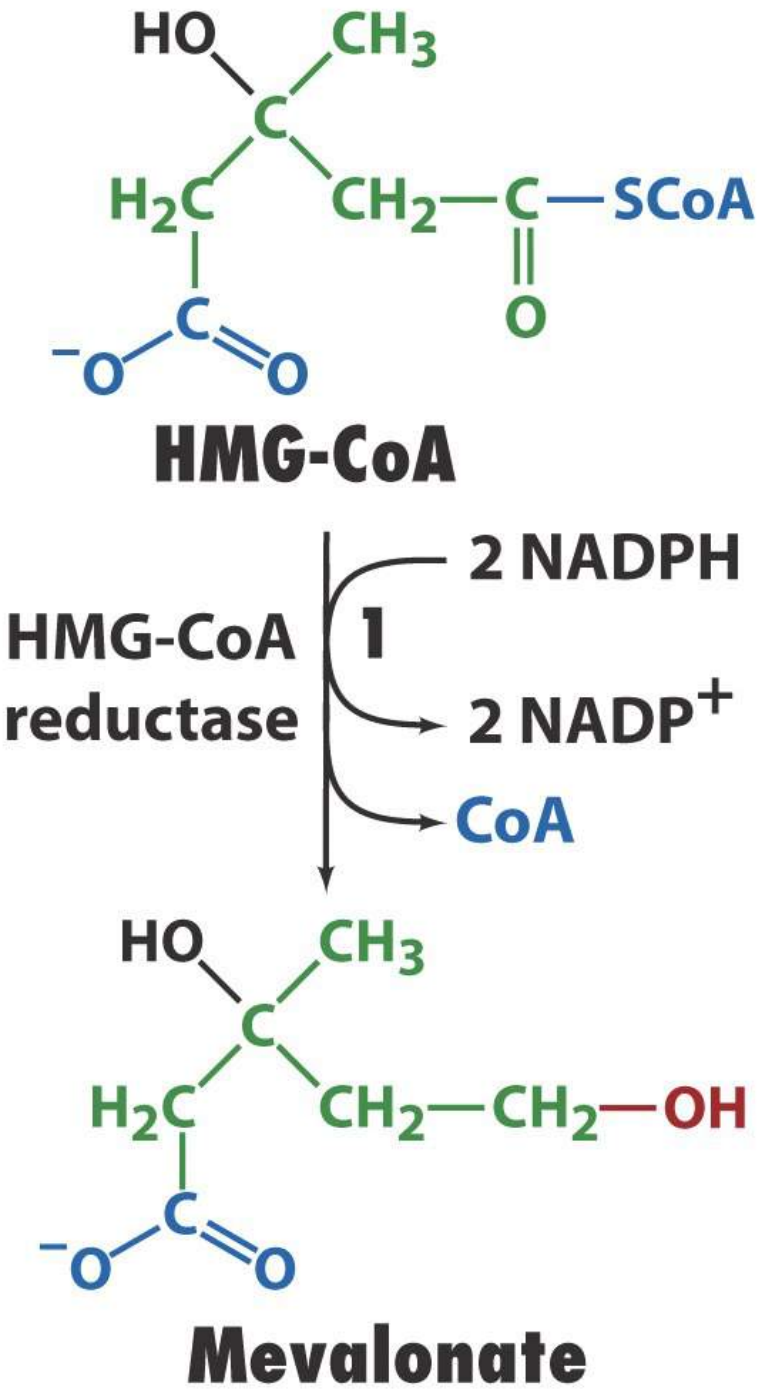
HMG-CoA is a key cholesterol precursor

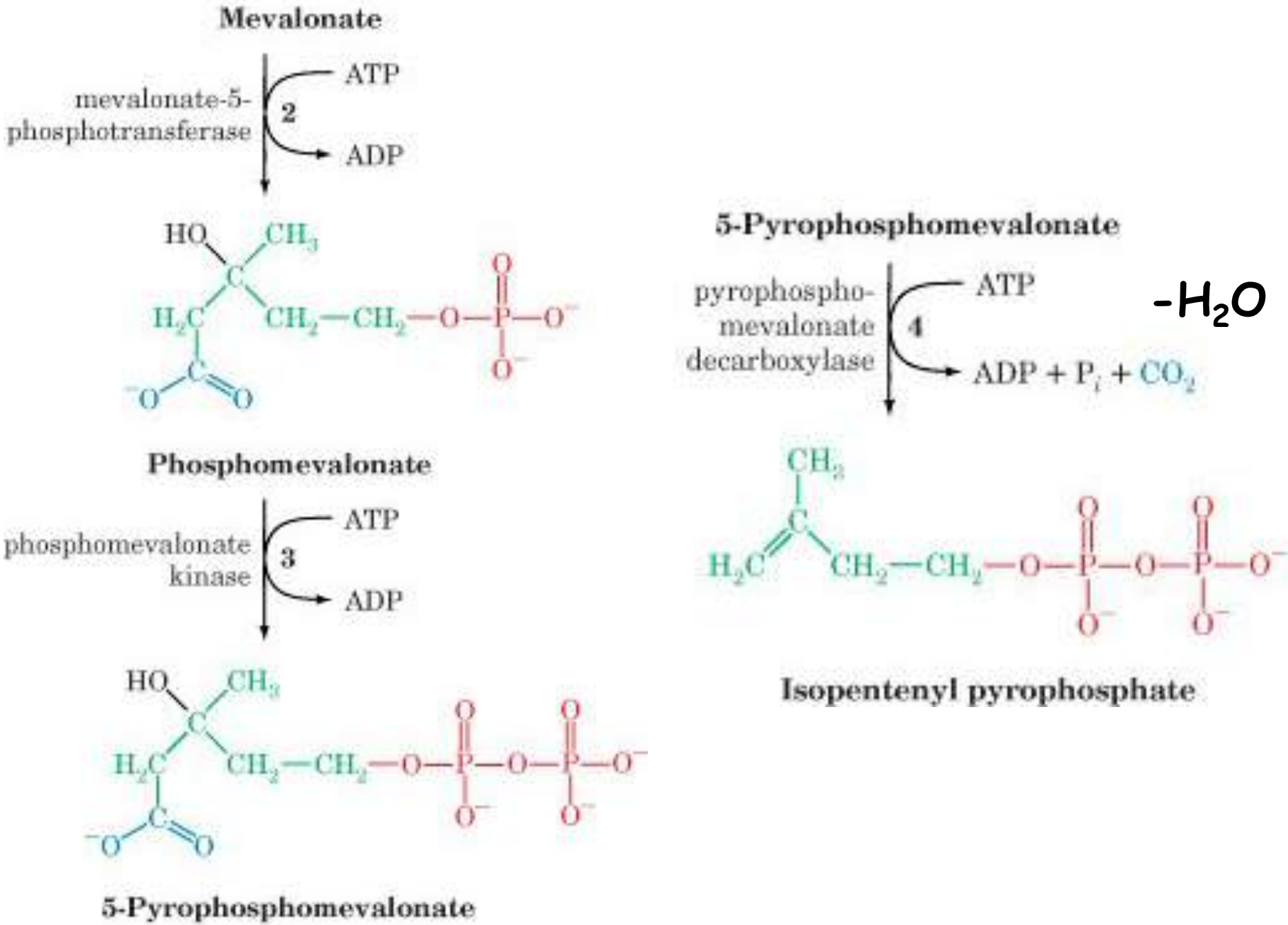
HMG-CoA is rate-limiting
ER membrane enzyme, 888 Aa

