Lipid Biosynthesis

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Why do we care about lipids?

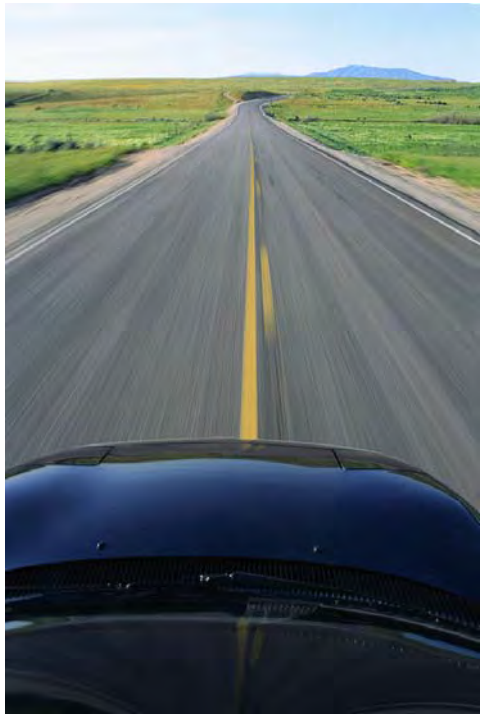
- ~80% of European population overweight
- ~ 1/3 obese
  - ➢=130 million obese adults in EU
  - ➢6% of total health costs
  - ➢10-13% of deaths in Europe

Contributes to diabetes, coronary heart disease, hypertension, stroke & cancer

Diseases of dyslipidemia are one of the greatest health challenges of the 21st century

Outline

- Lipid overview: synthesis and structure
- Fatty acids
- Eicosanoids
- Break . . . .
- Triacylglycerols
- Phospholipids
- Cholesterol
- Bile acids, enterohepatic circulation
- Summary



What is a lipid?

Classical definition:

biological molecule that is soluble in organic solvent, but insoluble in water

Modern (specific) definition:

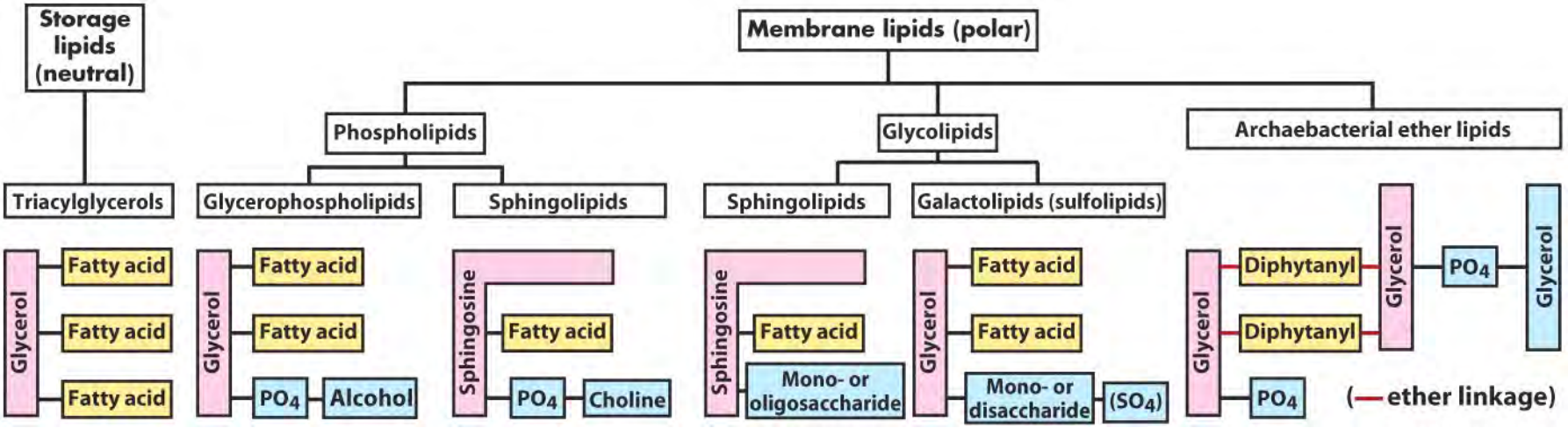
fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds

More specific definition:

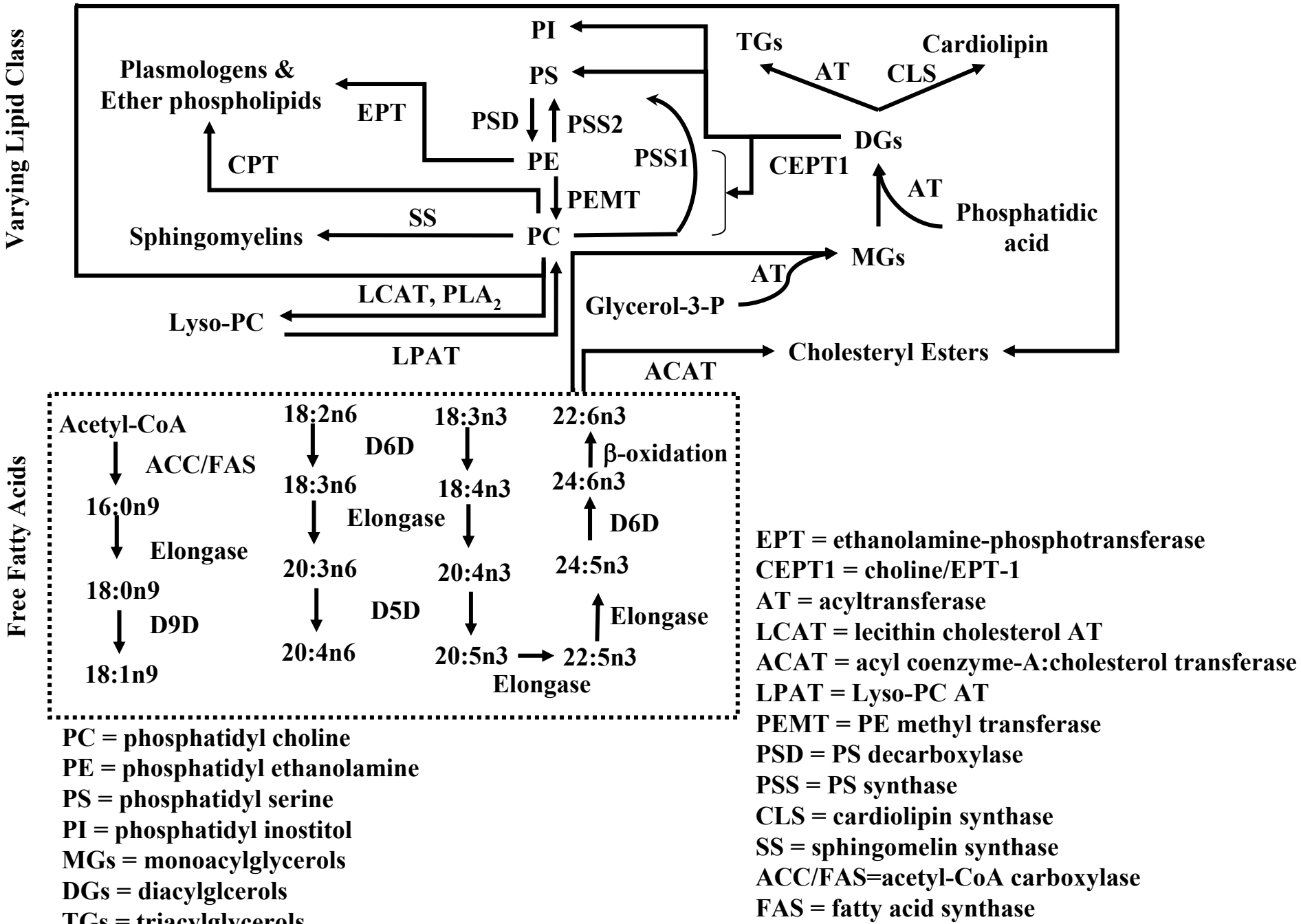
Hydrophobic small molecules that originate by carbanion-based condensations of thioesters (fatty acids, polyketides, etc.) and/or by carbocation-based condensations of isoprene units (prenols, sterols, etc)

Vary greatly in structure and function

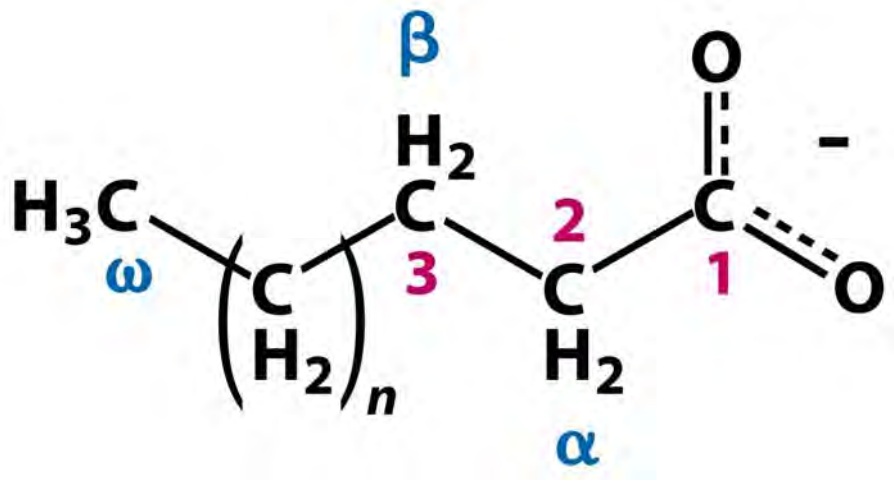
Some typical lipids



In addition:
cholesterol, cofactors, vitamins, bile acids, hormones, eicosanoids, other signaling molecules, etc……


Varying Lipid Class
PI
PS
TGs
Cardiolipin
AT
CLS
Plasmologens &
Ether phospholipids
EPT
PSD
PSS2
DGs
CPT
PE
PSS1
CEPT1
AT
PEMT
Phosphatidic
acid
SS
Sphingomyelins
PC
MGs
AT
LCAT, PLA2
Glycerol-3-P
Lyso-PC
LPAT
Cholesteryl Esters
ACAT
Free Fatty Acids
Acetyl-CoA
ACC/FAS
16:0n9
Elongase
18:0n9
D9D
18:1n9
18:2n6
D6D
18:3n6
Elongase
20:3n6
D5D
20:4n6
18:3n3
18:4n3
20:4n3
20:5n3
Elongase
22:5n3
22:6n3
β-oxidation
24:6n3
D6D
24:5n3
Elongase
PC = phosphatidyl choline
PE = phosphatidyl ethanolamine
PS = phosphatidyl serine
PI = phosphatidyl inostitol
MGs = monoacylglycerols
DGs = diacylglcerols
TGs = triacylglycerols
EPT = ethanolamine-phosphotransferase
CEPT1 = choline/EPT-1
AT = acyltransferase
LCAT = lecithin cholesterol AT
ACAT = acyl coenzyme-A:cholesterol transferase
LPAT = Lyso-PC AT
PEMT = PE methyl transferase
PSD = PS decarboxylase
PSS = PS synthase
CLS = cardiolipin synthase
SS = sphingomelin synthase
ACC/FAS=acetyl-CoA carboxylase
FAS = fatty acid synthase

Fatty acids (FA)



- compounds synthesized in nature via condensation of malonyl coenzyme A units by a fatty acid synthase complex
- contain even numbers of carbon atoms in straight chains (commonly C14- C24)
- may be saturated or unsaturated
- can contain variety of substituent groups

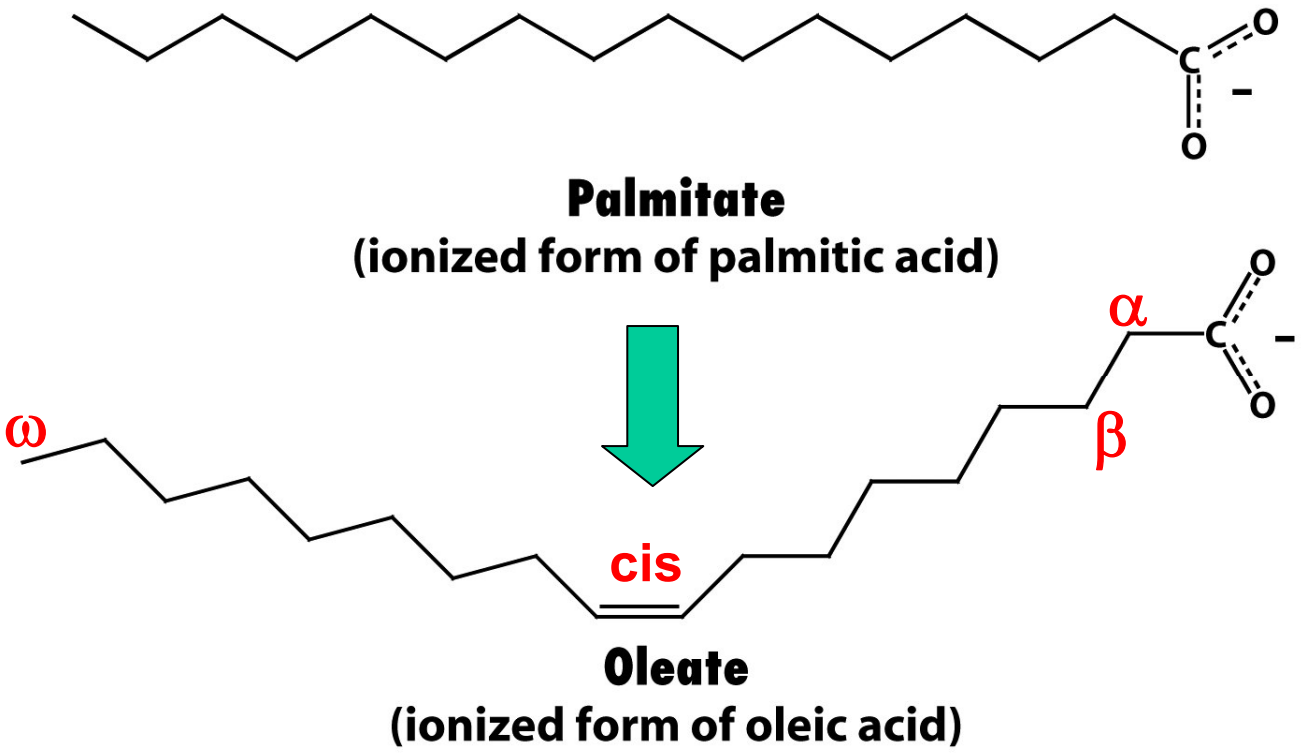
Fatty Acids

- Single(σ)-bonded carbon chains with a terminal carboxylic acid:

- Produced de novo by animals and plants
- Can contain double(π)-bonded carbons which are inserted by desaturases

Unsaturation & shorter chain

- ↓ melting point
- ↑ membrane fluidity (*cis* bond gives the "kink" in the carbon chain)



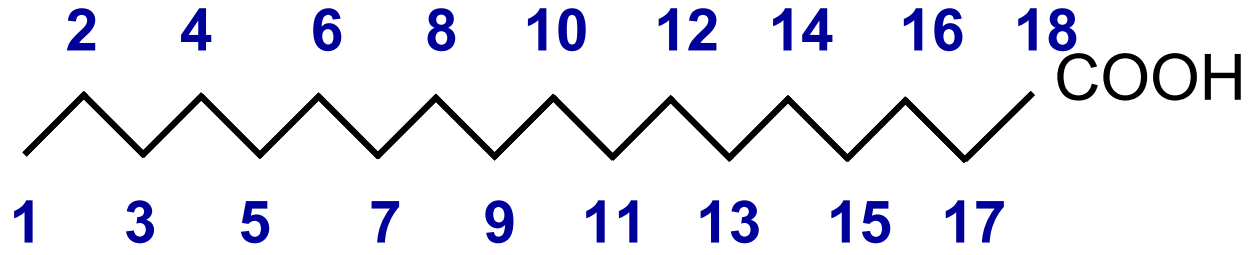
Nomenclature

- **Fatty acids are sigma-bonded carbon chains with a carboxylic acid functional group**

Nomenclature

- **Individual fatty acids can be identified by one of two numerical nomenclature systems**

n-Designation
Carbon numbering starts from methyl end

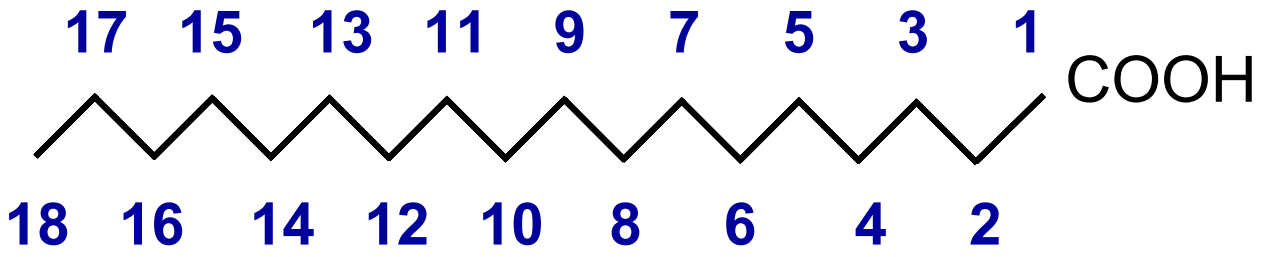


stearic acid 18:0

Nomenclature

- **Individual fatty acids can be identified by one of two numerical nomenclature systems**

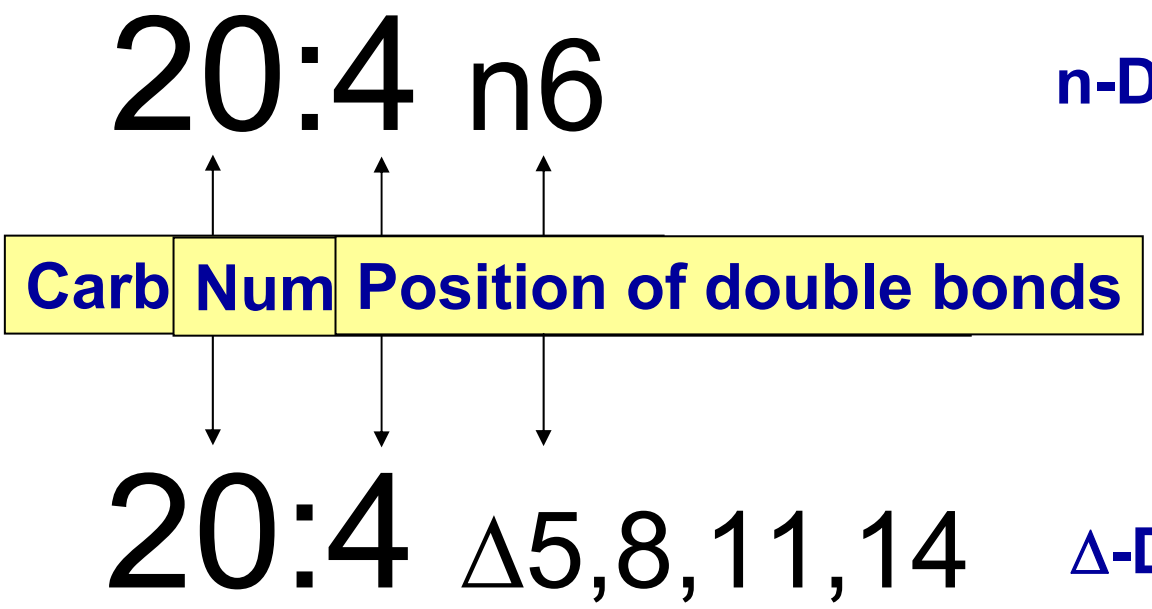
Δ-Designation
Carbon numbering starts from carboxyl group