1. Reduction to OH

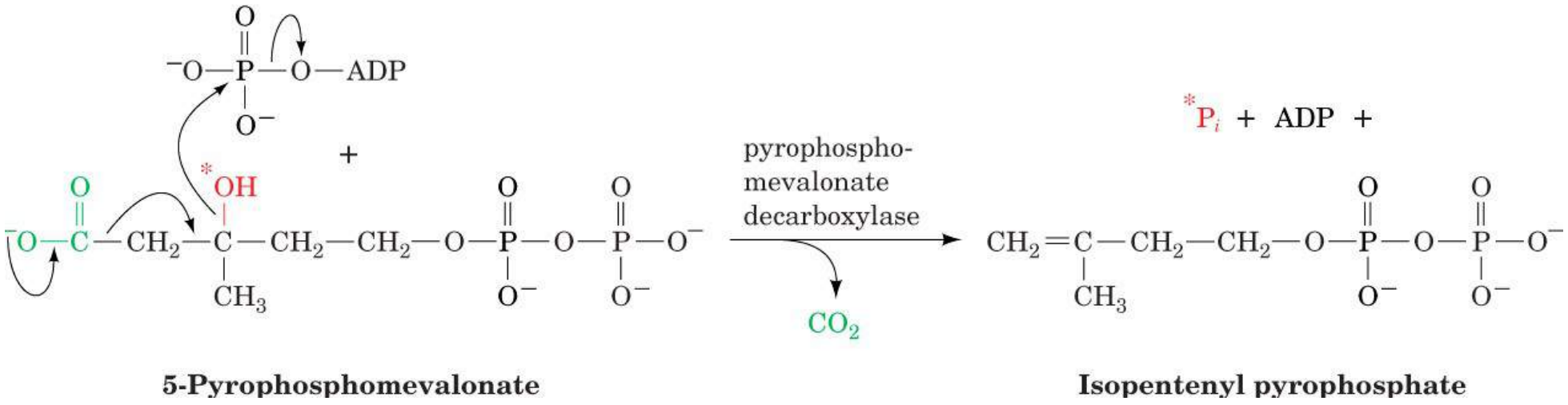
Then:

1. Phosphorylation
2. Pyrophosphate
3. Decarboxylation/ Dehydration



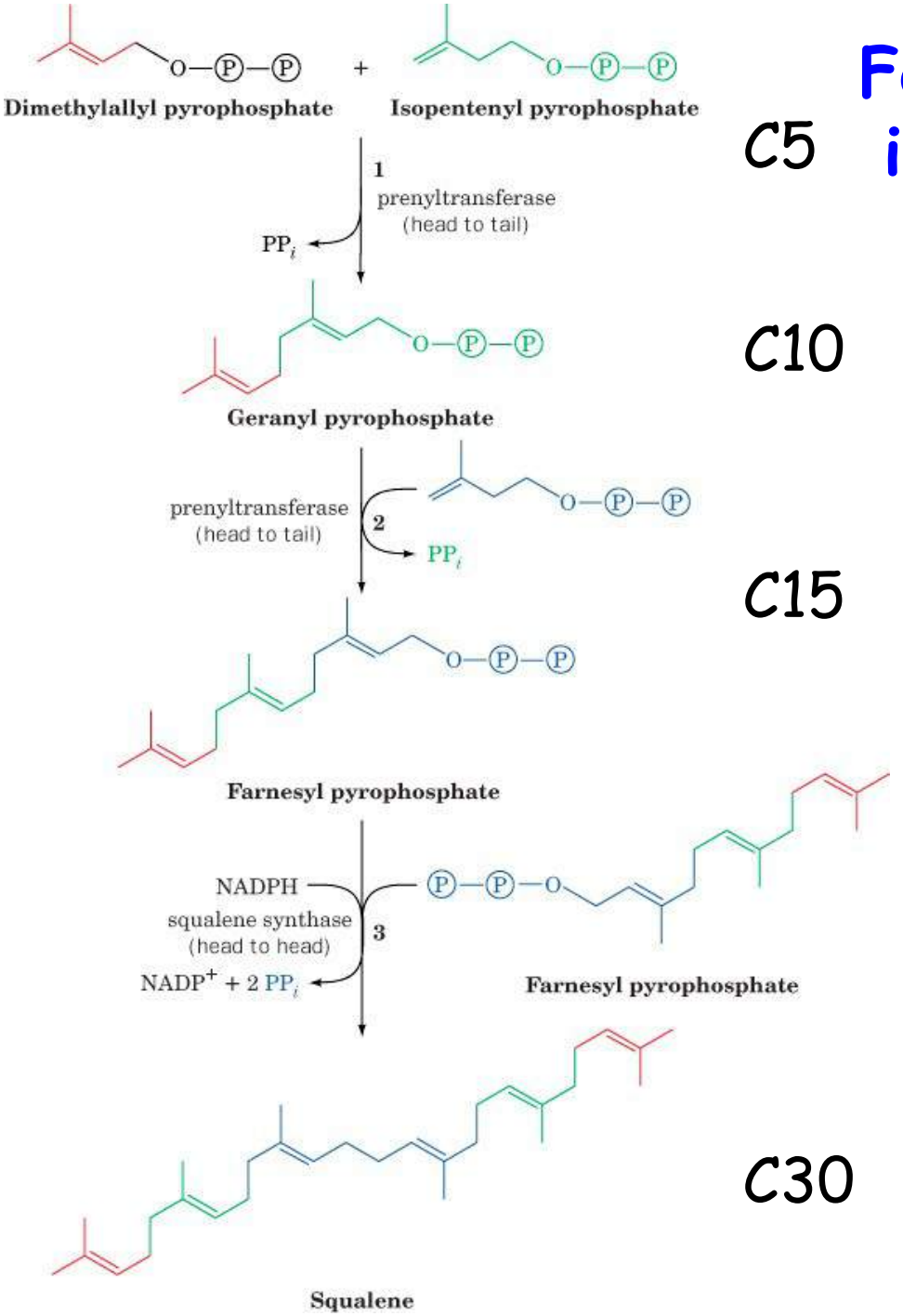

Mevalonate
mevalonate-5-phosphotransferase
2
ATP
ADP
Phosphomevalonate
phosphomevalonate kinase
3
ATP
ADP
5-Pyrophosphomevalonate
pyrophospho-mevalonate decarboxylase
4
ATP
ADP + Pi + CO2
Isopentenyl pyrophosphate
-H2O

Action of pyrophosphomevalonate decarboxylase



5-Pyrophosphomevalonate **Isopentenyl pyrophosphate**

Formation of squalene from isopentenyl pyrophosphate and dimethylallyl pyrophosphate



C5

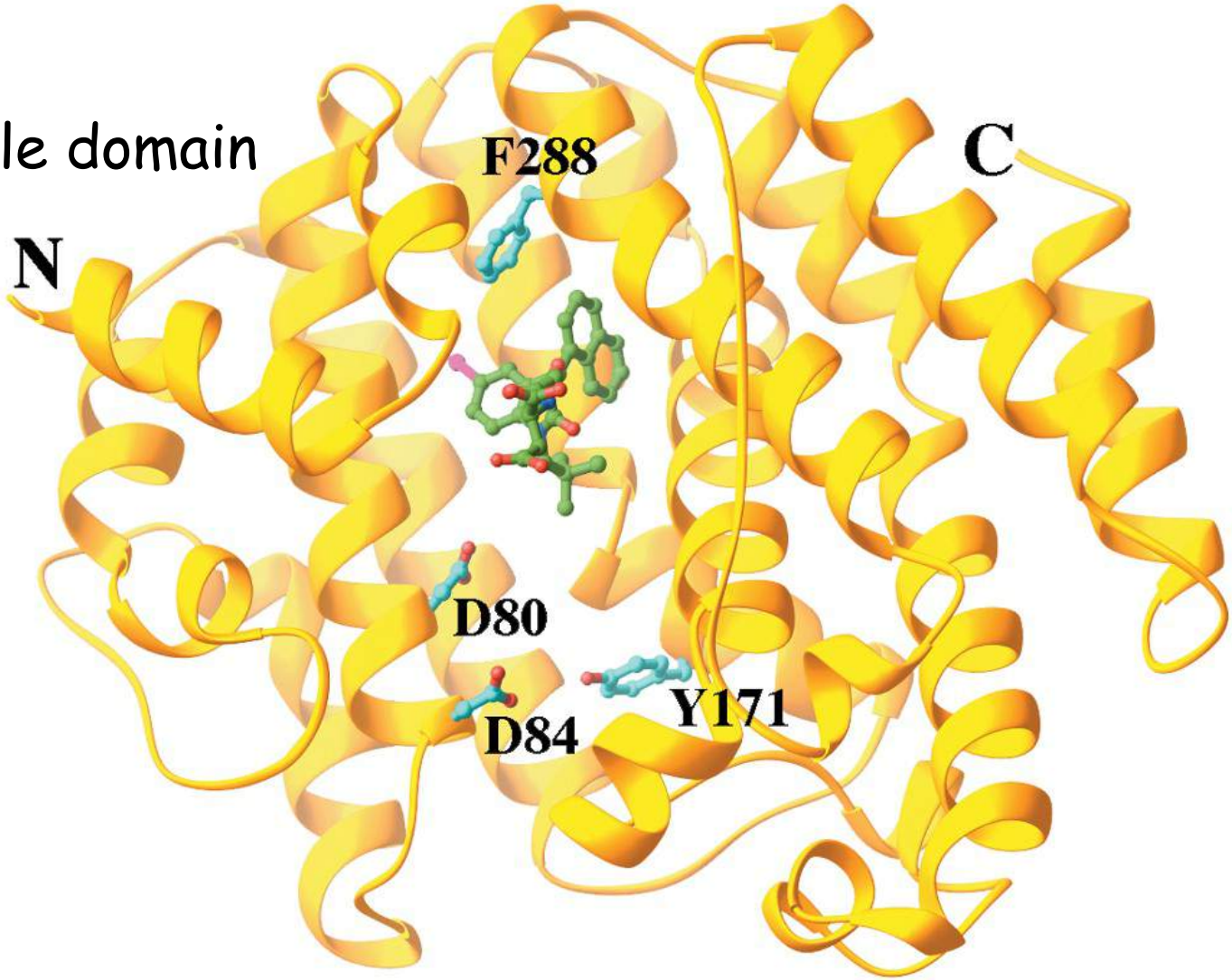
C10

C15

C30

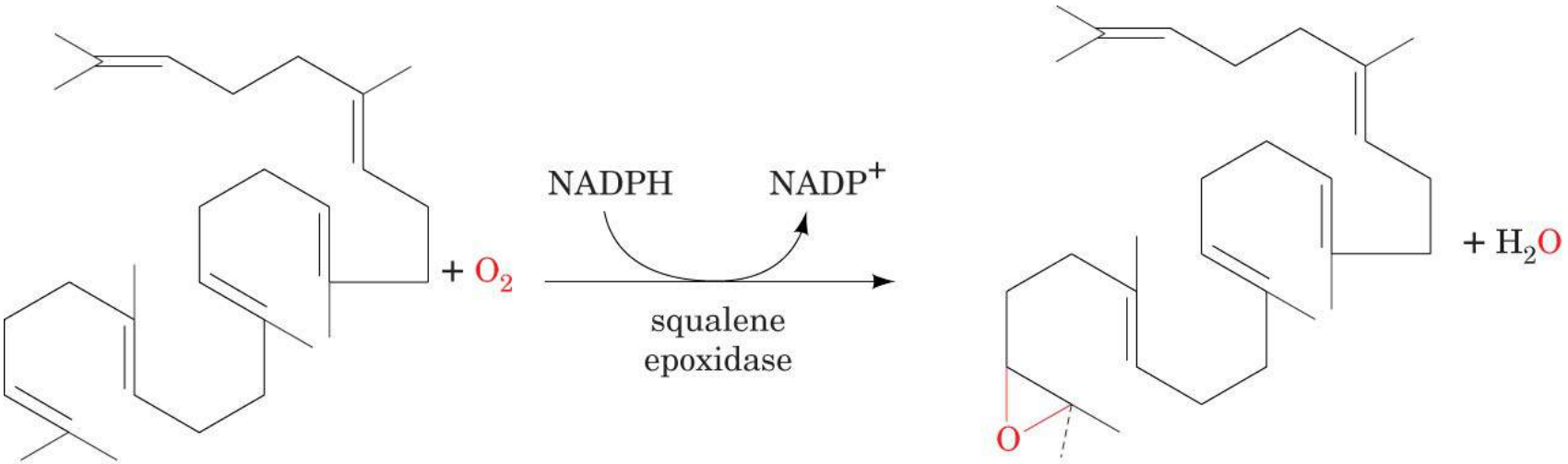
Squalene synthase

- ER anchored
- Monomer single domain



The squalene epoxidase reaction

- Preperation for cyclization
- Oxygen required for cholesterol synthesis

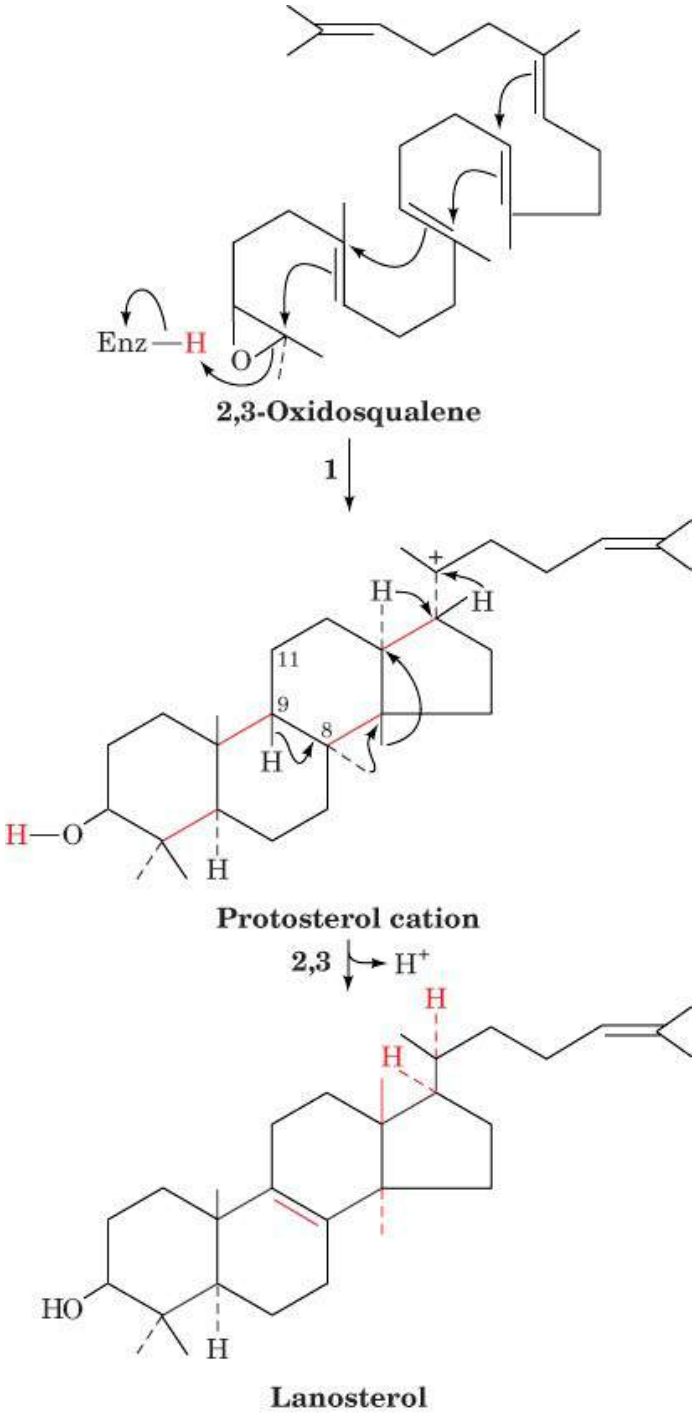


Squalene **2,3-Oxidosqualene**

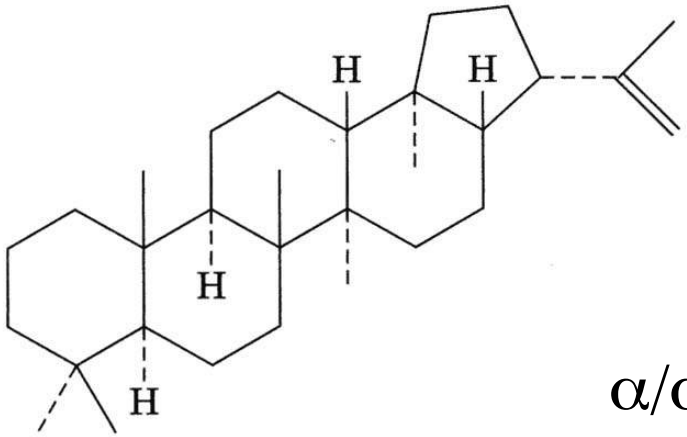
The oxidosqualene cyclase reaction

Lanosterol synthase
Folding of oxidosqualene
on the enzyme !