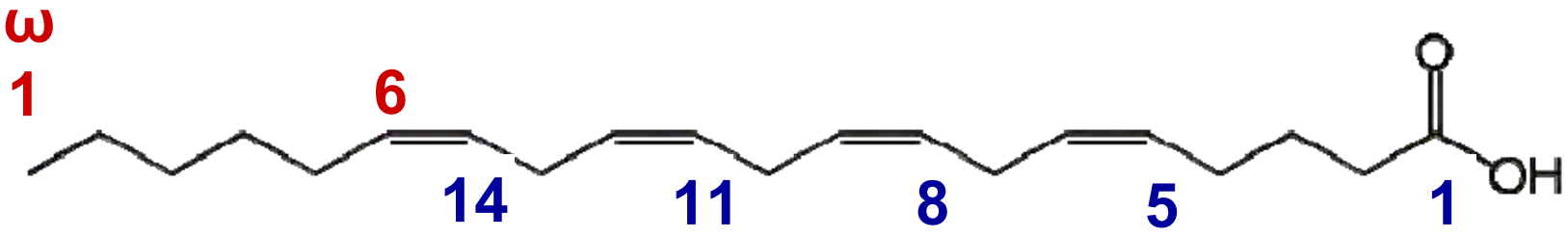


stearic acid 18:0

Nomenclature

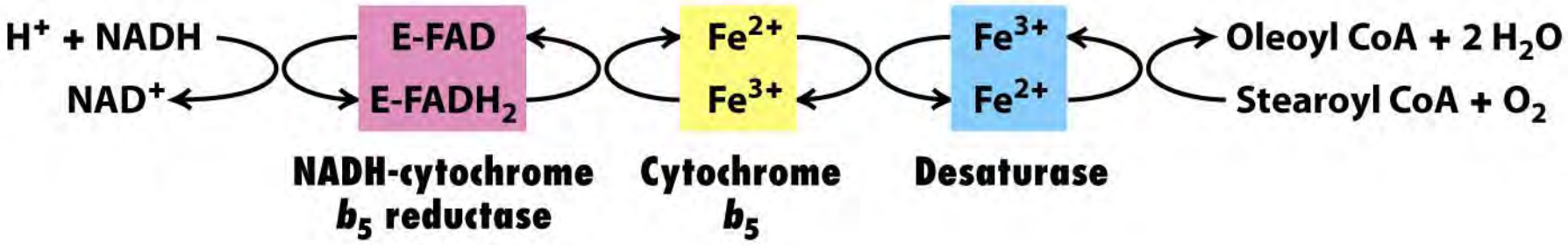
- **Standard nomenclature (arachidonic acid):**



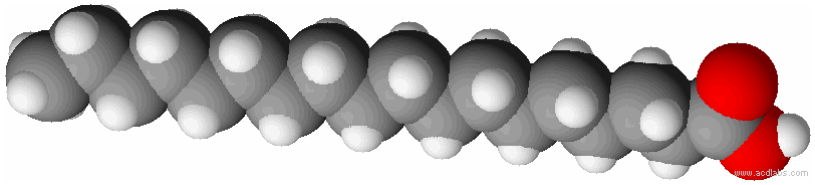


Desaturation of Fatty Acids

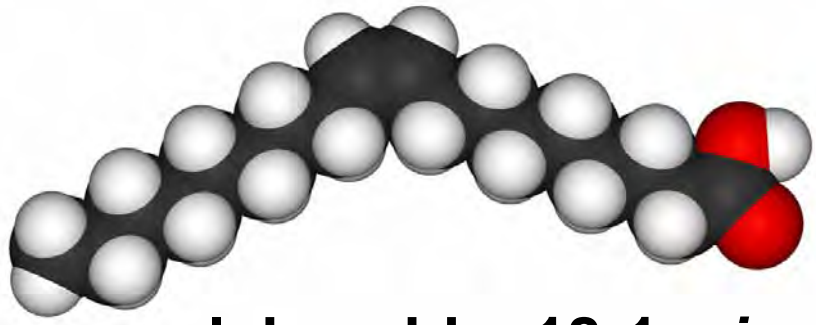
complex of 3 membrane proteins in E.R.



series of desaturase enzymes creates position-specific double bonds



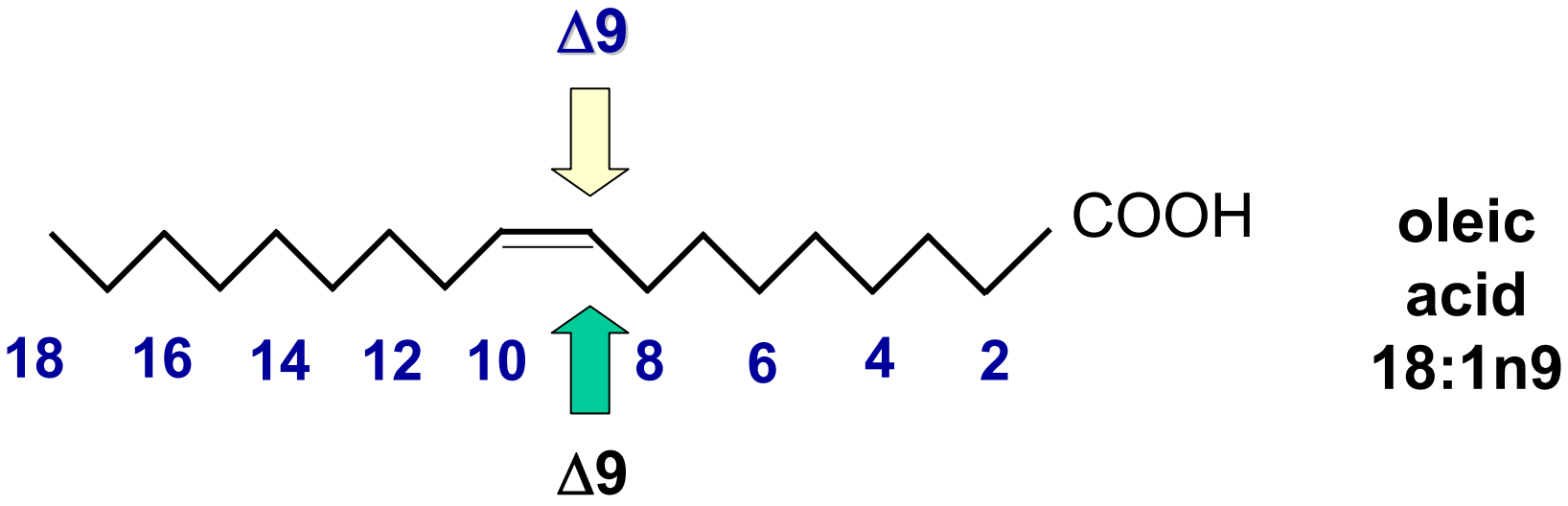
stearic acid –18:0



oleic acid – 18:1, *cis*

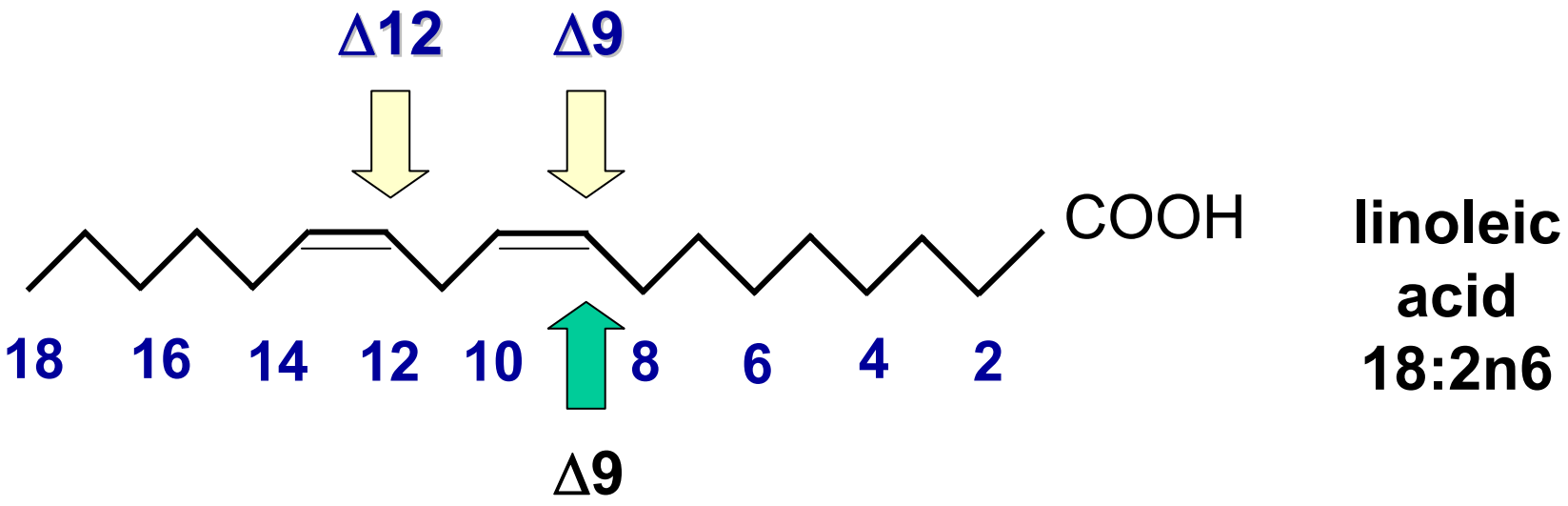
Fatty Acid Metabolism

- **The first desaturation of a saturated fatty acid is always at the Δ9 position**



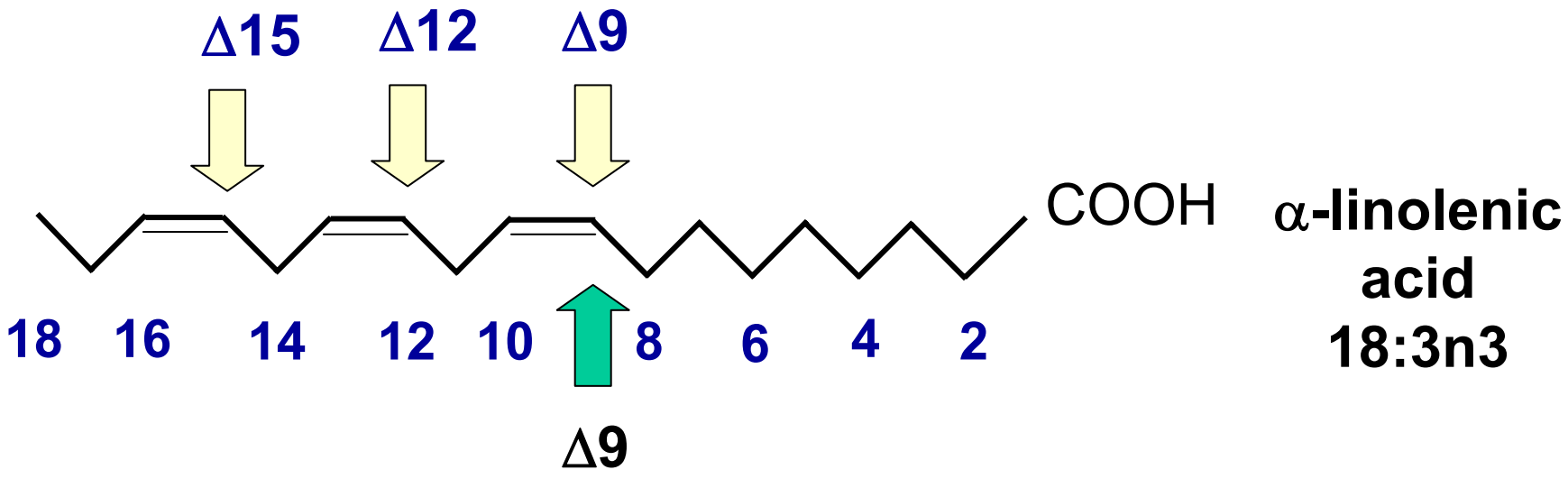
Fatty Acid Metabolism

- **Plants can also desaturate at the Δ12**



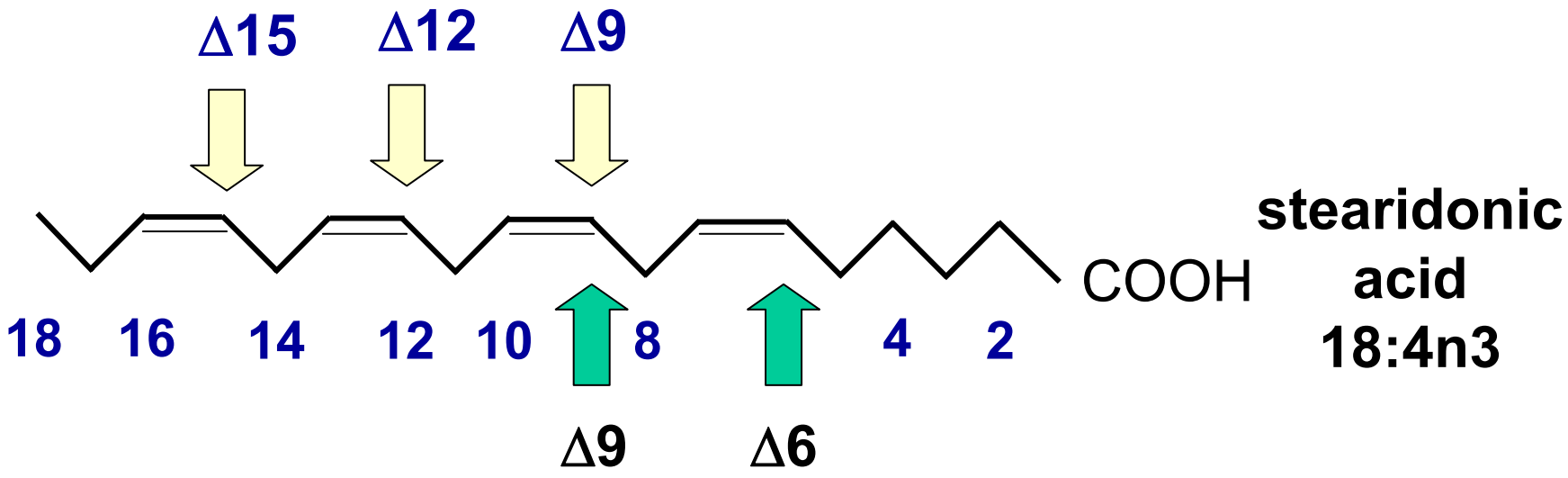
Fatty Acid Metabolism

- **Plants can also desaturate at the Δ12 and the Δ15 carbon**



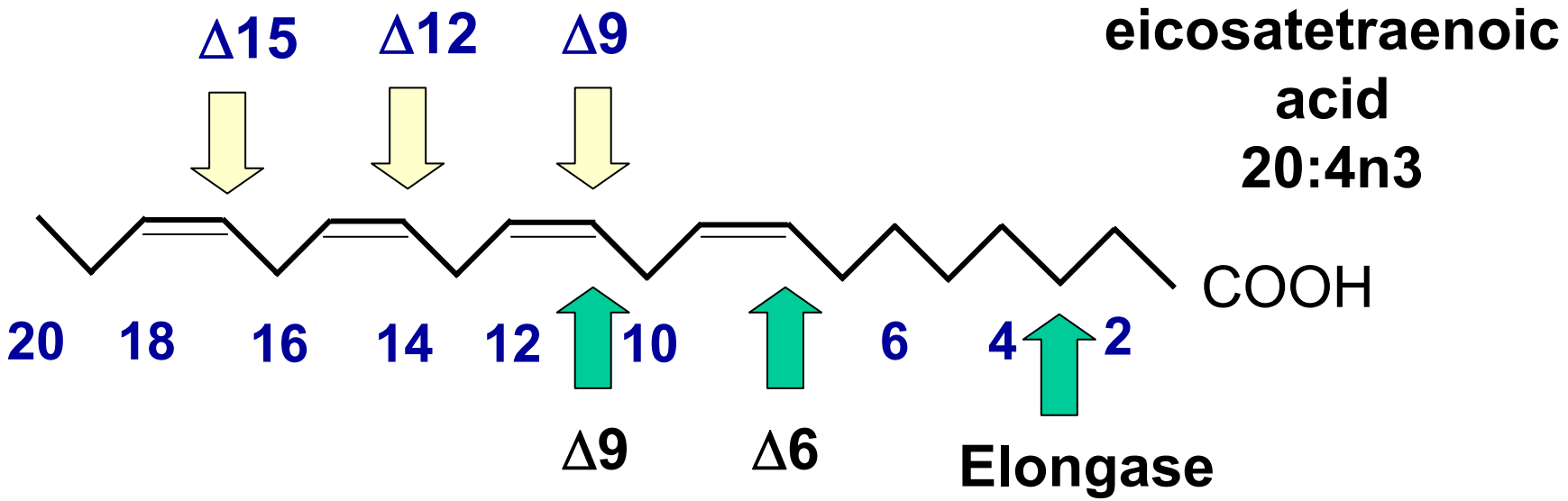
Fatty Acid Metabolism

- **Animals desaturate plant-derived poly unsaturated fatty acids (PUFAs) at the Δ6 carbon**



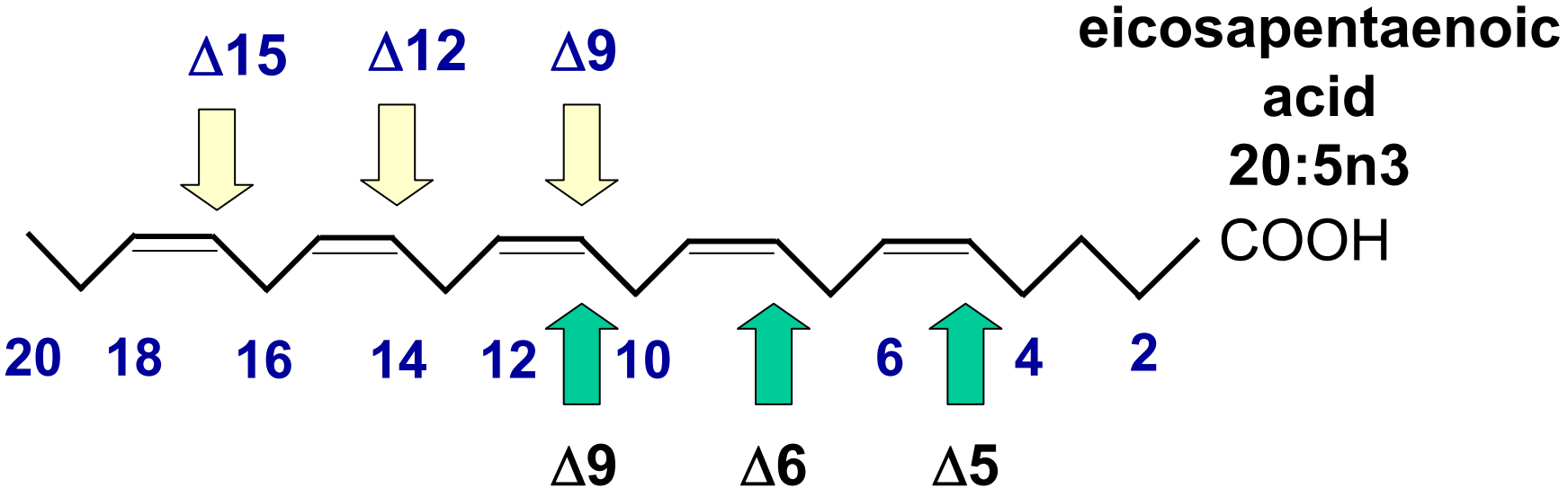
Fatty Acid Metabolism

- **To add another double bond, animals must first elongate the fatty acid**



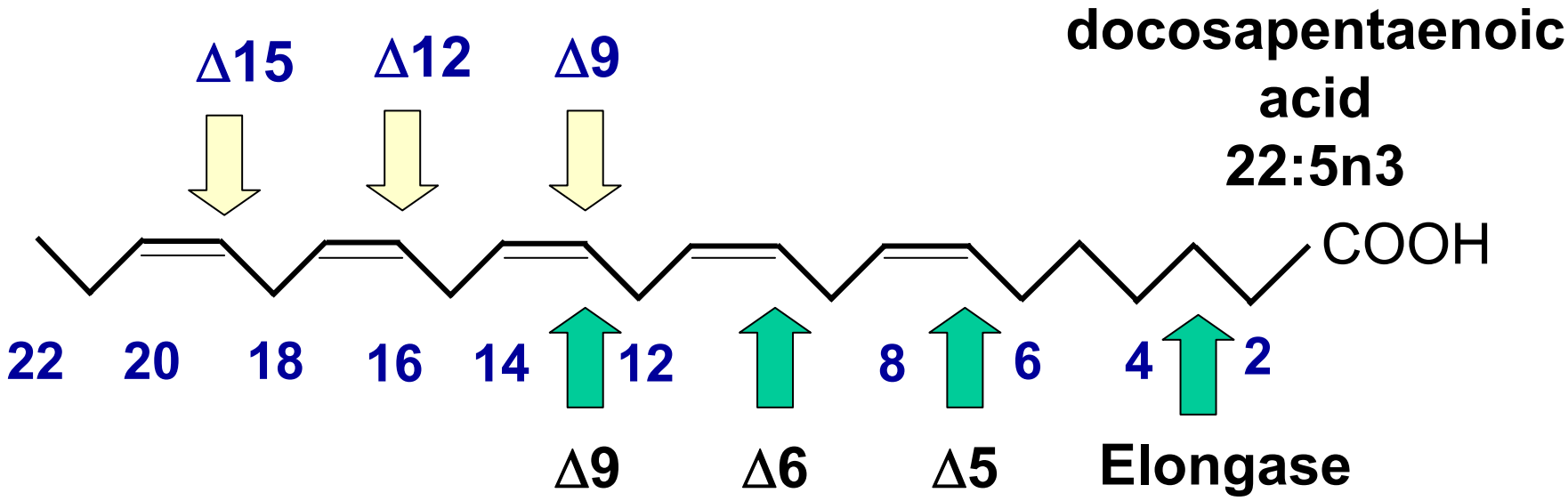
Fatty Acid Metabolism

- **Animals can then add a Δ5 double bond**



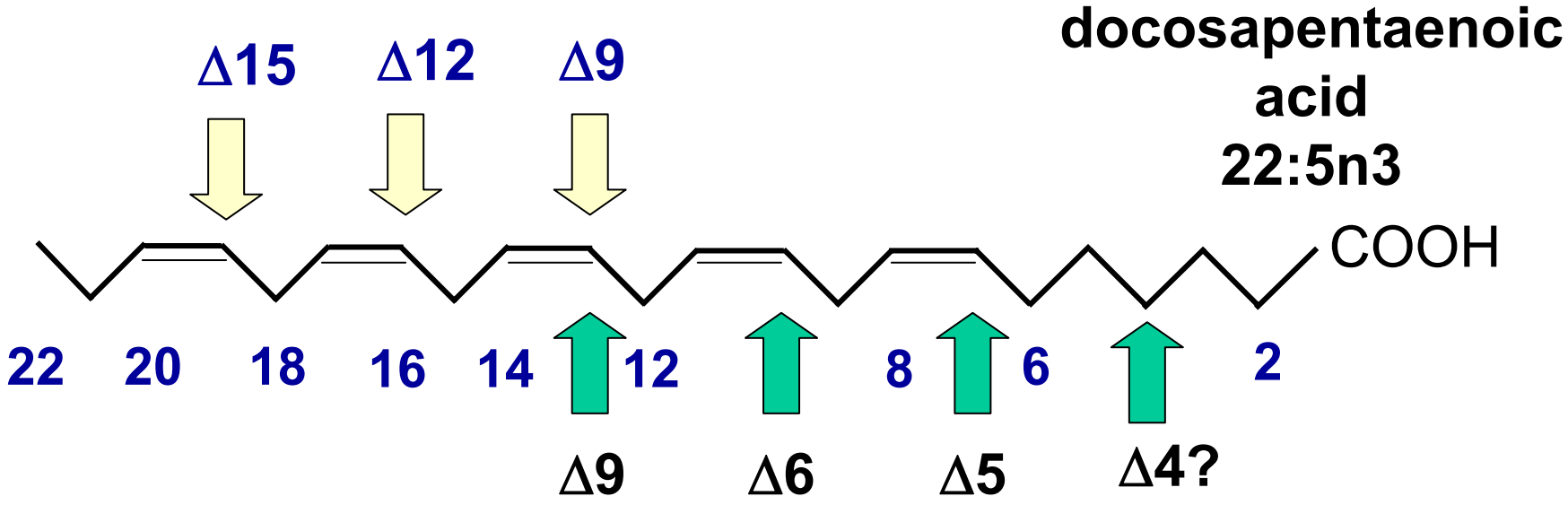
Fatty Acid Metabolism

- **To make docosahexaenoic acid (DHA, 22:6n3) animals must further elongate the acyl chain to 22 carbons**



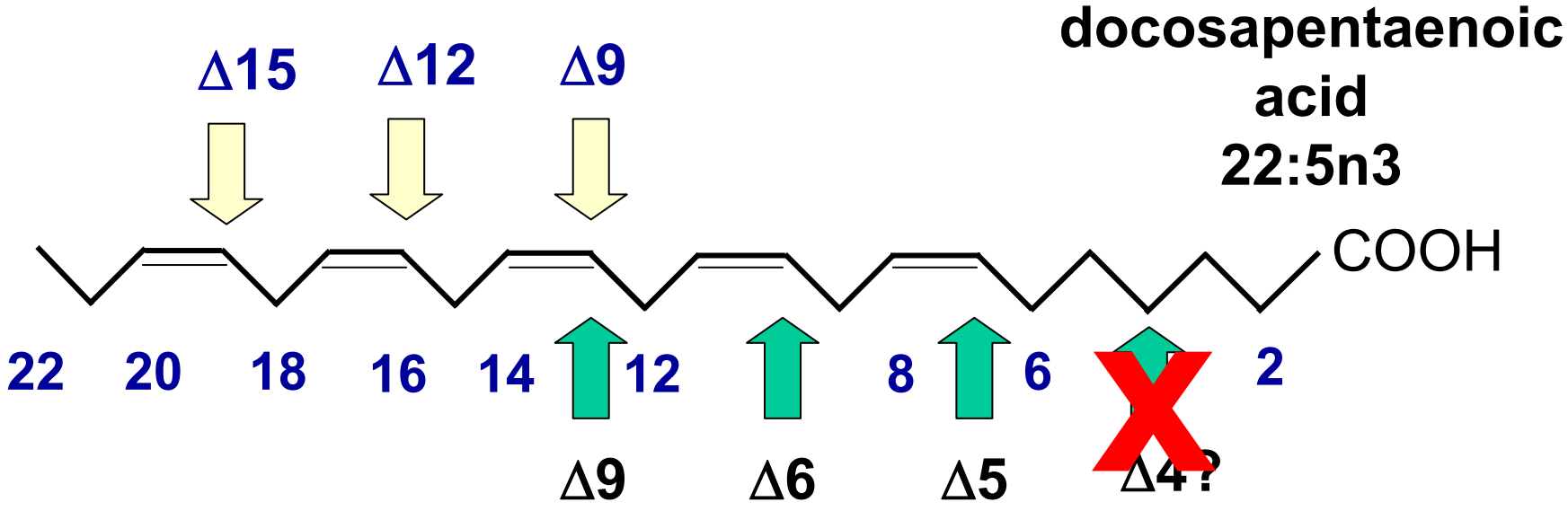
Fatty Acid Metabolism

- **Another double bond is inserted at the Δ4 position**



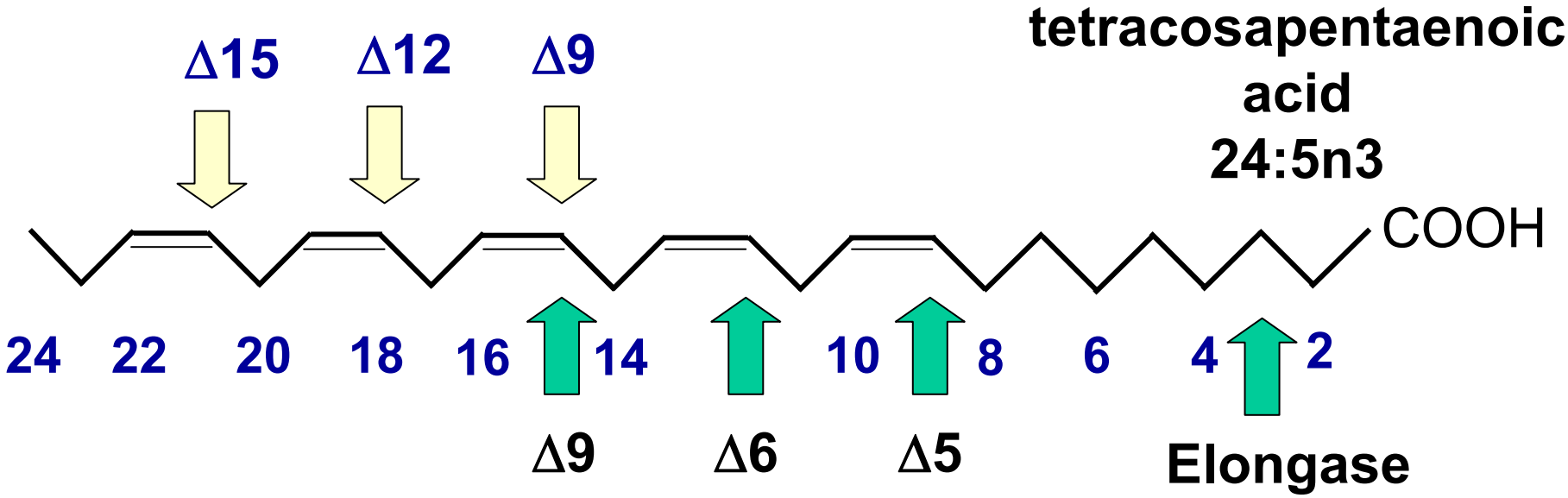
Fatty Acid Metabolism

- **BUT THERE IS NO Δ4 DESATURASE**



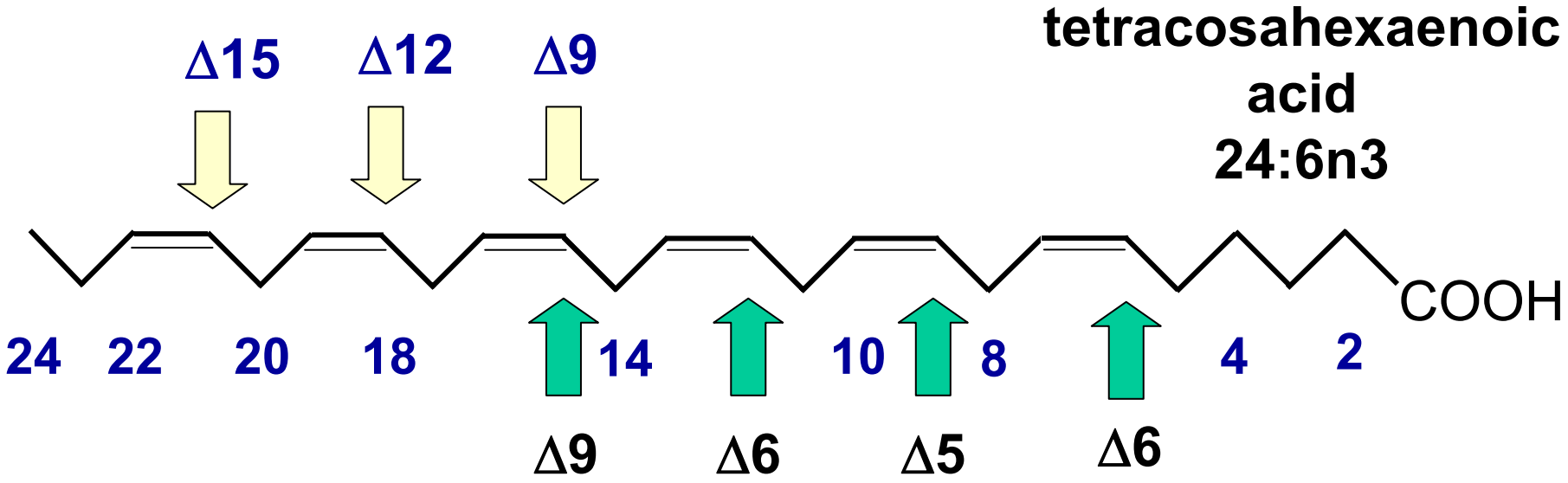
Fatty Acid Metabolism

- **To make DHA (22:6n3) the fatty acid must first be elongated again to a 24 carbon chain**



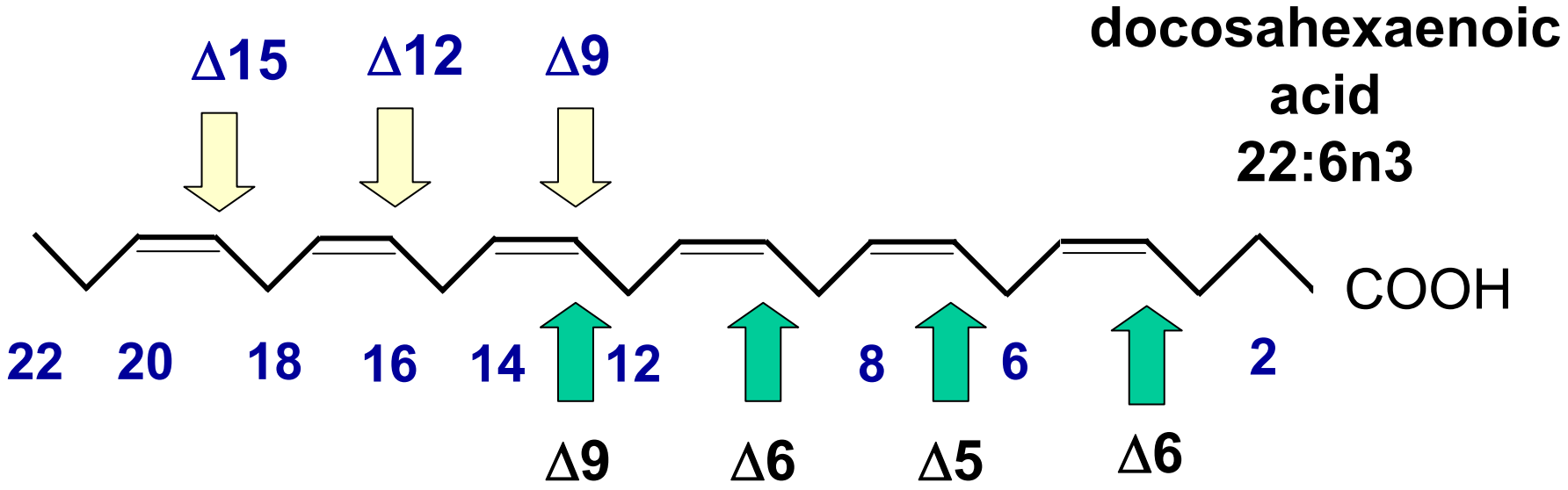
Fatty Acid Metabolism

- **Then the chain can be acted upon again by the Δ6 desaturase yielding 24:6n3**



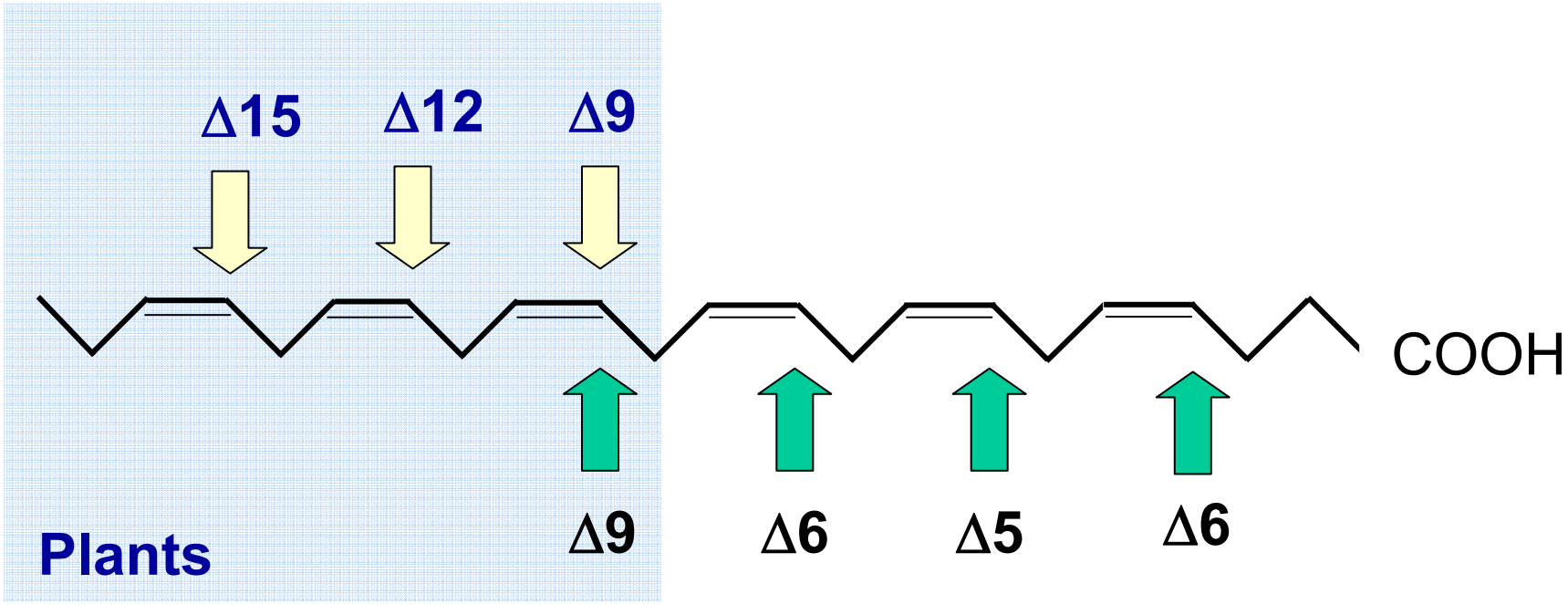
Fatty Acid Metabolism

- **The last step in DHA synthesis is a 2-carbon chain shortening by peroxisomal β-oxidation**