Related reaction in bacteria:
O_2-independent
Squalene-hopene cyclase



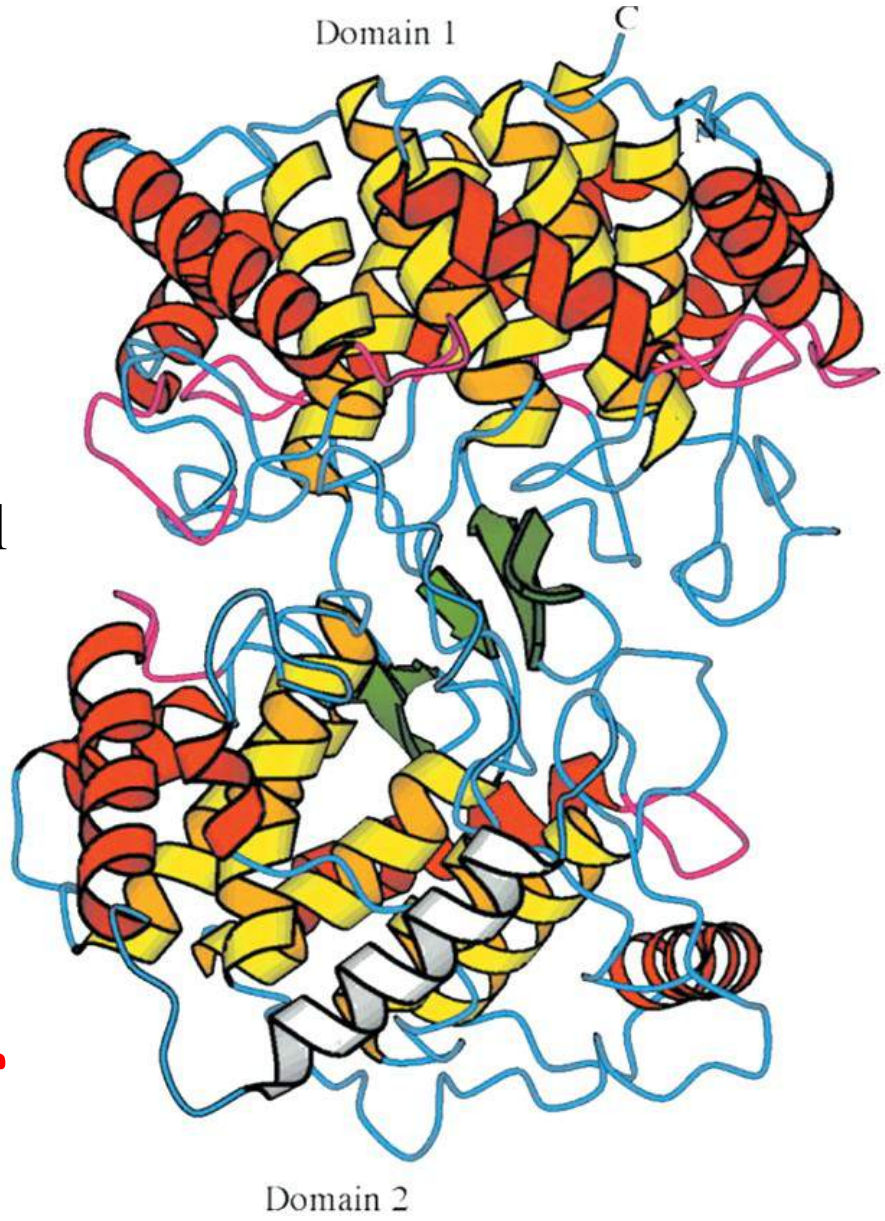
Squalene–hopene cyclase



Hopene

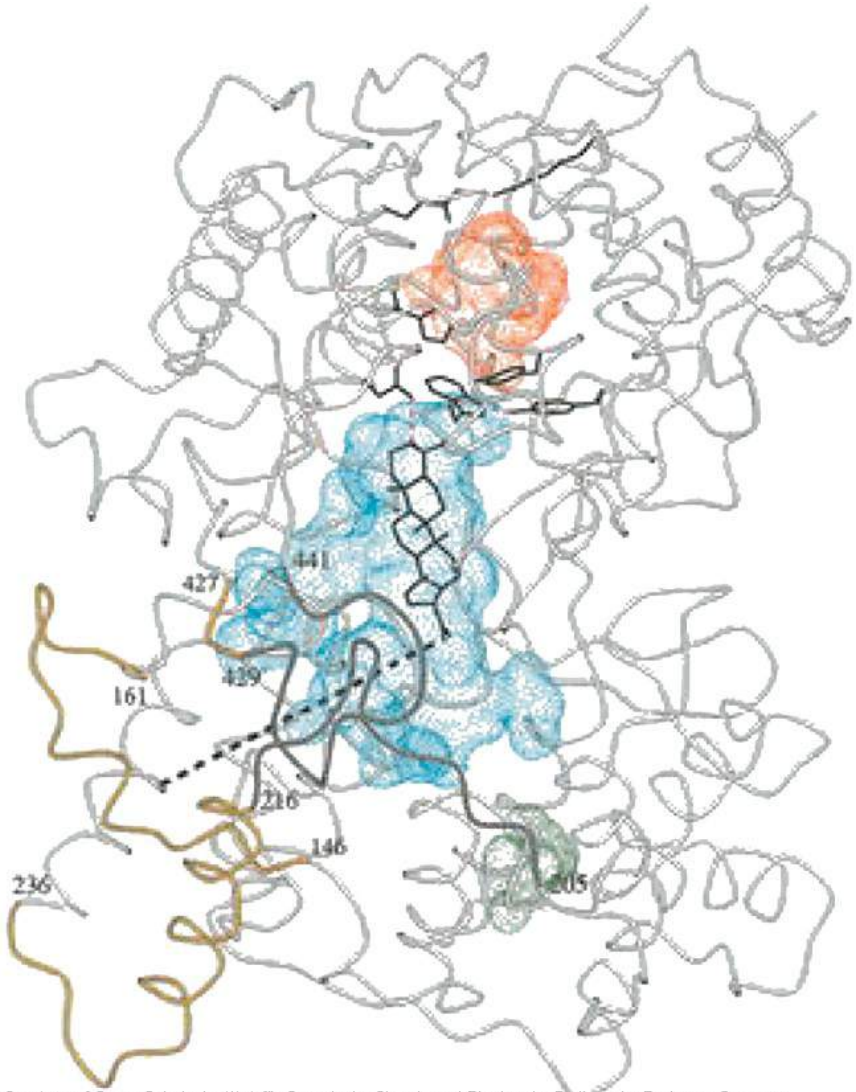
α/α barrel

μονοτοπιχ
membrane protein
Active as homodimer

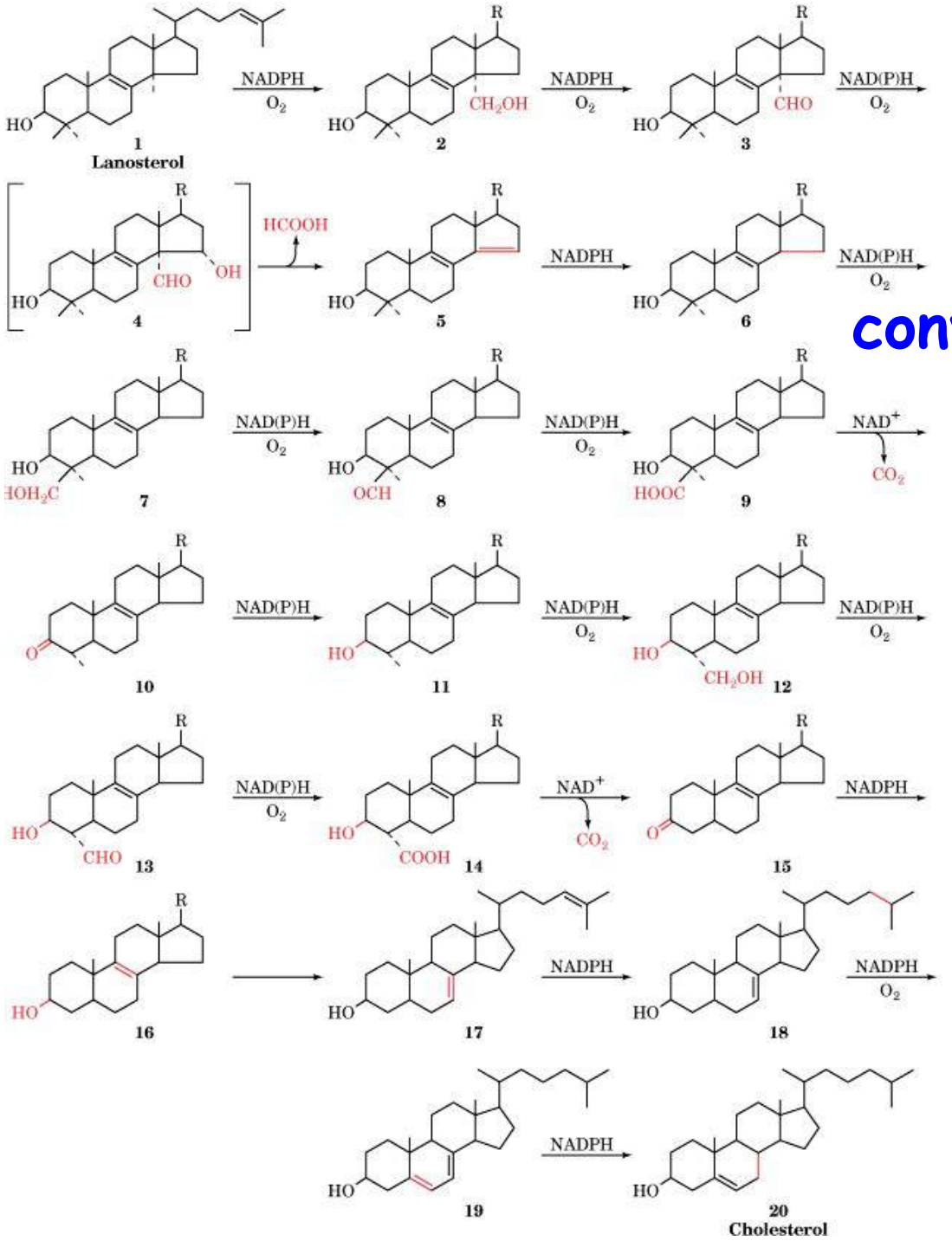


Squalene-hopene cyclase with its membrane-bound region yellow

Hydrophobic channel from active site to membrane



Courtesy of Georg Schulz, Institut für Organische Chemie und Biochemie, Freiburg im Breisgau, Germany



The 19-reaction conversion of lanosterol to cholesterol

Lanosterol -> cholsterol

- 19 steps
- Loss of 3 methyl groups
- C30 -> C27
- One oxidation
- 9 O_2 dependent
- ER localized enzymes

Cholesterol