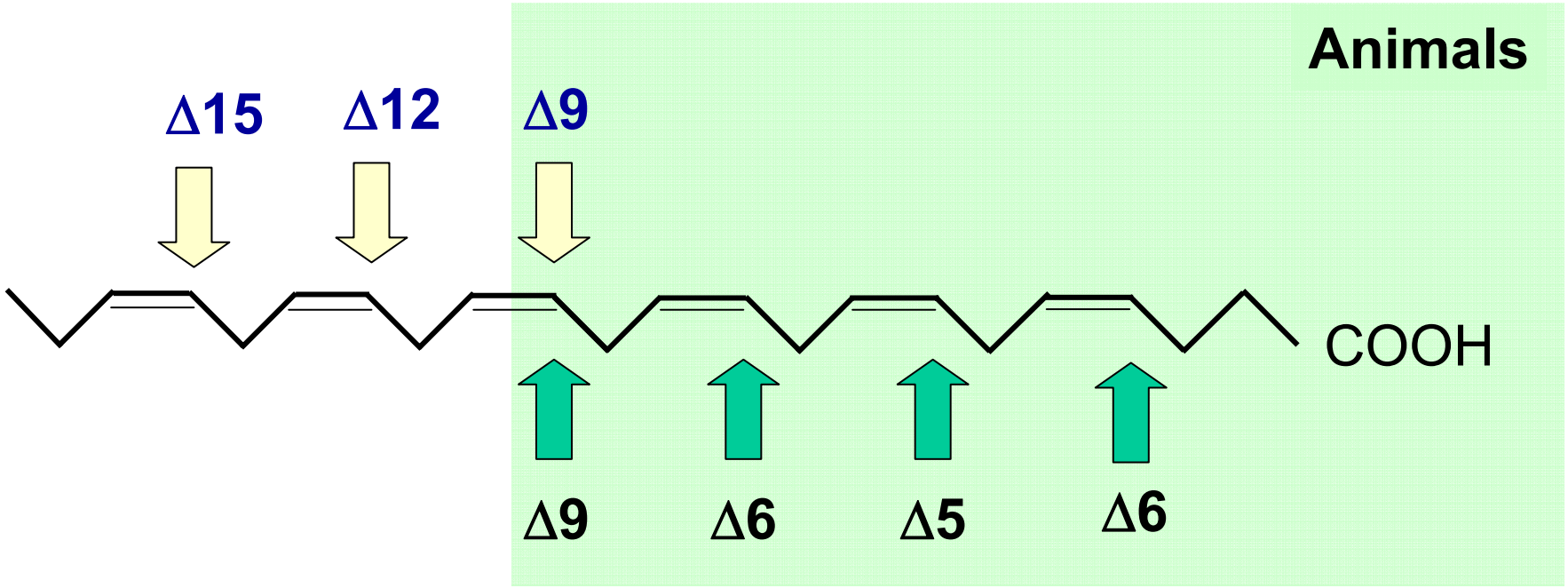
Fatty Acid Metabolism

- **Fatty acids with double bonds on the methylene side of an original Δ9 double bond (n3 and n6 bonds) are of plant origin**



Fatty Acid Metabolism

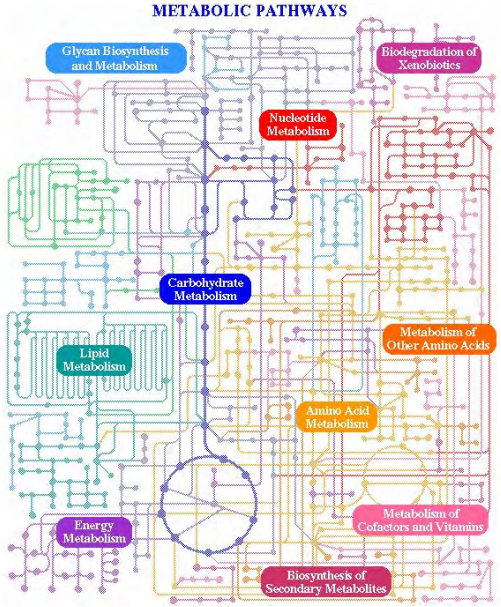
- **Animals then modify these polyunsaturated fatty acids utilizing their own distinct set of desaturases.**



Fatty Acid Metabolism

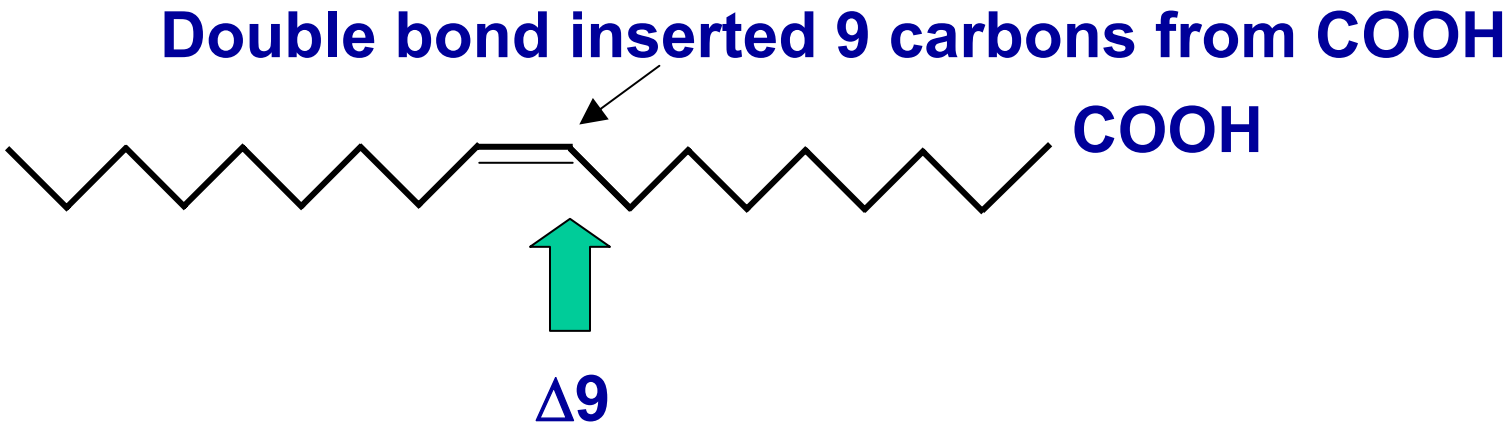
- **Why two designations?**
  - **One is useful to describe biochemical reactions**
  - **One is useful to track families of fatty acids in nutrition**

vs



Biochemical Reactions

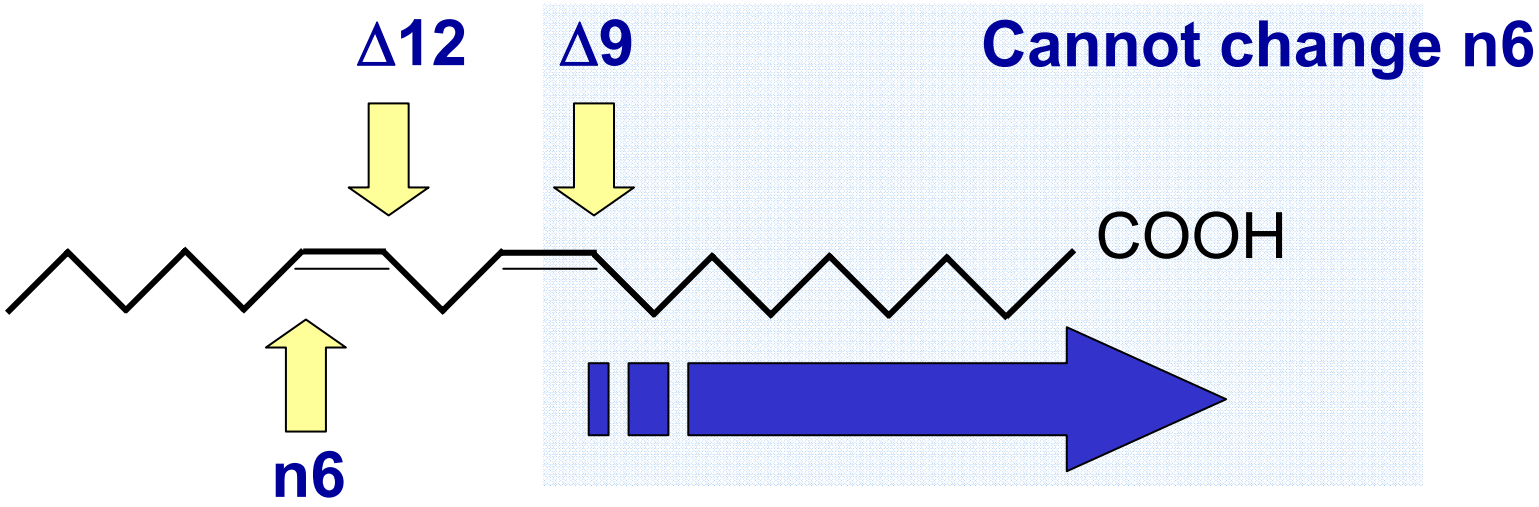
- Desaturases and elongases act from the carboxy-terminus of the fatty acid
- Therefore, the Δ-designation is useful to describe the biochemistry of fatty acid metabolism



Nutrition

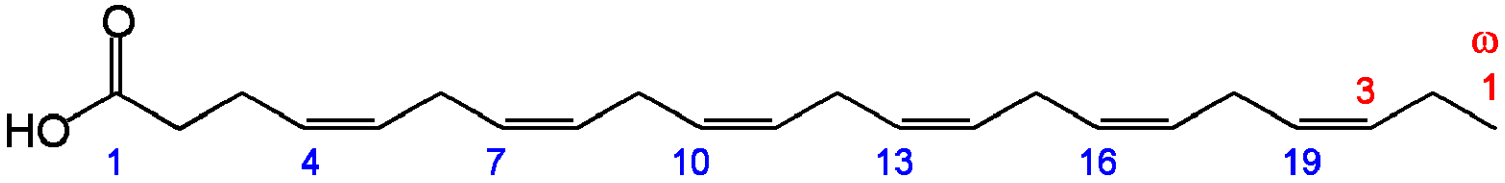
- **The n-designation is useful as it allows nutritionists to link diet with tissue fatty acid composition**

Linoleic acid (18:2n6)



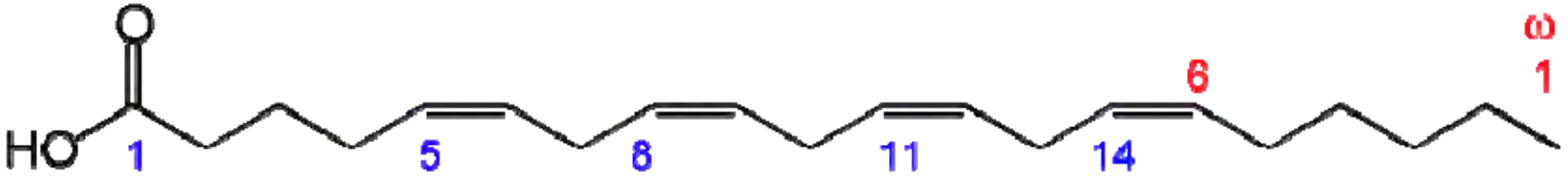
Omega fatty acids (ω)

- Nomenclature based upon position of the first double bond relative to the carbon chain terminal methyl
- Omega-3 fatty acids cannot be synthesized de novo by humans, obtained from fish



docosahexaenoic acid (DHA)

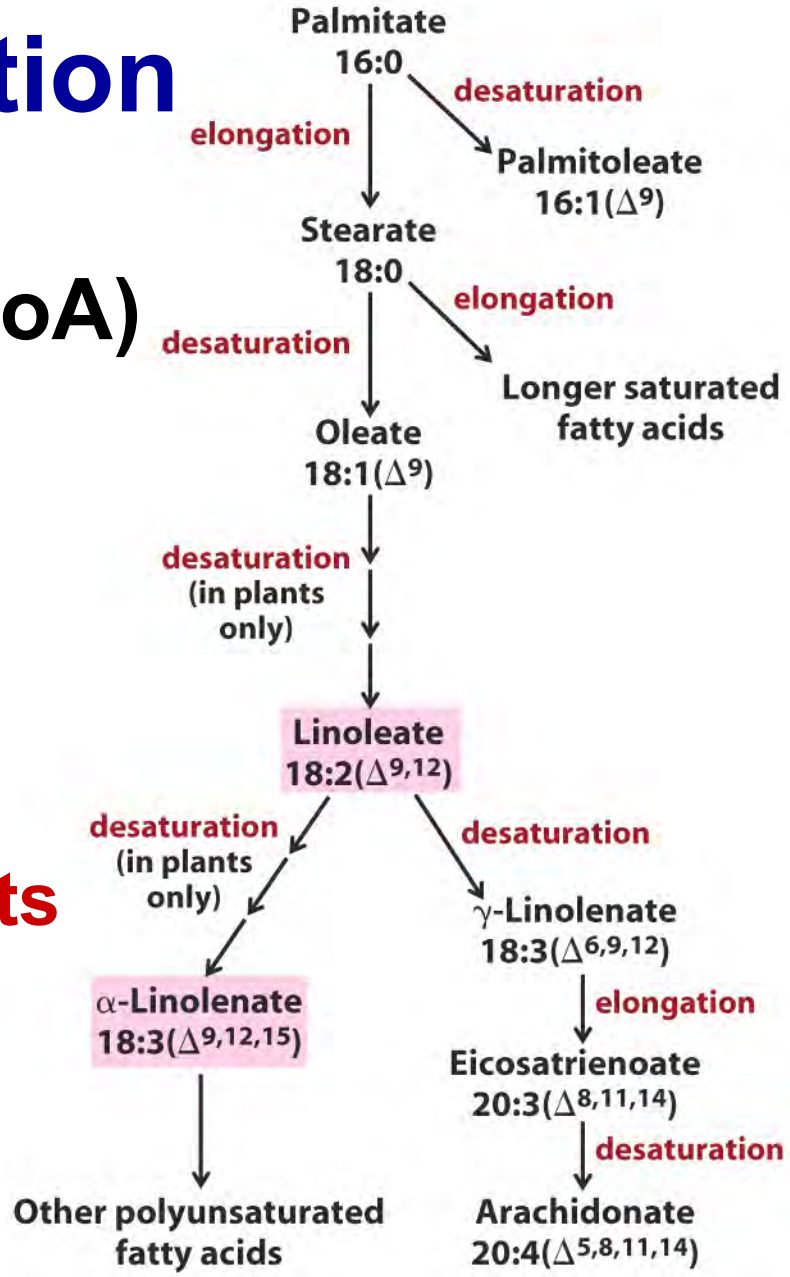
•Omega-6 fatty acids are obtained from diet (grains, etc) and can be synthesized



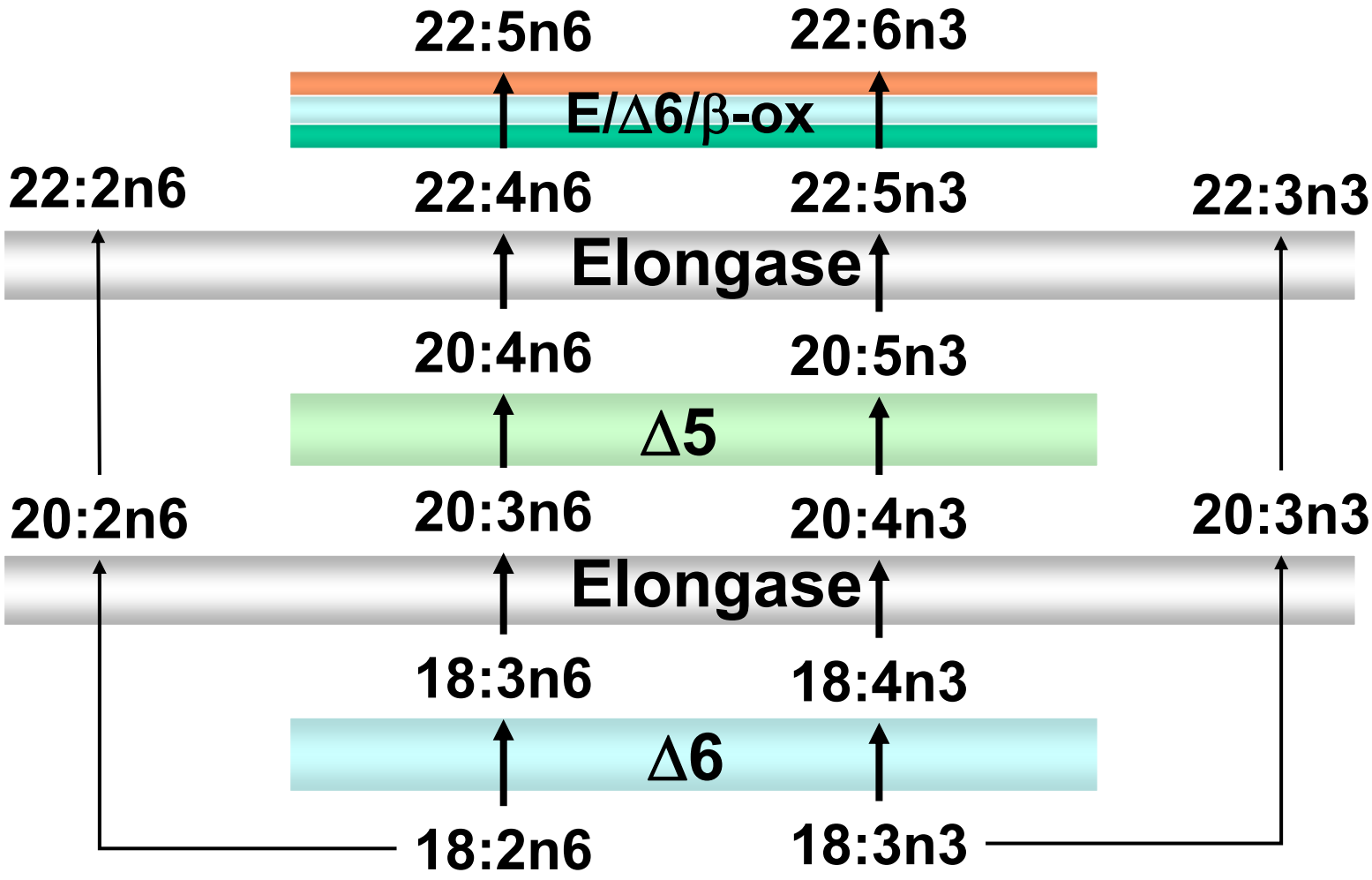
arachidonic acid (AA)

Fatty acid modification

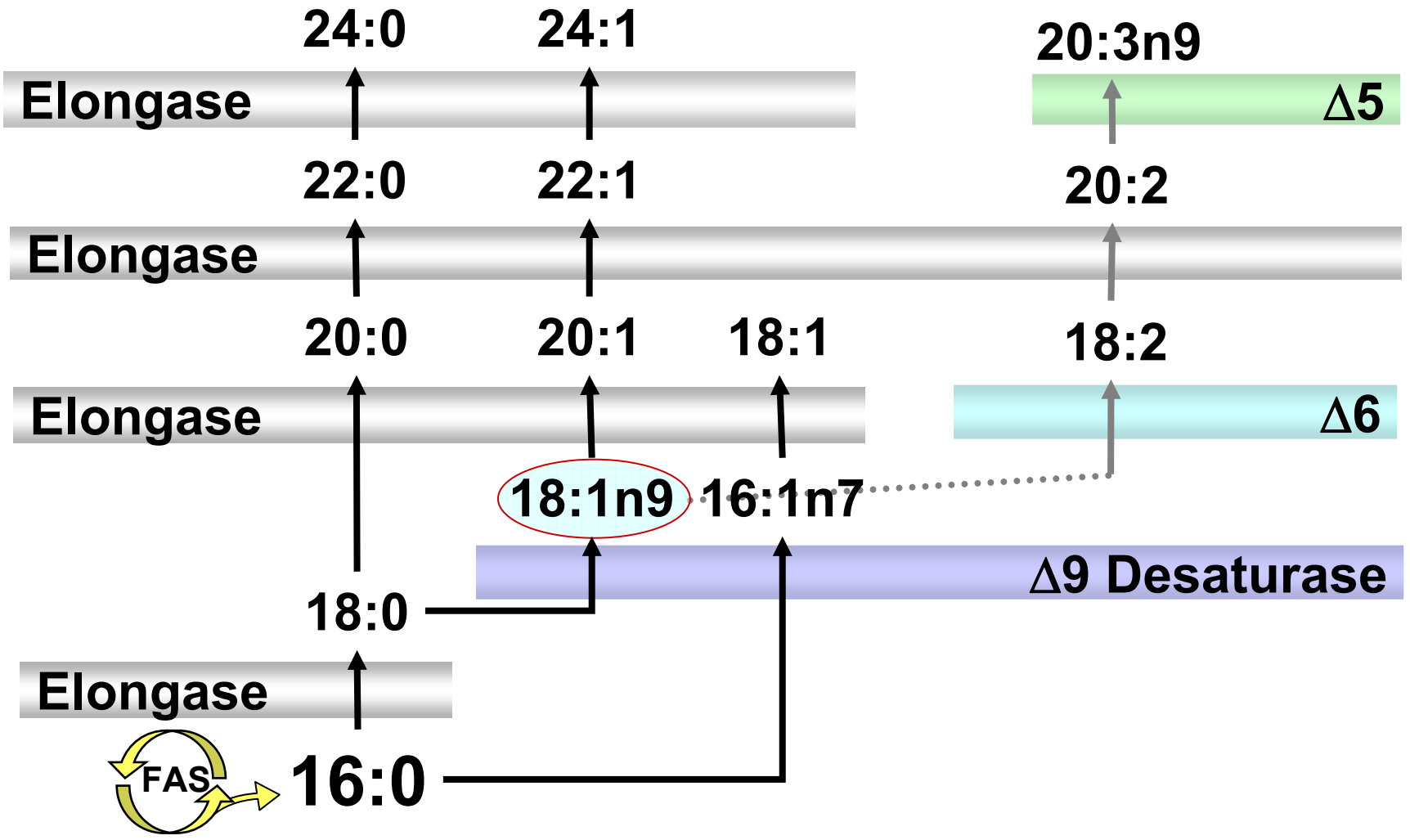
- Activated FFA (acyl-CoA)
- Elongation
- β-oxidation
- Desaturation
  - up to C9 in animals
  - >C9 occurs only in plants



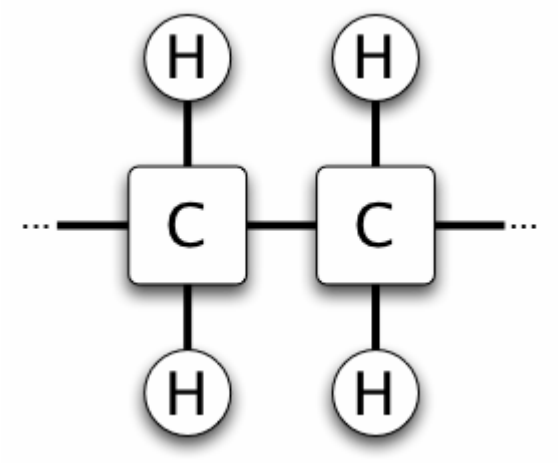
Essential FA Metabolism



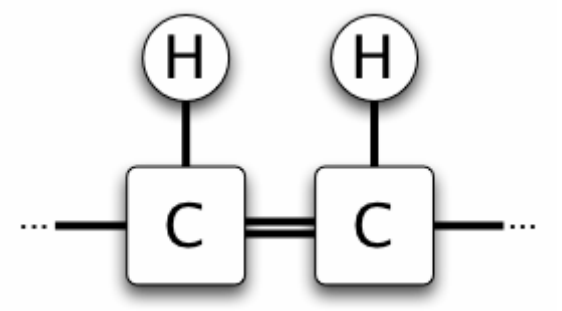
De Novo Metabolism



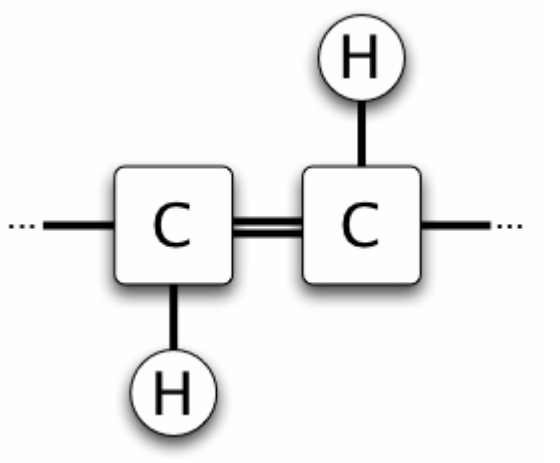
Trans-fat contains “trans” vs. “cis” bond



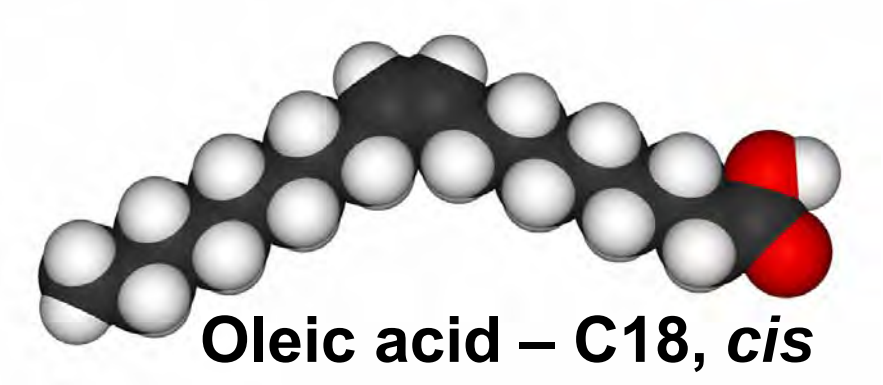
saturated



***cis* double bond**



***trans* double bond**



Oleic acid – C18, *cis*
Melting point = 13°C

Elaidic acid – C18, *trans*
Melting point = 45°C

TABLE 12.1 Some naturally occurring fatty acids in animals

Number of carbons	Number of double bonds	Common name	Systematic name	Formula
12	0	Laurate	*n*-Dodecanoate	$CH_3(CH_2)_{10}COO^-$
14	0	Myristate	*n*-Tetradecanoate	$CH_3(CH_2)_{12}COO^-$
16	0	Palmitate	*n*-Hexadecanoate	$CH_3(CH_2)_{14}COO^-$
18	0	Stearate	*n*-Octadecanoate	$CH_3(CH_2)_{16}COO^-$
20	0	Arachidate	*n*-Eicosanoate	$CH_3(CH_2)_{18}COO^-$
22	0	Behenate	*n*-Docosanoate	$CH_3(CH_2)_{20}COO^-$
24	0	Lignocerate	*n*-Tetracosanoate	$CH_3(CH_2)_{22}COO^-$
16	1	Palmitoleate	*cis*-Δ^9-Hexadecenoate	$CH_3(CH_2)_5CH{=}CH(CH_2)_7COO^-$
18	1	Oleate	*cis*-Δ^9-Octadecenoate	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COO^-$
18	2	Linoleate	*cis,cis*-Δ^9, Δ^{12}-Octadecadienoate	$CH_3(CH_2)_4(CH{=}CHCH_2)_2(CH)_6COO^-$
18	3	Linolenate	all-*cis*-$\Delta^9,\Delta^{12},\Delta^{15}$-Octadecatrienoate	$CH_3CH_2(CH{=}CHCH_2)_3(CH_2)_6COO^-$
20	4	Arachidonate	all-*cis* $\Delta^5,\Delta^8,\Delta^{11},-\Delta^{14}$ Eicosatetraenoate	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2COO^-$

Ex) Linoleate, linoleic acid **18:2n6**

cis,cis-Δ^9,Δ^{12} –octadecatrienoate

an **ω-6** fatty acid

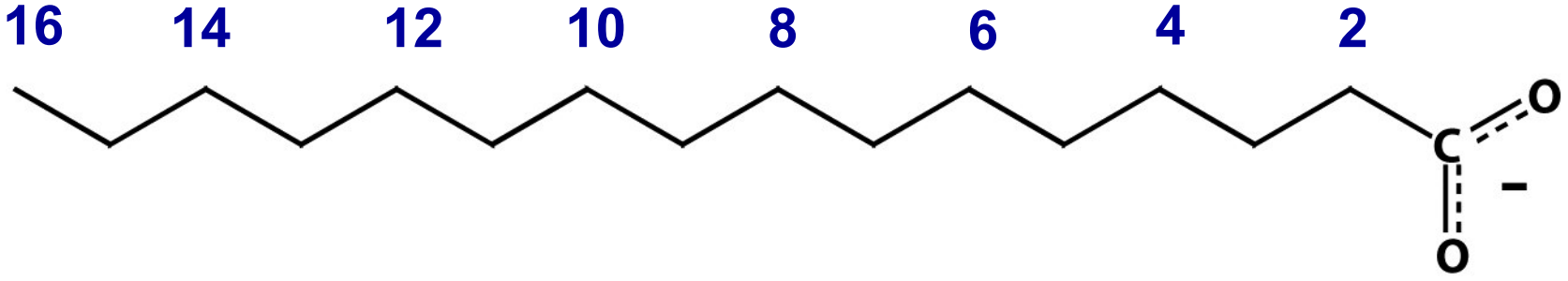
Fatty acid biosynthesis

- **Where?** In the cytoplasm in: liver, adipose and mammary glands
- **How?** Stepwise incorporation of 2 carbon atoms from Acetyl-CoA
- **Cost?** both ATP and NADPH

Overall equation for synthesis of 16:0 (palmitate, hexadecanoate)

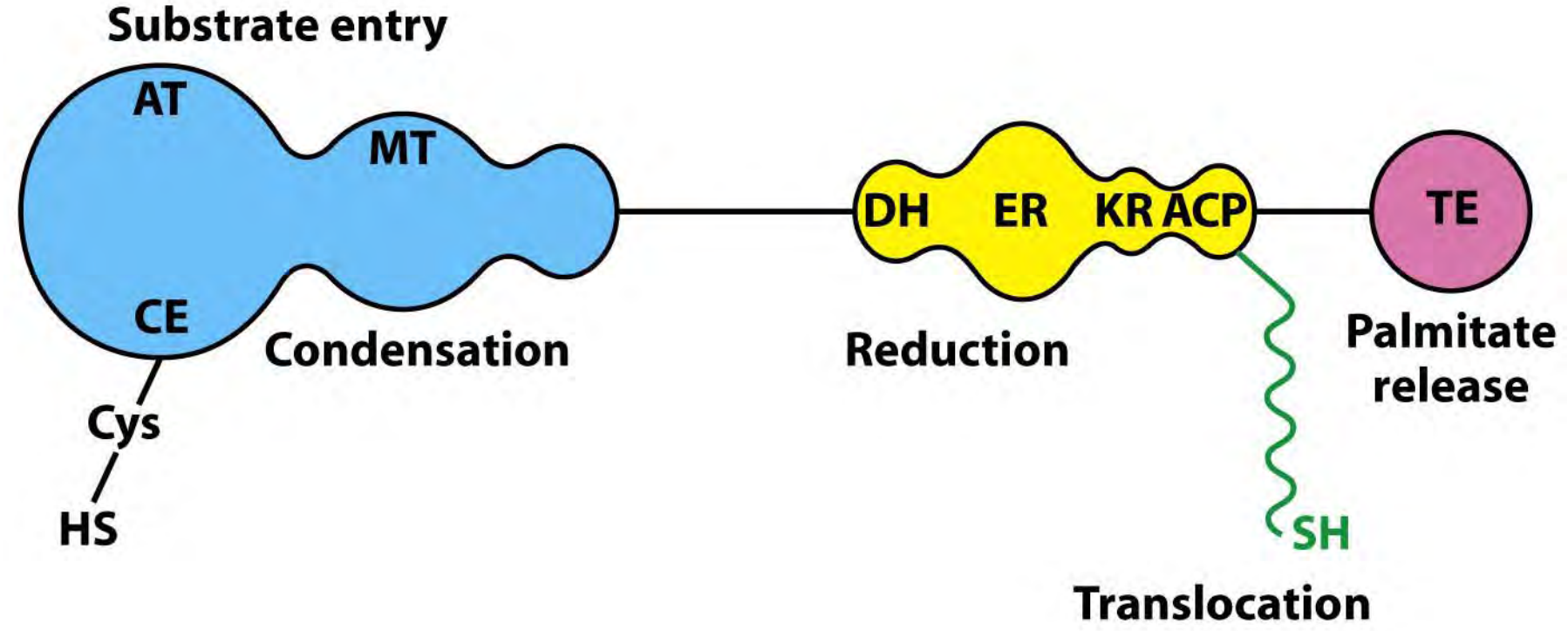
$$8\ \text{Ac-CoA} + 7\text{ATP} + 14\ \text{NADPH} + 14\text{H}^{+} \longrightarrow$$

$$16{:}0 + 8\ \text{CoA} + 7\text{ADP} + 7\text{P}_{i} + 14\text{NADP}^{+} + 6\text{H}_{2}\text{O}$$



Palmitate

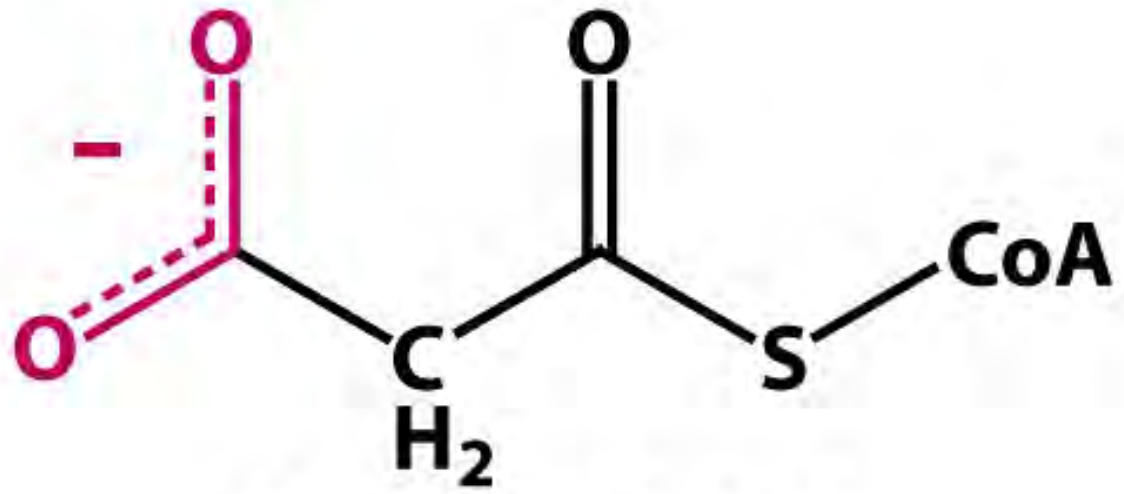
Fatty acid synthase system



Domain 1:
AT acetyl transferase
MT malonyl transferase
CE condensing enzyme
(=β-ketoacyl synthase, KS)

Domain 2:
DH dehydratase
ER enoyl reductase
KR β-ketoacyl reductase
ACP acyl carrier protein

Domain 3:
TE thioesterase

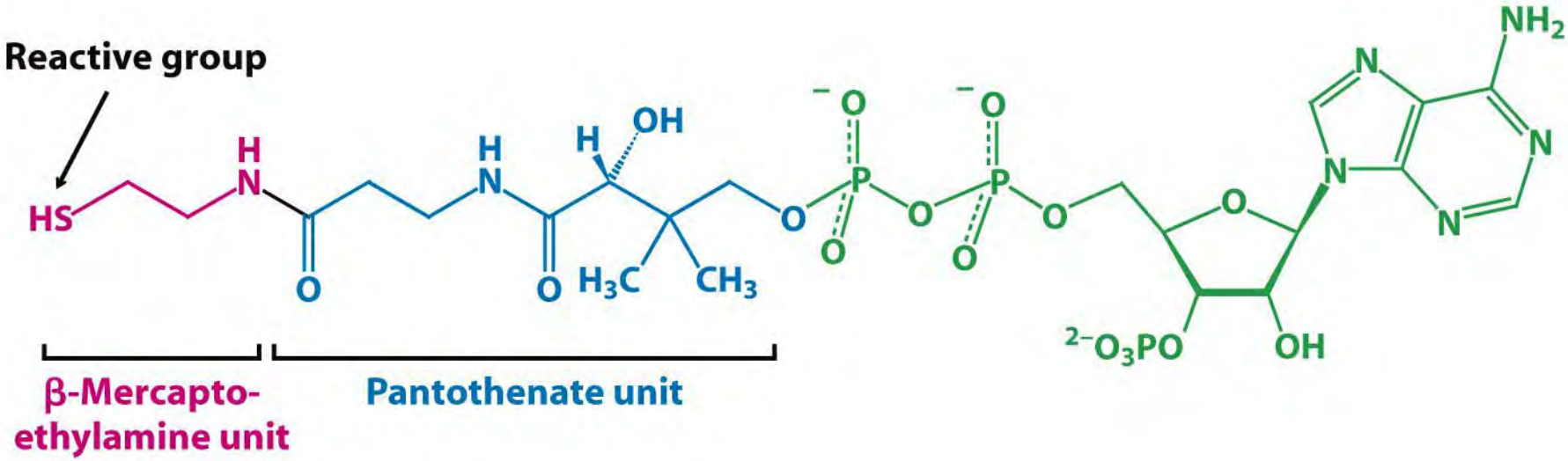


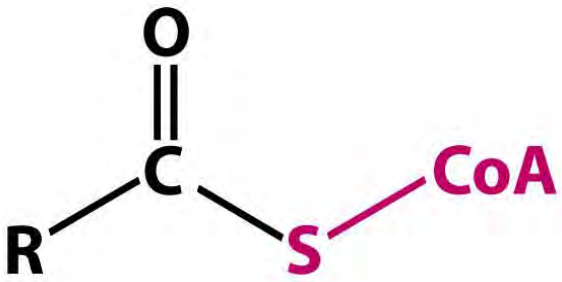
Malonyl CoA

”activated 2-carbon donor”

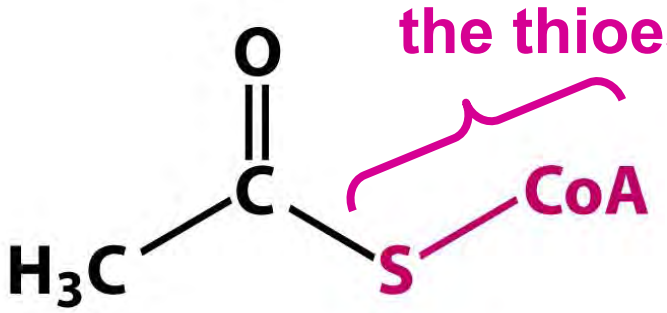
committed step in FA synthesis

Coenzyme A (CoA-SH)