Liver synthesized cholesterol is:

- converted to bile salts
- esterified to cholesteryl ester, ACAT

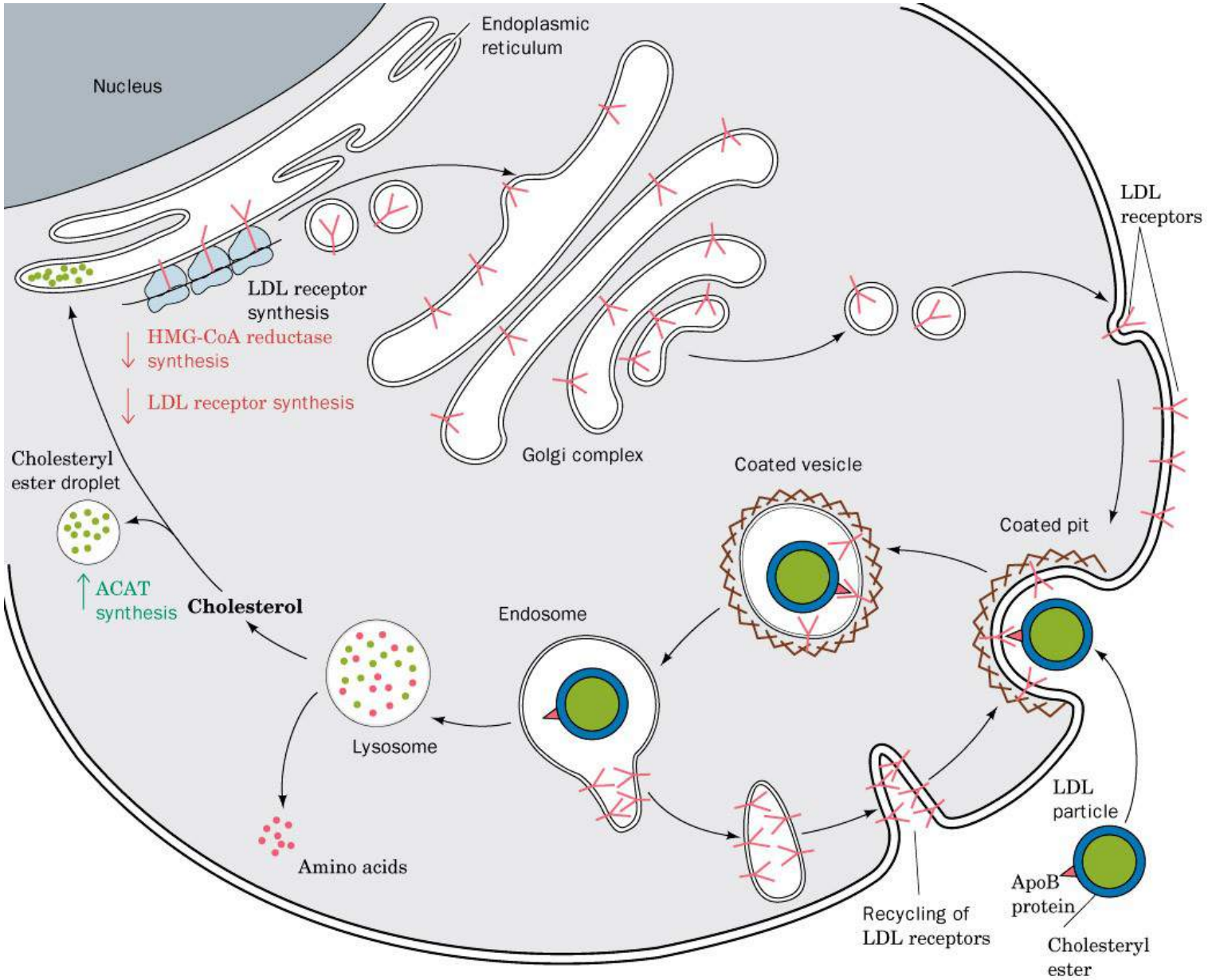
which are then packaged into lipoprotein complexes, VLDL and taken up by the tissue by LDL receptor mediated endocytosis

Mammalian cells thus have 2 ways to acquire cholesterol:
de novo synthesis or via LDL uptake

Dietary sterols are absorbed in small intestine and transported as chylomicrons in lymph to tissue/liver

HDL transports cholesterol from the peripheral tissue to the liver

LDL receptor-mediated endocytosis in mammalian cells



Regulation of cholesterol levels

Sterol Homeostasis:

1. HMG-CoA reductase, i.e. de novo synthesis

   short-term: competitive inhib., allosteric, cov. mod.