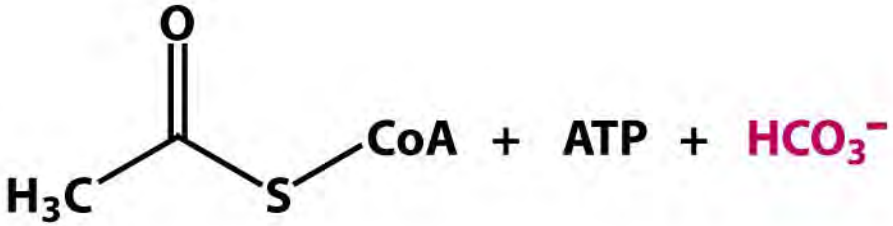




Acyl CoA

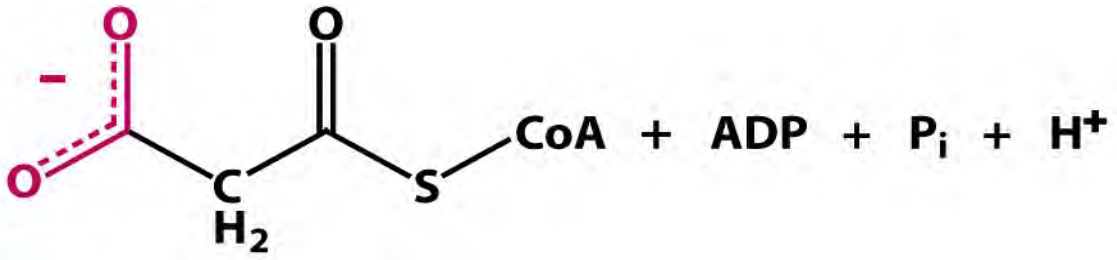


Acetyl CoA



Acetyl-CoA

Acetyl-CoA-carboxylase (ACC)
the committed step in FA synthesis



Malonyl-CoA

Elongation phase of FA synthesis

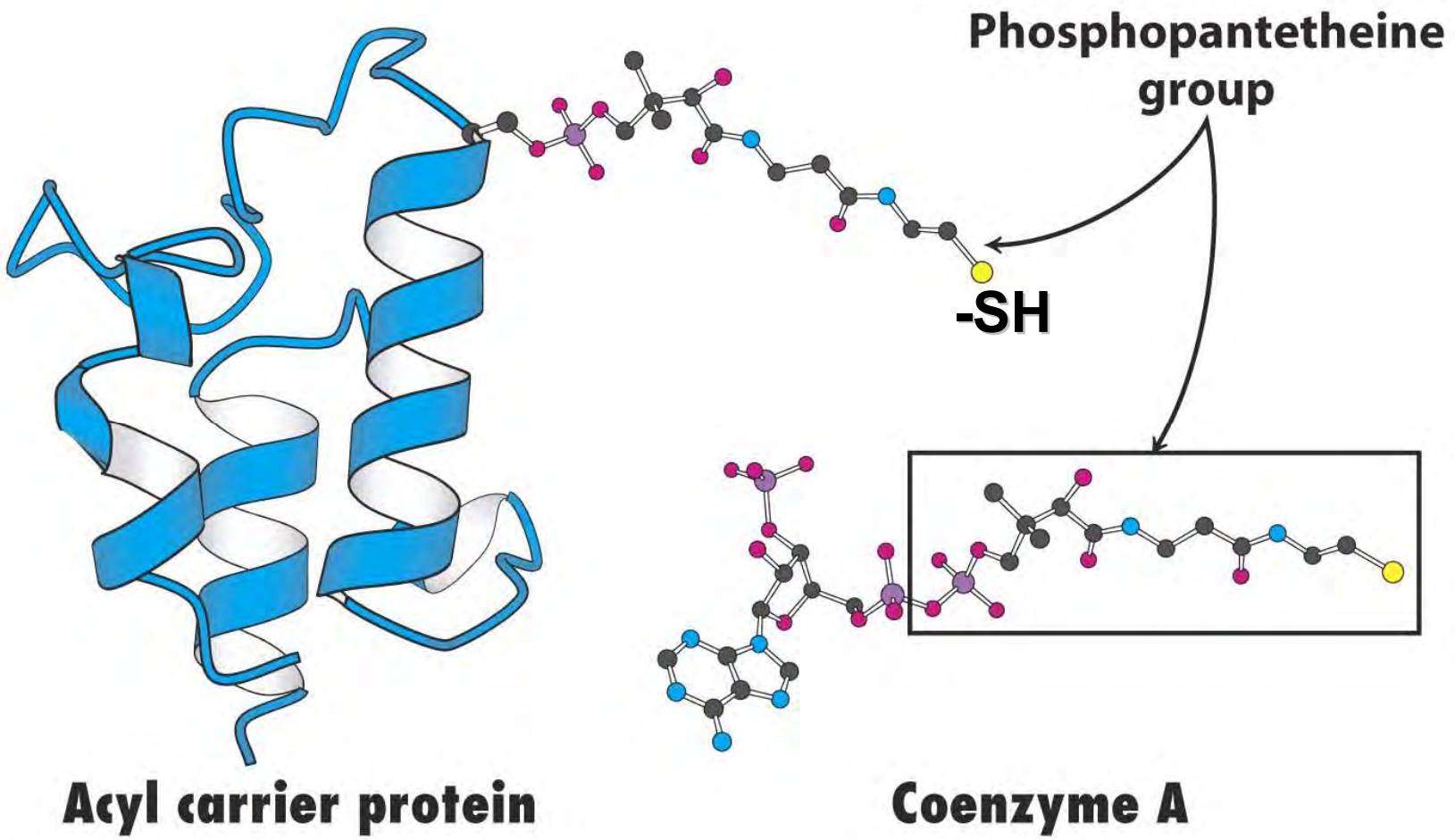
Acetyl transacylase

Acetyl CoA + ACP ↔ acetyl ACP + CoA

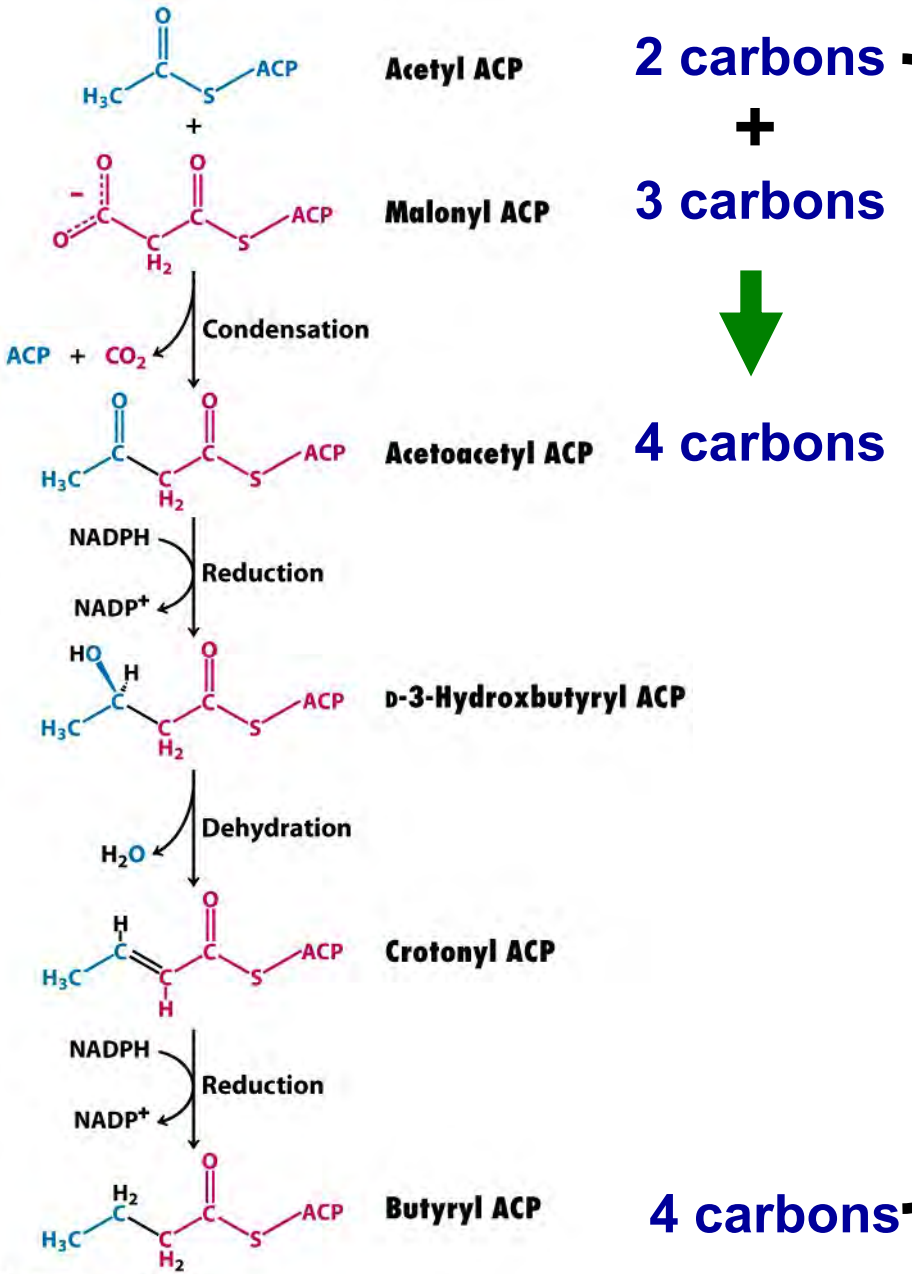
Malonyl transacylase

Malonyl CoA + ACP ↔ malonyl ACP + CoA

ACP – acyl carrier protein

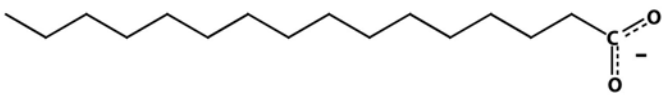


single polypeptide chain of 77 residues

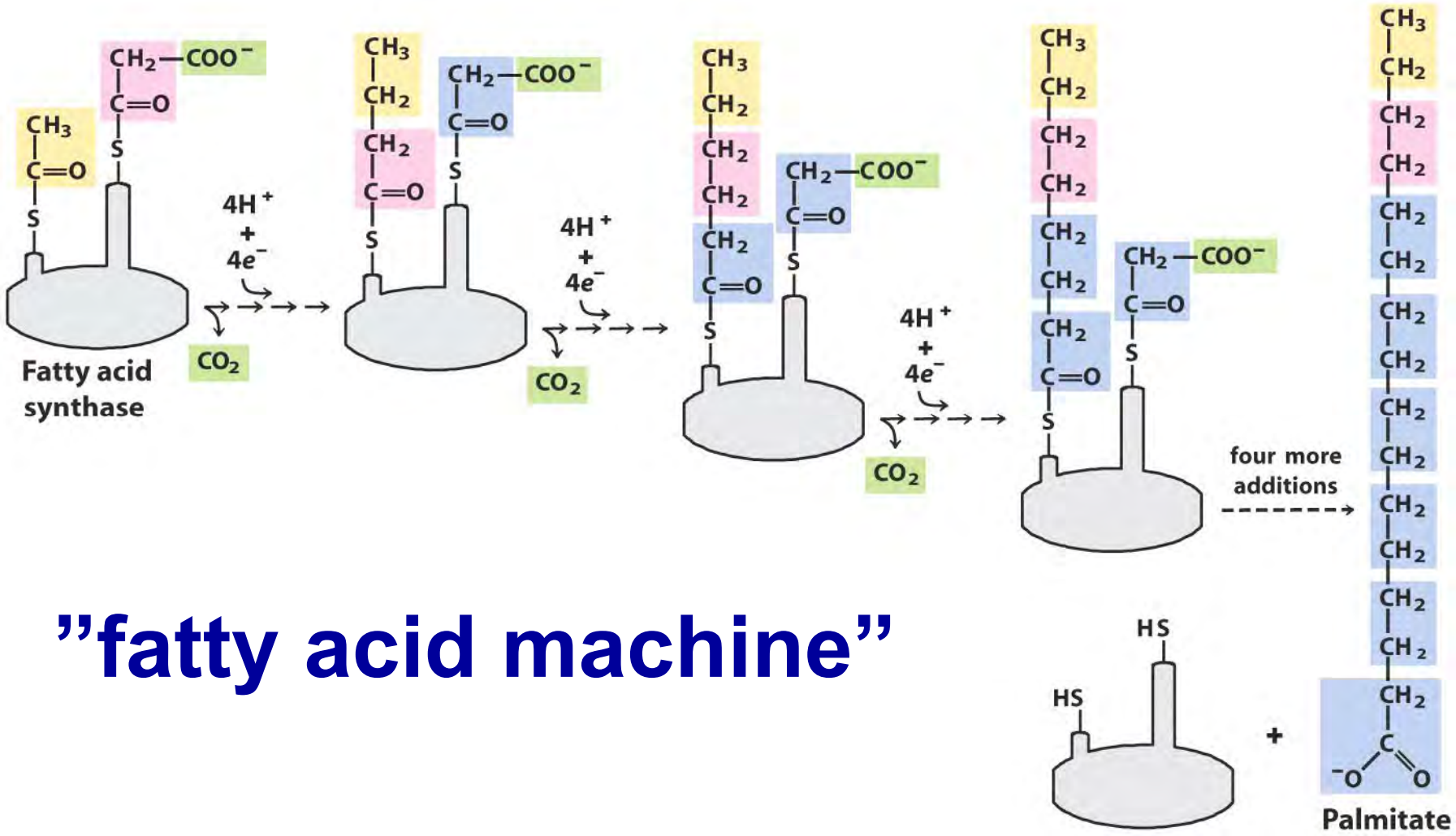


Fatty acid synthase reaction sequence

7 rounds gives:
16:0, palmitate



Palmitate



”fatty acid machine”

AT = acetyl transferase

MT = malonyl transferase

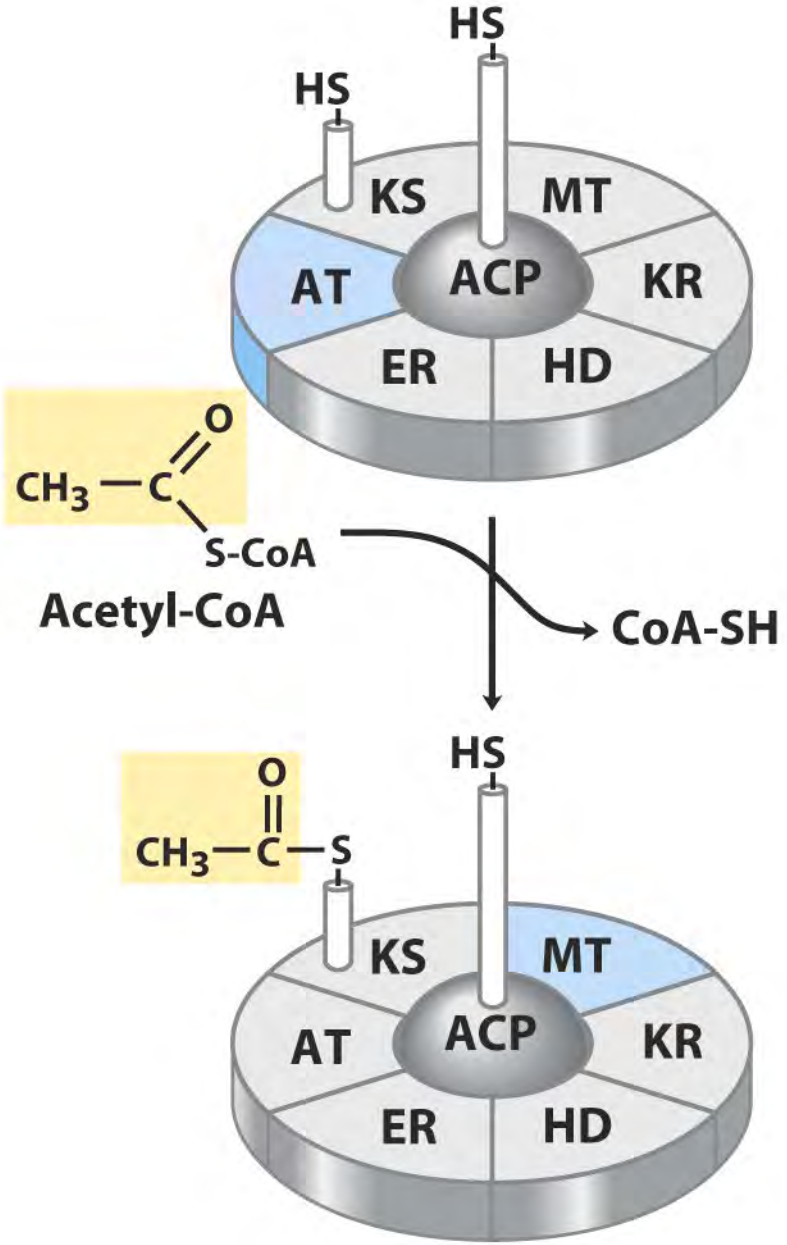
KS = β-ketoacyl synthase,
(CE condensing enzyme)