   long-term, rate of enzyme synthesis and degradation

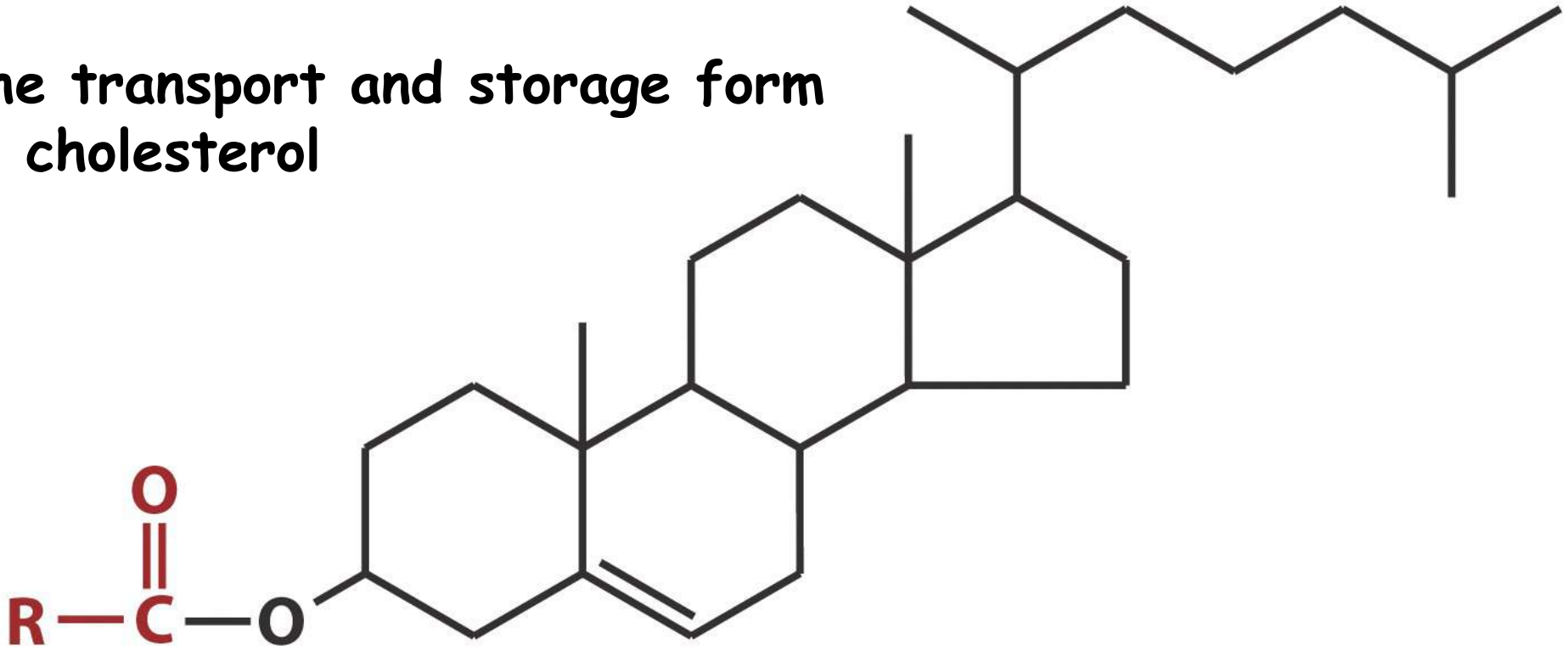
   => SREBP PATHWAY !!

2. Regulation of LDL Receptor

3. Regulating esterification, ACAT

Cholesteryl esters

The transport and storage form of cholesterol



Cholesteryl ester

The SREBP Pathway

SREBP, membrane anchored transcription factor (1160 Aa)
480 Aa N-term, basic helix-loop-helix/leucine zipper dom. => binds SRE element
central 2 TMD, loop
590 Aa C-term regulatory domain

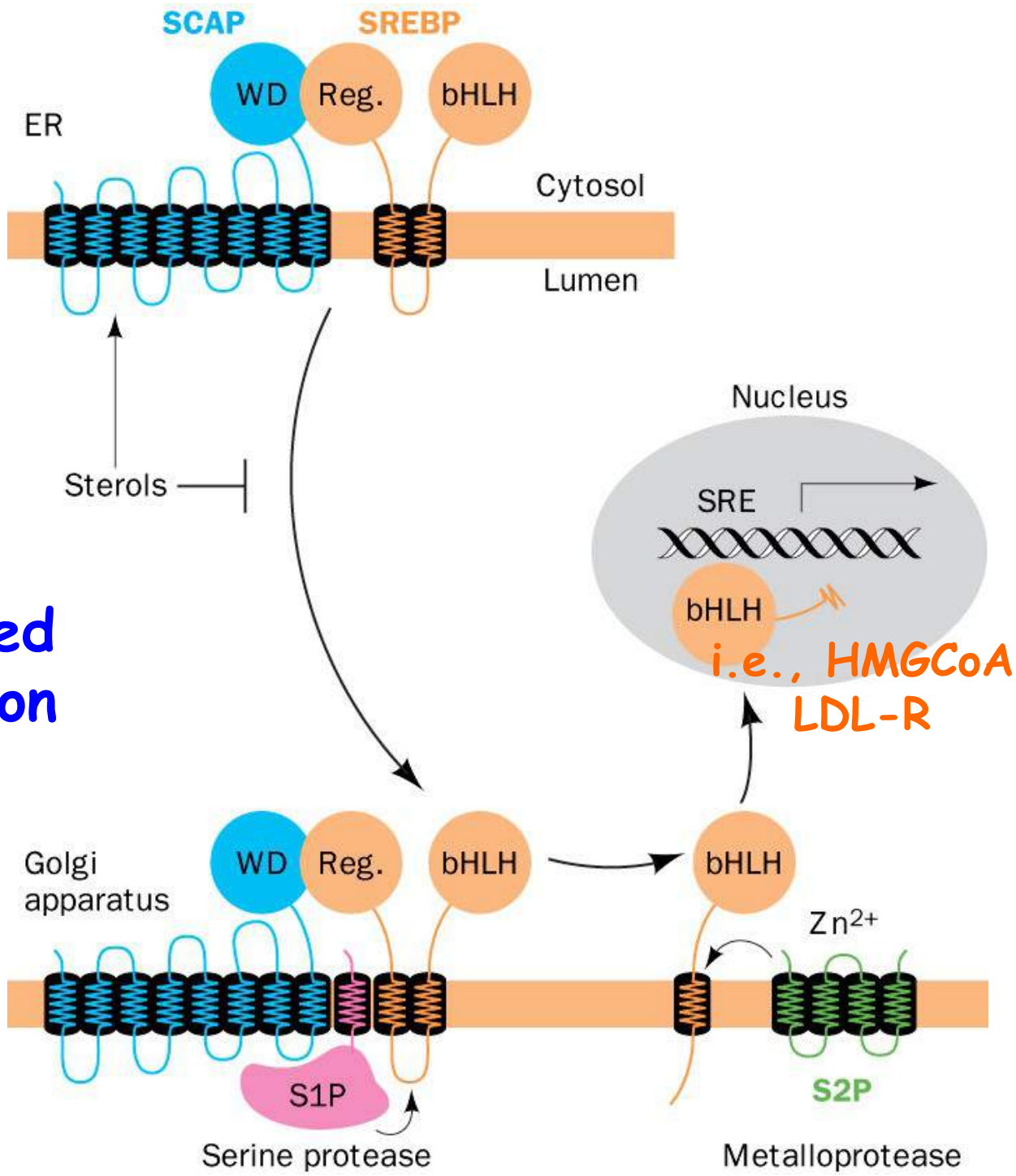
SCAP, integral membrane protein, ER, 1276 Aa
N-term 8 TMDs (730 Aa), Sterol-sensing domain
C-term, WD40 repeat => protein interaction (546 Aa)

1) Long term regulation of HMG-CoA reductase
2) Short term by phosphorylation via AMPK (see ACC1),
P-form less active
3) LDL receptor

Little cholesterol in ER

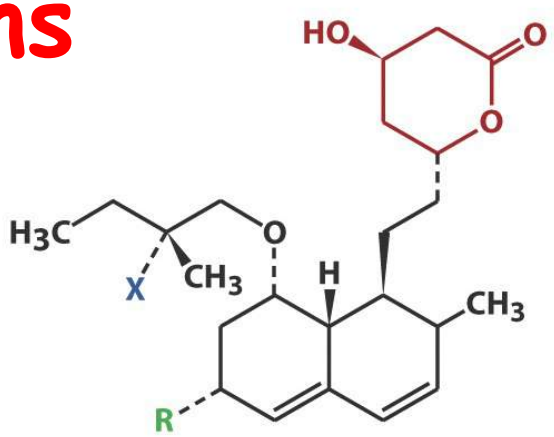
Model for the cholesterol-mediated proteolytic activation of SREBP

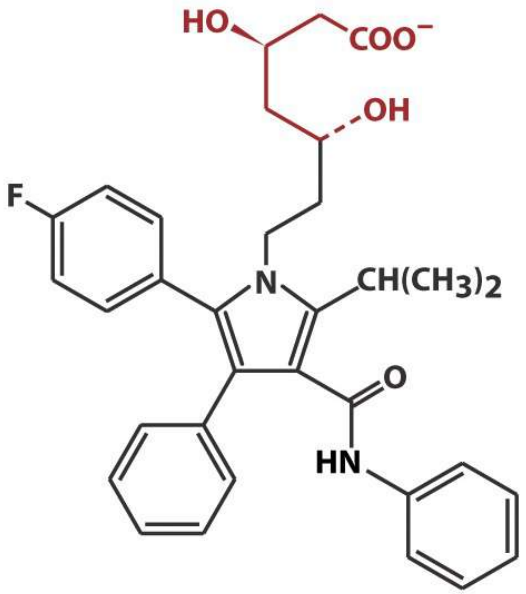
Too much cholesterol in ER



Competitive inhibitors of HMG-CoA reductase used for the treatment of hypercholesterolemia

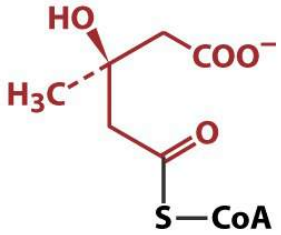
statins



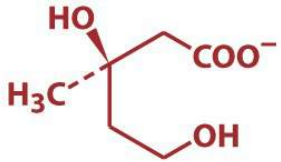


Atorvastatin (Lipitor)

X = H	R = CH_3	Lovastatin (Mevacor)
X = H	R = OH	Pravastatin (Pravachol)
X = CH_3	R = CH_3	Simvastatin (Zocor)



HMG-CoA



Mevalonate

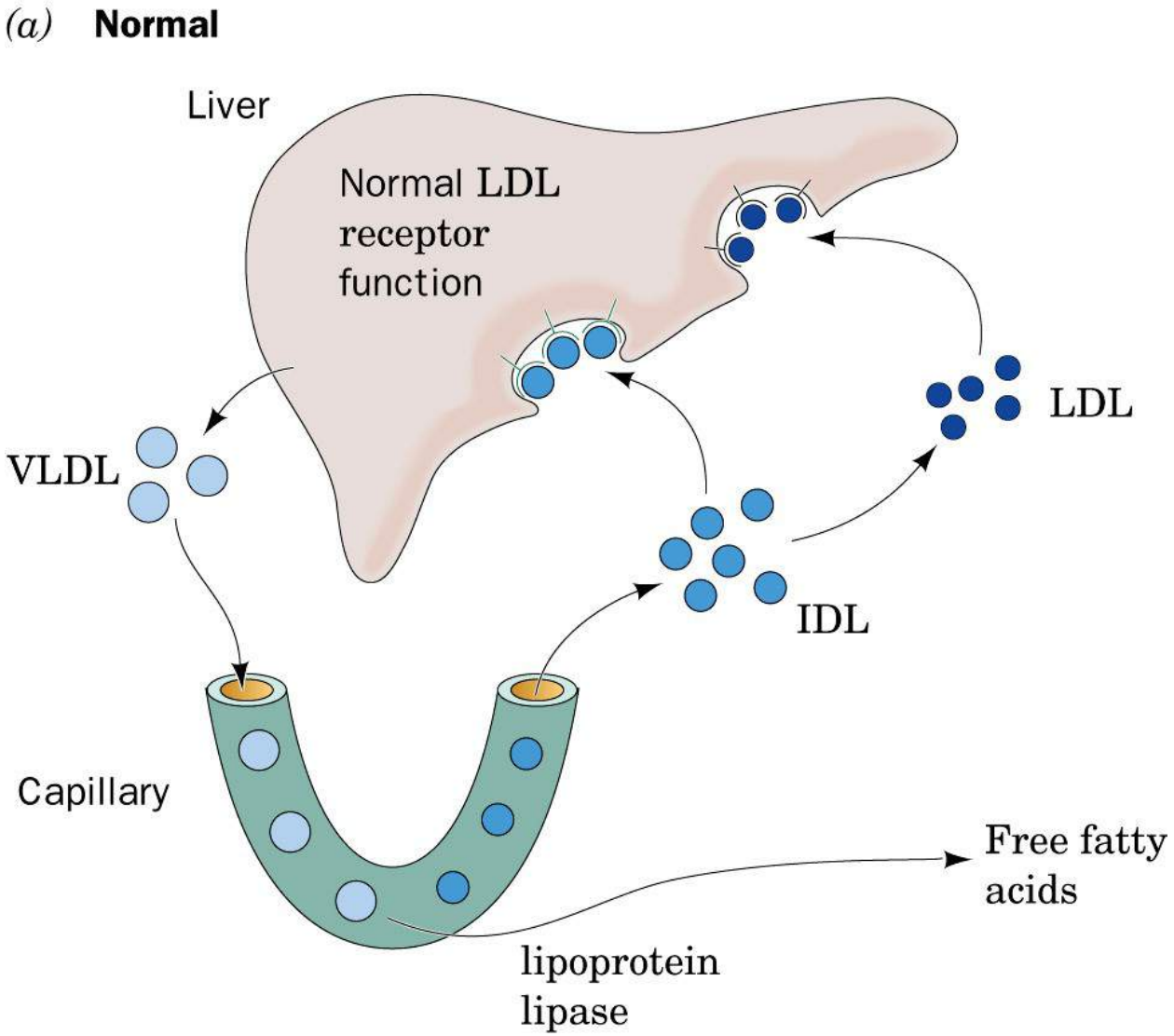
COMBINATORIAL THERAPHY

1) Anion exchanger,
   cholestyramine, reduced recycling of bile acids and uptake of dietary cholesterol => 15-20% drop

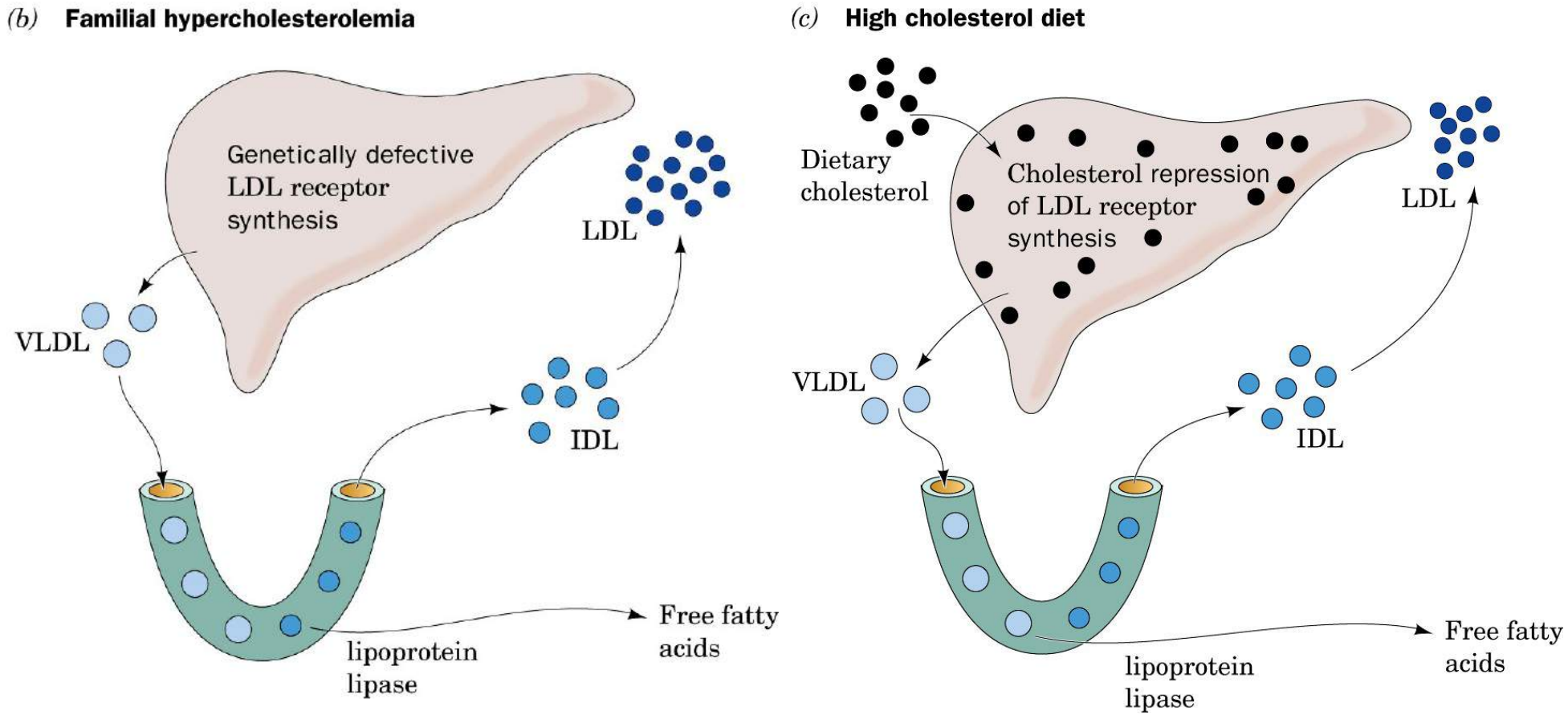
2) HMG-CoA inhibitor
   statins

Combined => 50-60% reduction of blood cholesterol levels

Control of plasma LDL production and uptake by liver LDL receptors. (*a*) Normal human subjects