HD = dehydratase

ER = enoyl reductase

KR = β-ketoacyl reductase

ACP = acyl carrier protein



AT = acetyl transferase

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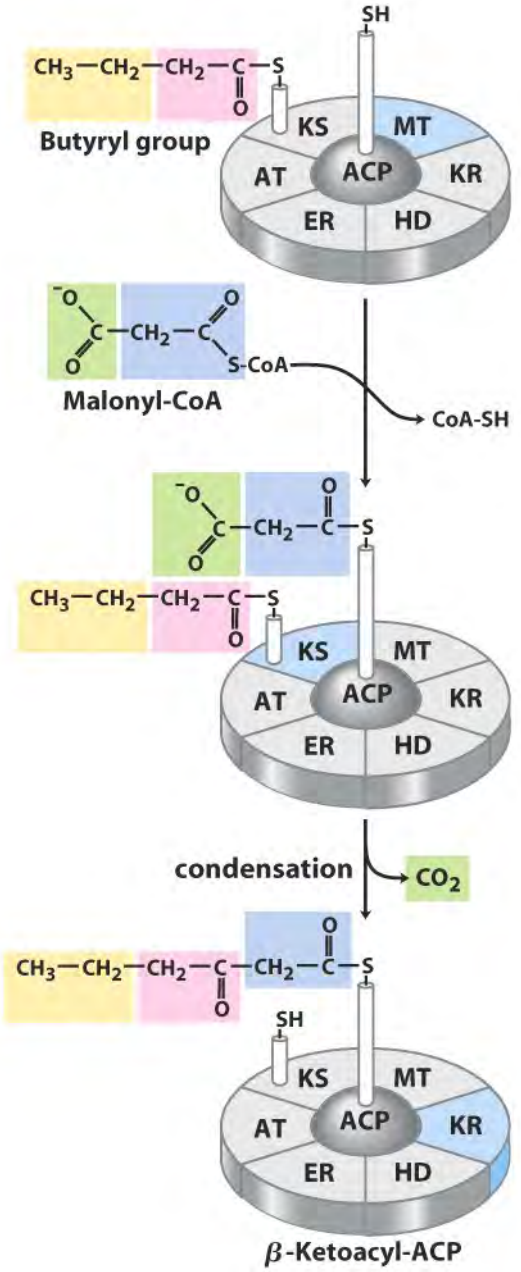
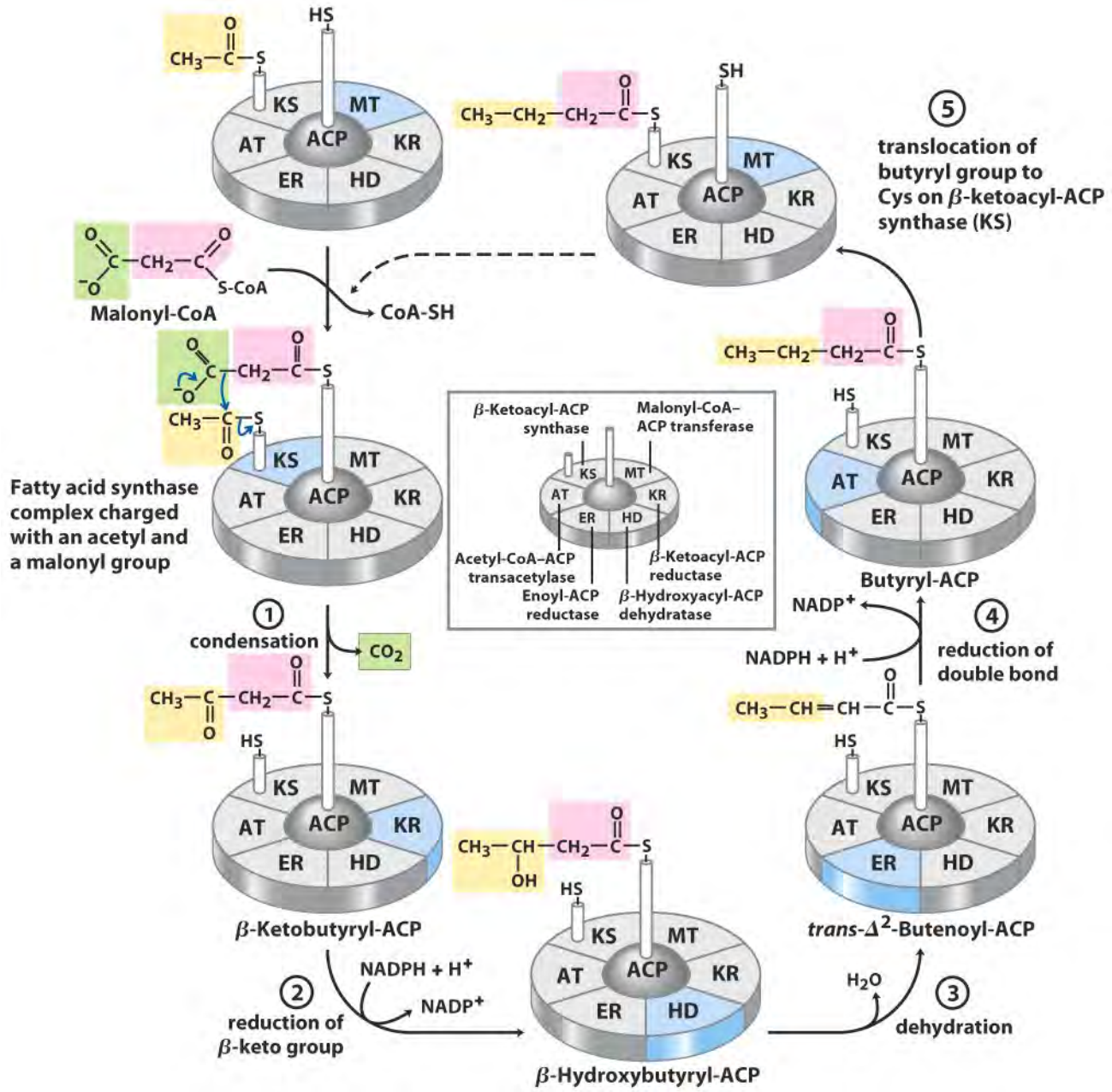
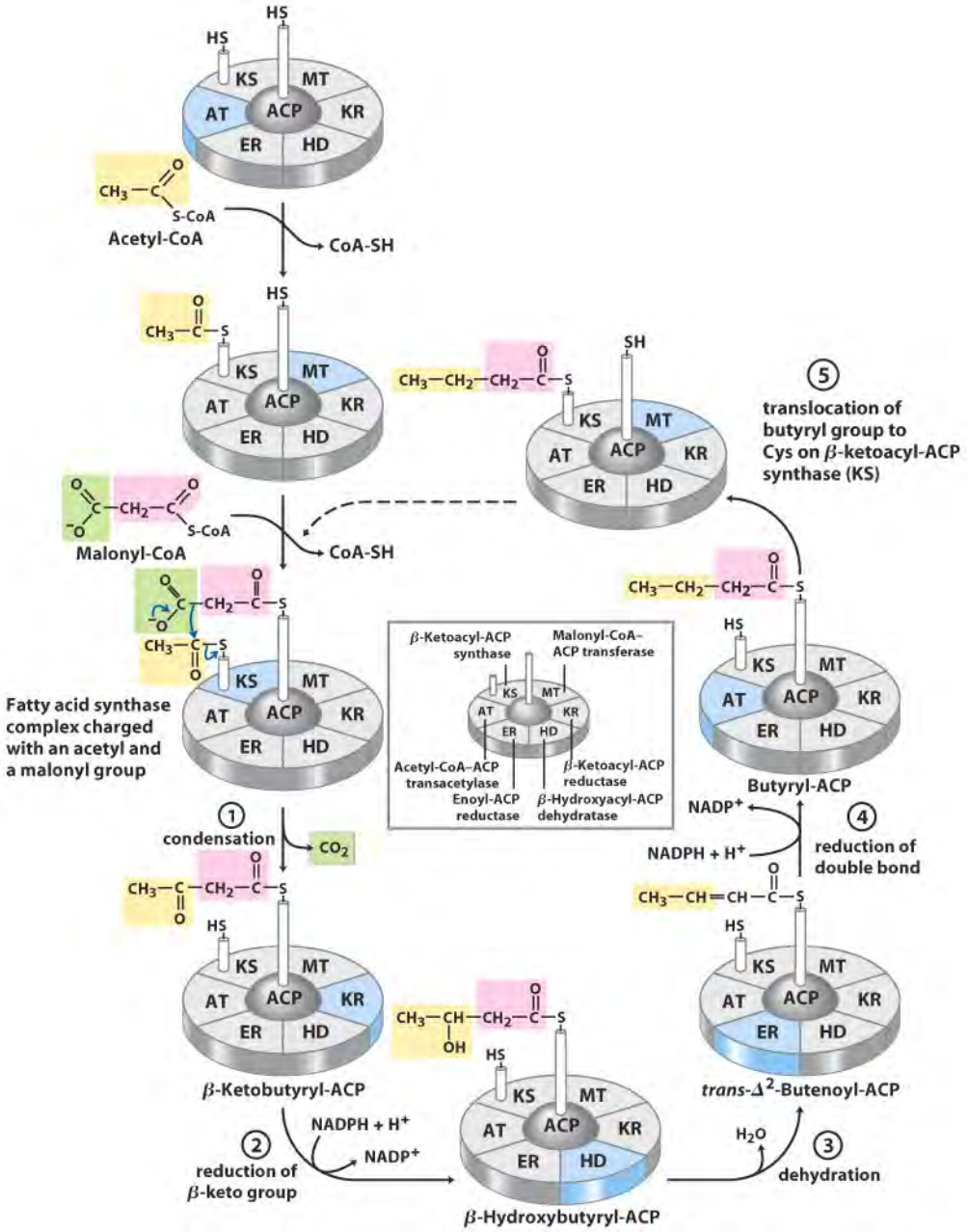



HS
KS
MT
AT
ACP
KR
ER
HD
Malonyl-CoA
S-CoA
CoA-SH
Fatty acid synthase complex charged with an acetyl and a malonyl group
β-Ketoacyl-ACP synthase
Malonyl-CoA–ACP transferase
Acetyl-CoA–ACP transacetylase
β-Ketoacyl-ACP reductase
Enoyl-ACP reductase
β-Hydroxyacyl-ACP dehydratase
1 condensation
CO2
β-Ketobutyryl-ACP
2 reduction of β-keto group
NADPH + H+
NADP+
β-Hydroxybutyryl-ACP
3 dehydration
H2O
trans-Δ2-Butenoyl-ACP
4 reduction of double bond
Butyryl-ACP
5 translocation of butyryl group to Cys on β-ketoacyl-ACP synthase (KS)
SH

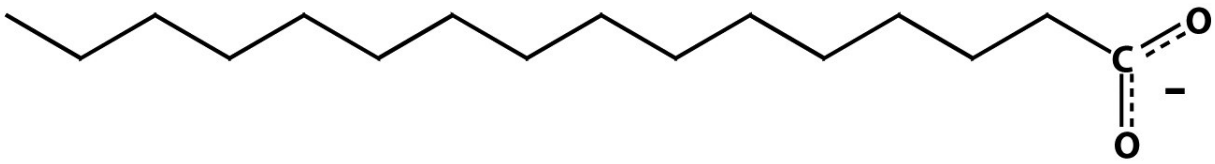

HS
KS
MT
AT
ACP
KR
ER
HD
Acetyl-CoA
CoA-SH
Malonyl-CoA
Fatty acid synthase complex charged with an acetyl and a malonyl group
β-Ketoacyl-ACP synthase
Malonyl-CoA–ACP transferase
Acetyl-CoA–ACP transacetylase
Enoyl-ACP reductase
β-Ketoacyl-ACP reductase
β-Hydroxyacyl-ACP dehydratase
1 condensation
CO2
β-Ketobutyryl-ACP
2 reduction of β-keto group
NADPH + H+
NADP+
β-Hydroxybutyryl-ACP
3 dehydration
H2O
trans-Δ2-Butenoyl-ACP
4 reduction of double bond
Butyryl-ACP
5 translocation of butyryl group to Cys on β-ketoacyl-ACP synthase (KS)
SH

Ex) The complete reaction for synthesis of 16:0

= 1 Ac-CoA + 7 Mal-CoA

$$8\ \text{Ac-CoA} + 7\text{ATP} + 14\ \text{NADPH} + 14\text{H}^{+} \longrightarrow$$

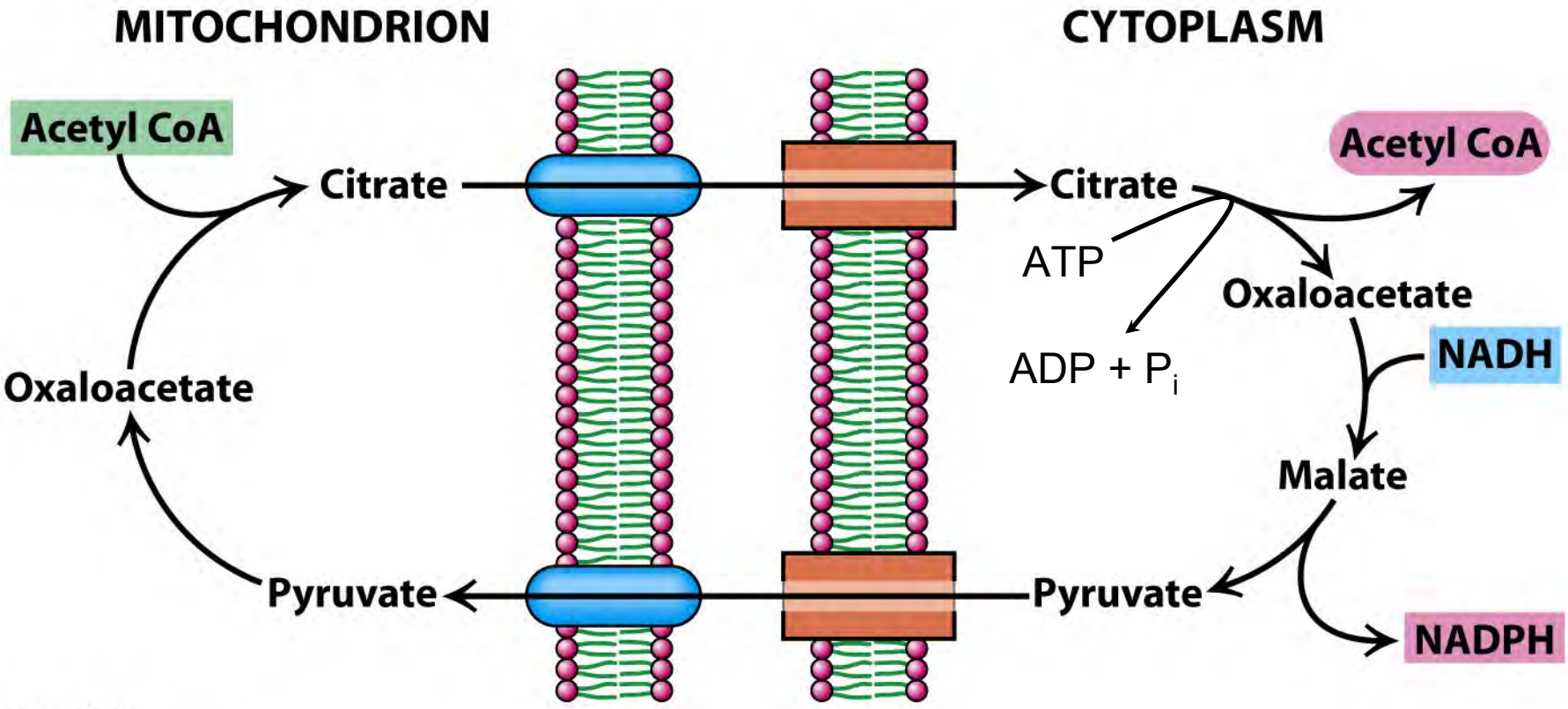
$$16{:}0 + 8\ \text{CoA} + 7\text{ADP} + 7\text{P}_i + 14\text{NADP}^{+} + 6\text{H}_2\text{O}$$



Palmitate
(ionized form of palmitic acid)

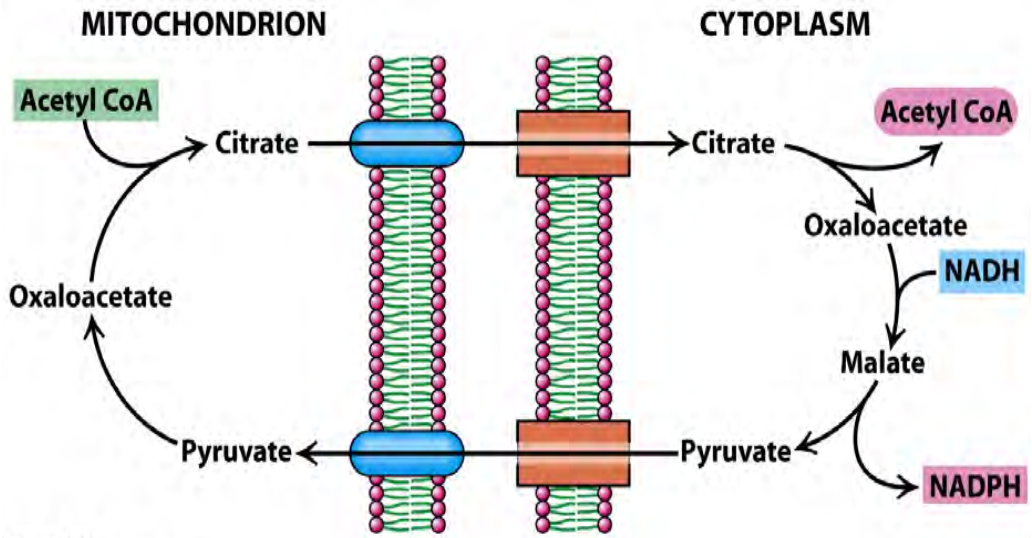
Transfer of Acetyl-CoA to the cytosol

→**FA synthesized in cytoplasm, acetyl CoA formed from pyruvate in mitochondria**

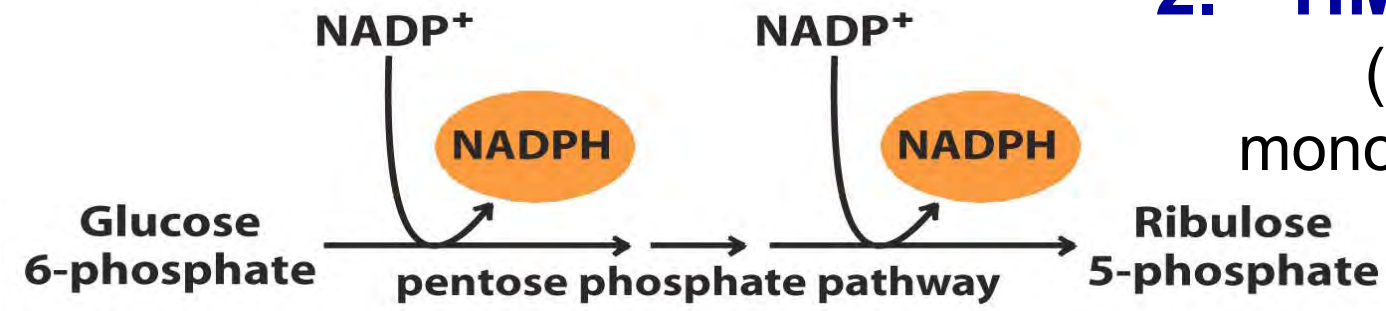


Citrate + ATP + CoA +H_2O ⟶ acetyl CoA + ADP + P_i + oxaloacetate

2 Ways to Generate NADPH



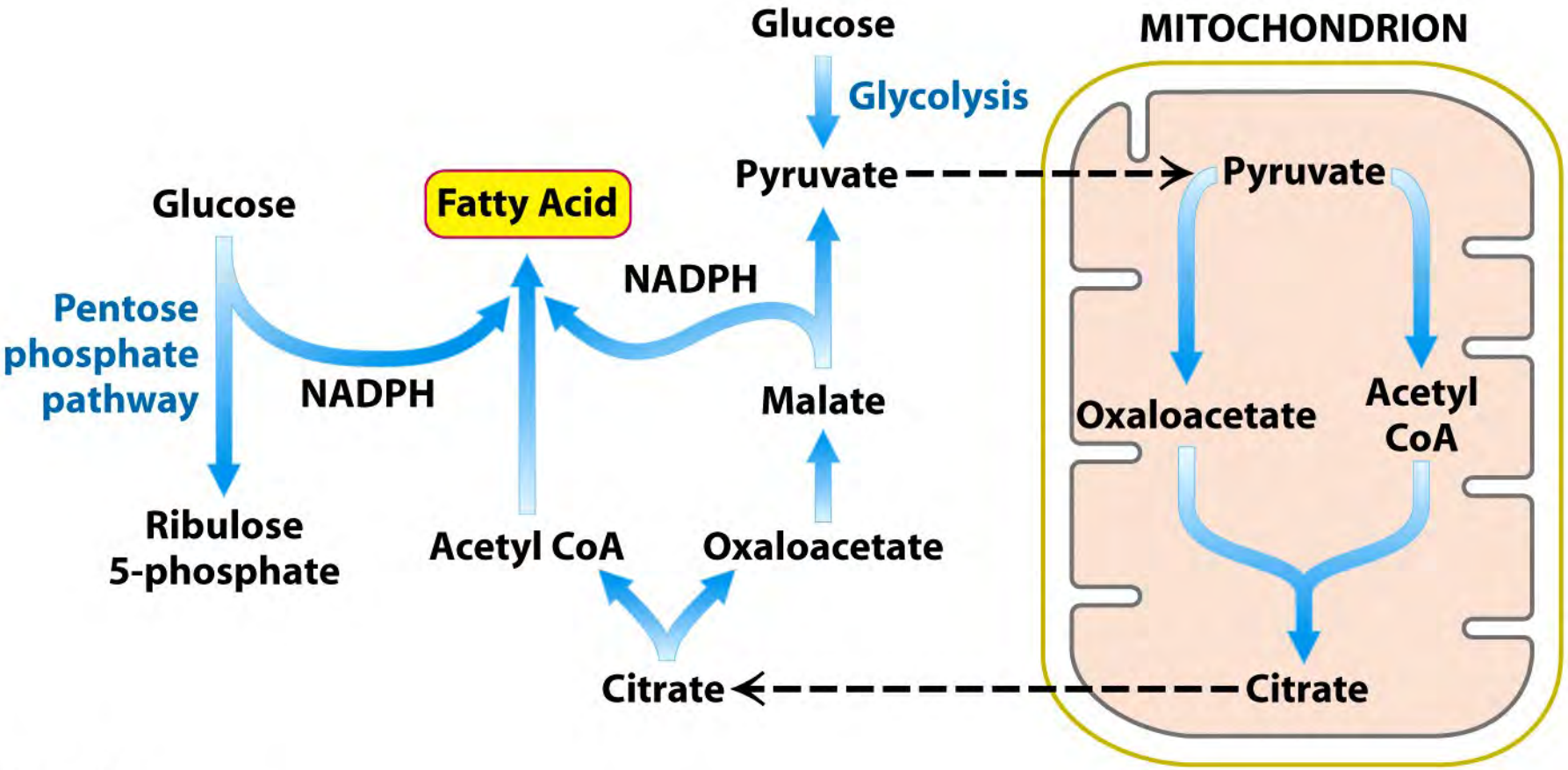
1. Malic enzyme
(NADP$^+$-linked malate enzyme)