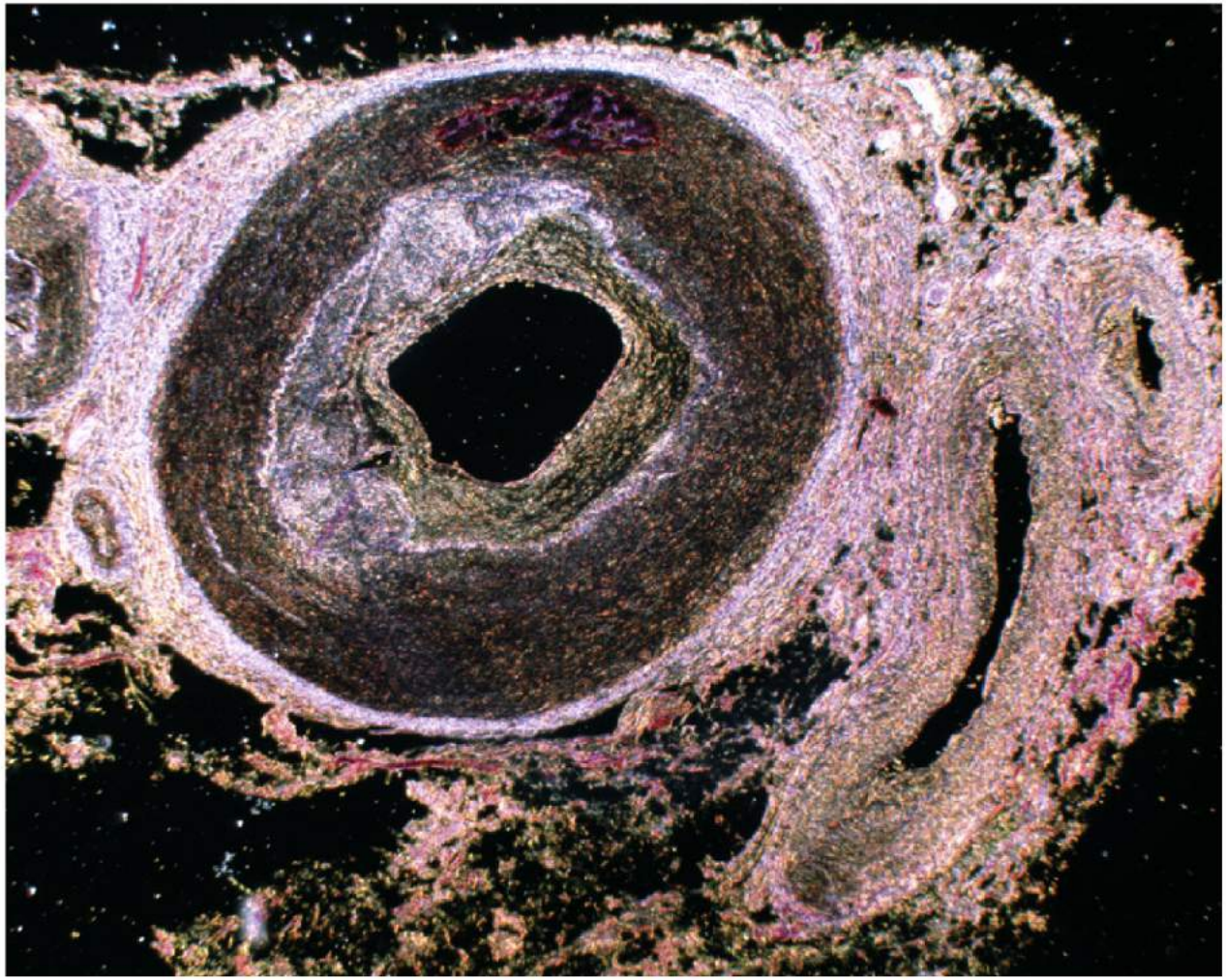


Control of plasma LDL production and uptake by liver LDL receptors

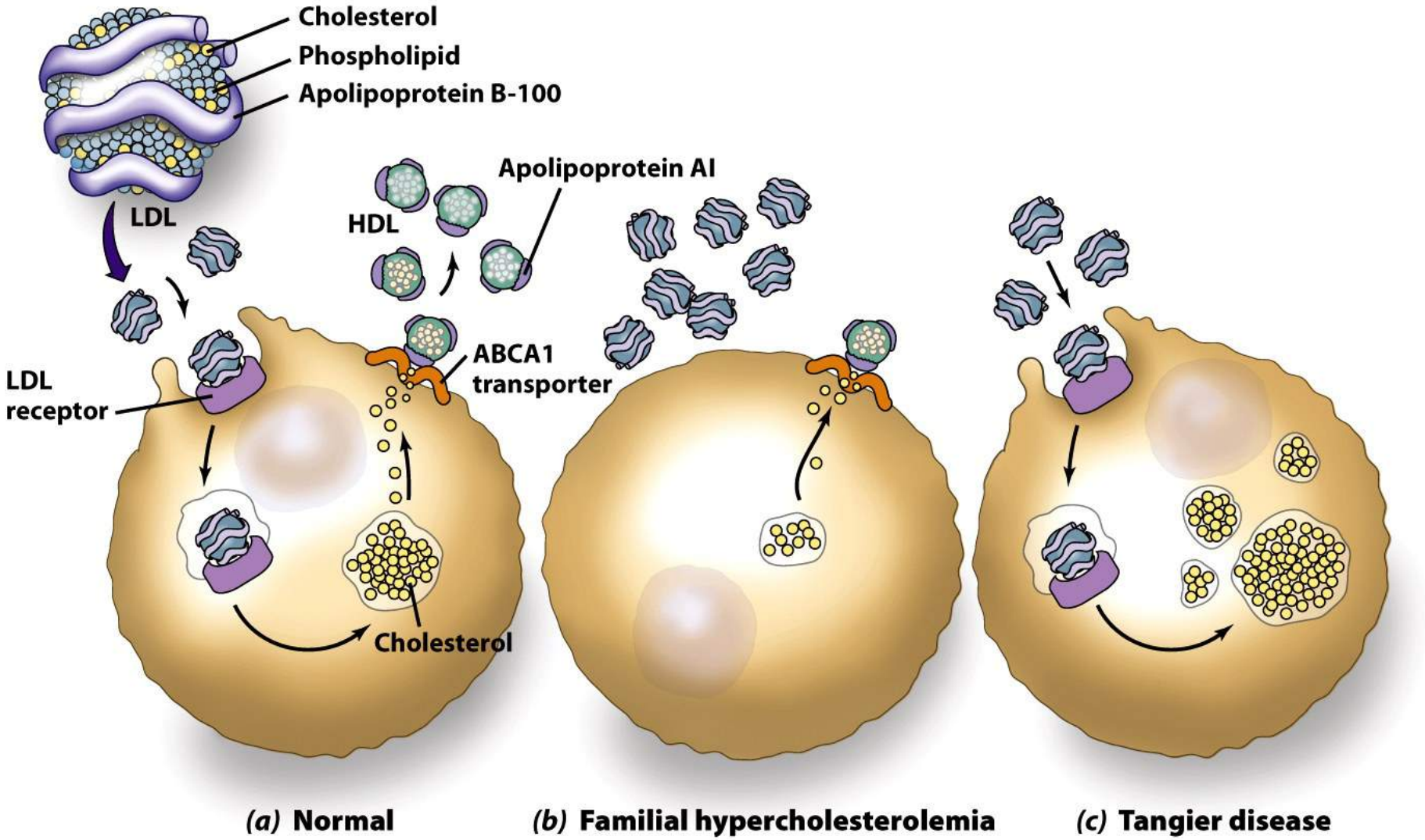


d) Overexpression of LDL receptor prevents diet-induced hypercholesterolemia

An atherosclerotic plaque in a coronary artery



The role of LDL and HDL in cholesterol metabolism



Familial Hypercholesterolemia

M. Brown and J. Goldstein

- 1972, Brown and Goldstein, Nobel Price1985, second for SREBP ?
- "you are as good as your next experiment"

A RECEPTOR-MEDIATED PATHWAY FOR CHOLESTEROL HOMEOSTASIS

Nobel lecture, 9 December, 1985

by

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LDL deposits, Xanthomas