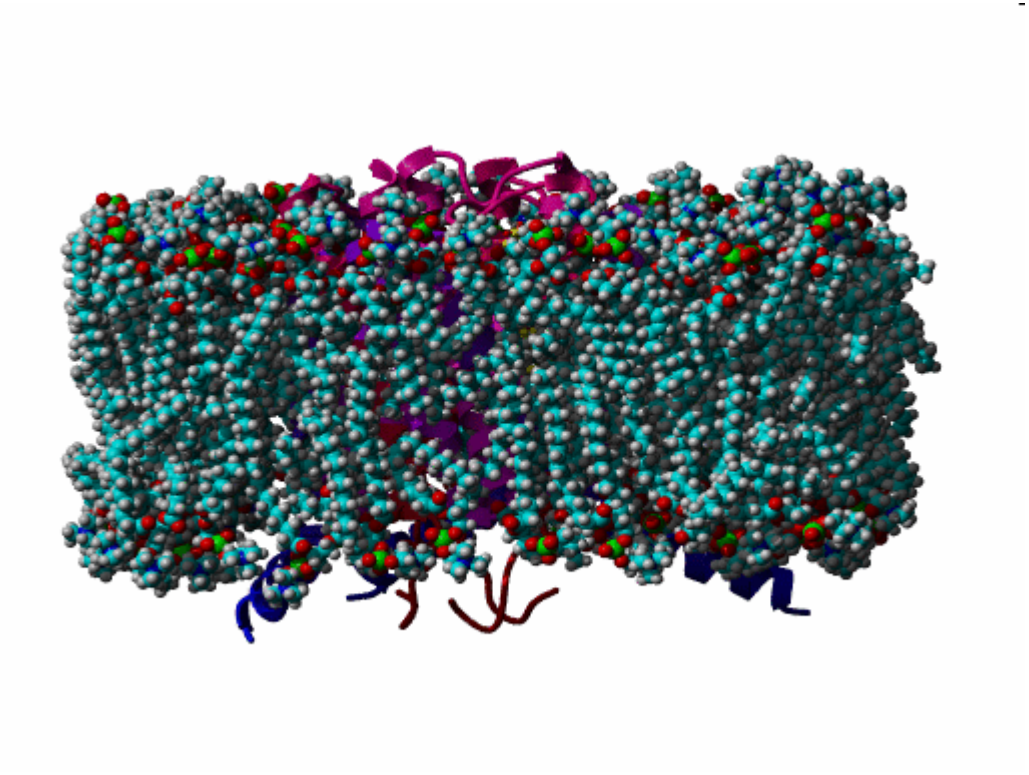
2. HMP-shunt
(hexose monophosphate)

occurs exclusively in the cytoplasm = accounts for 60% of NADPH

Fatty acid synthesis requires the integration of multiple metabolic pathways

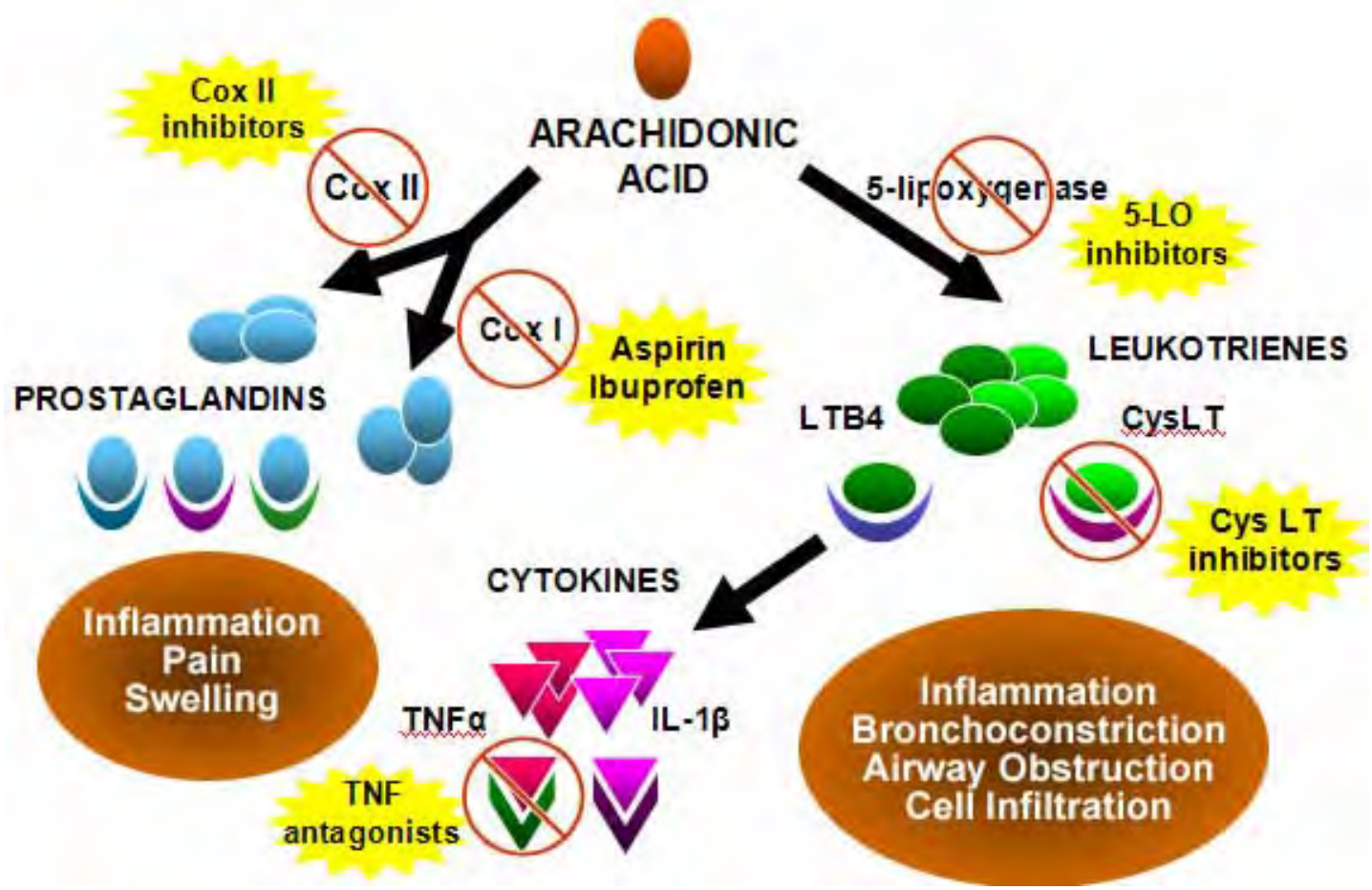


EICOSANOIDS



AA is metabolized to inflammatory mediators

Many current anti-inflammatory & pain medicines inhibit some portion of the AA pathway

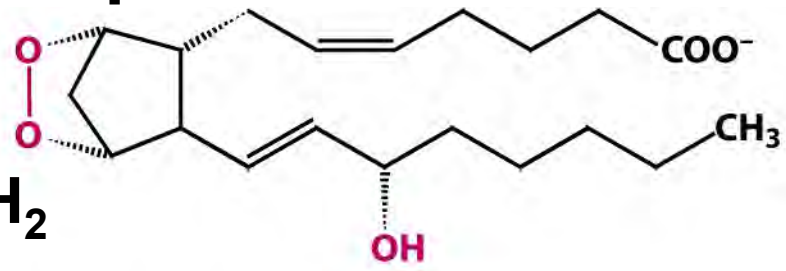


Eicosanoid hormones are derived from PUFAs

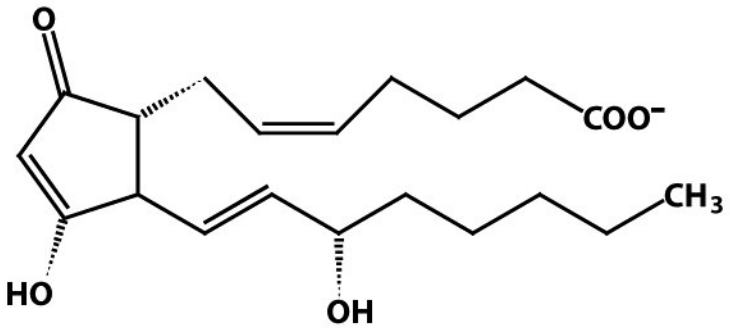
- **Arachidonic acid (20:4n6) is major precursor of multiple signal molecules:**

  prostaglandins (PG), prostacyclins, thromboxanes (TX) and leukotrienes (LT)

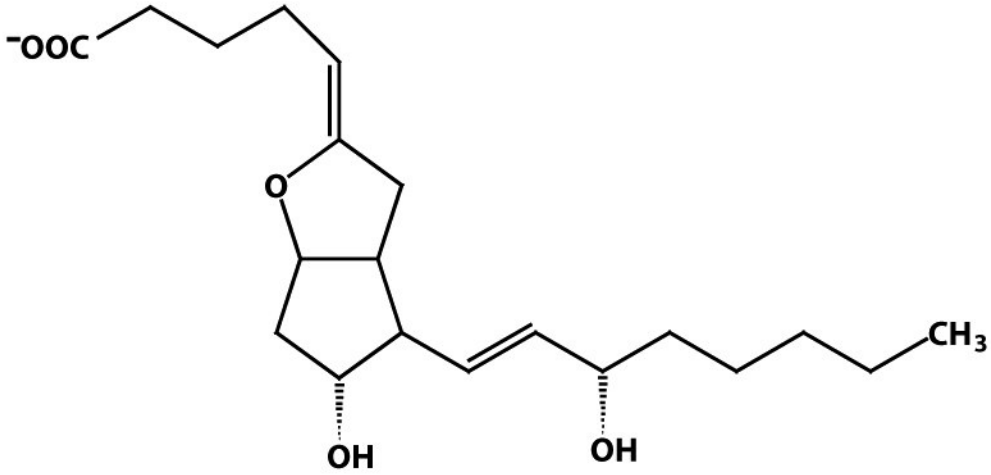
- **PGs = 20 carbon fatty acids containing a 5-carbon ring**
- **PGs stimulate inflammation, regulate blood flow, control ion transport, modulate synaptic transmission & induce sleep**



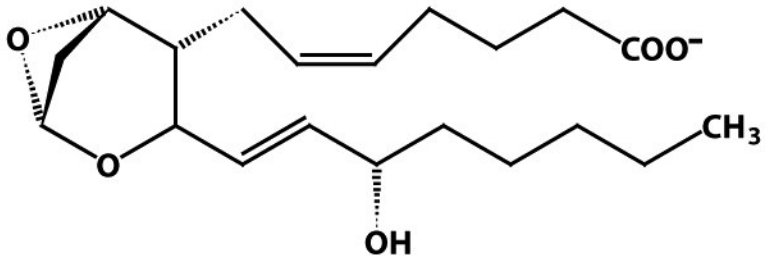
PGH_2



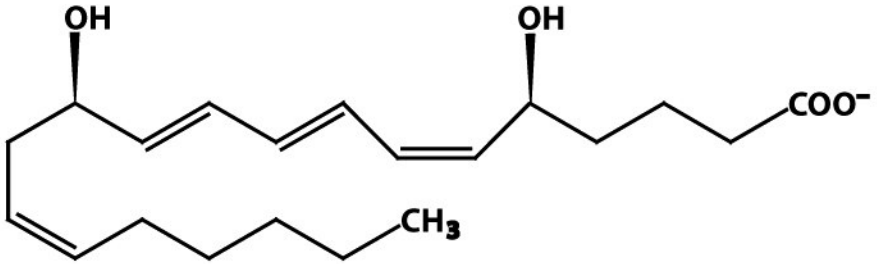
Prostaglandin E_2



Prostacyclin (PGI_2)



Thromboxane A_2 (TXA_2)



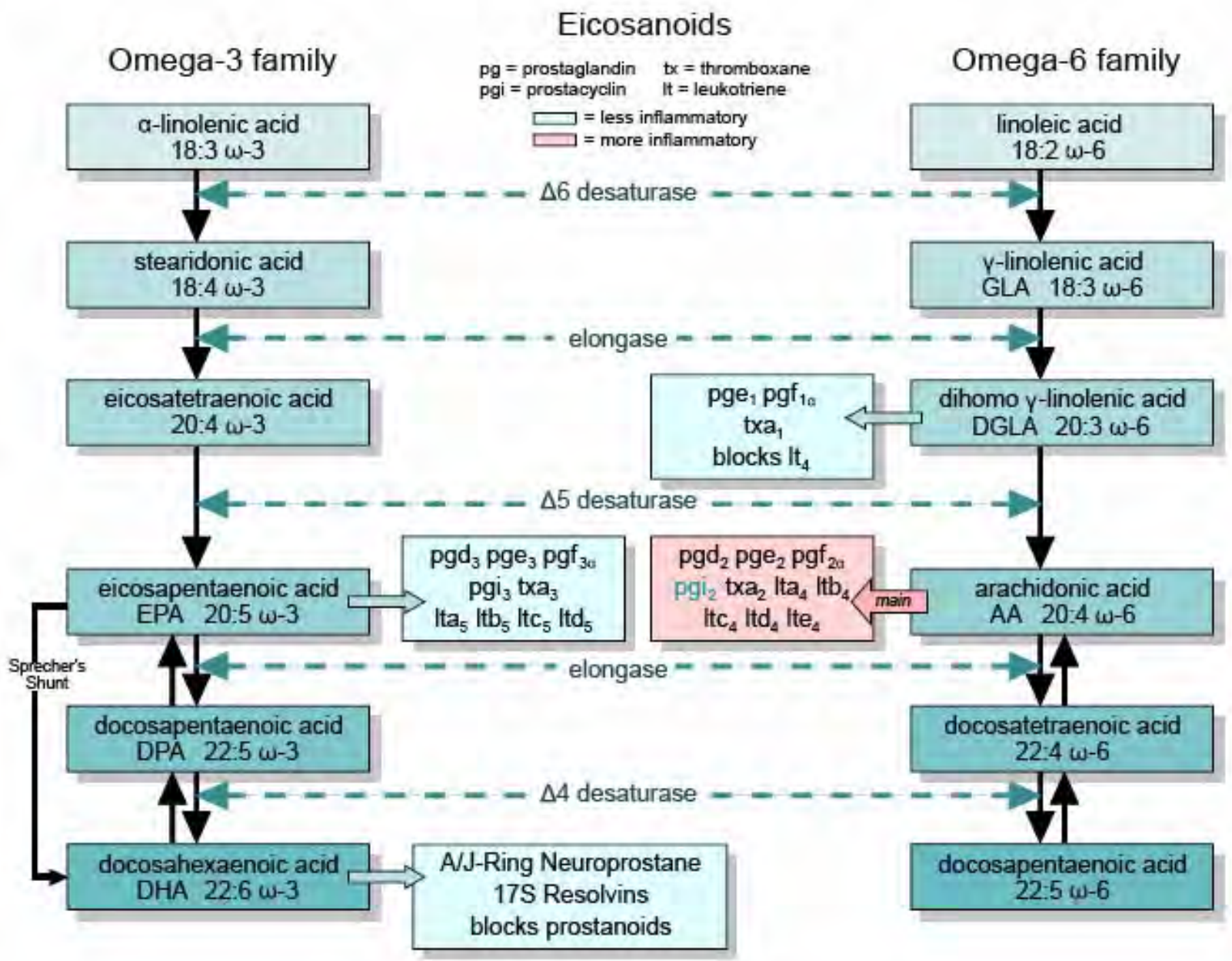
Leukotriene B_4

Importance of eicosanoids

- **Nobel Prize in 1982 for discovery of PG biological role and 1990 for PG synthesis**
- **PGs are found in almost all tissues & organs**
- **Ex of PG antagonists:**
  - **NSAIDs (inhibit COX → aspirin, ibuprofen)**
  - **corticosteroids (inhibit phospholipase A2 production)**
- **TXs are vasoconstrictors & hypertensive agent**
  - **role in thrombosis (clot in blood vessel)**
- **LTs & cysteinyl-LTs important in inflammation**
  - **asthma, psoriasis, anaphylaxis & atherosclerosis**

Eicosanoid-based medicines

Type	Medical condition
PGI_1 analog	Pulmonary hypertension, avoiding reperfusion injury
PG analog	Glaucoma, ocular hypertension
PG analog	Labor induction
PGE_2	Labor induction
PGI_2 analog	Pulmonary arterial hypertension
PGE_1 analog	Stomach ulcers, labor induction
LT receptor antagonist	Asthma, seasonal allergies
PGI analog	Pulmonary hypertension


Eicosanoids
Omega-3 family
Omega-6 family
pg = prostaglandin
pgi = prostacyclin
tx = thromboxane
lt = leukotriene
= less inflammatory
= more inflammatory
α-linolenic acid
18:3 ω-3
linoleic acid
18:2 ω-6
Δ6 desaturase
stearidonic acid
18:4 ω-3
γ-linolenic acid
GLA 18:3 ω-6
elongase
eicosatetraenoic acid
20:4 ω-3
pge1 pgf1α
txa1
blocks lt4
dihomo γ-linolenic acid
DGLA 20:3 ω-6
Δ5 desaturase
pgd3 pge3 pgf3α
pgi3 txa3
lta5 ltb5 ltc5 ltd5
pgd2 pge2 pgf2α
pgi2 txa2 lta4 ltb4
ltc4 ltd4 lte4
main
eicosapentaenoic acid
EPA 20:5 ω-3
arachidonic acid
AA 20:4 ω-6
Sprecher's Shunt
elongase
docosapentaenoic acid
DPA 22:5 ω-3
docosatetraenoic acid
22:4 ω-6
Δ4 desaturase
docosahexaenoic acid
DHA 22:6 ω-3
A/J-Ring Neuroprostane
17S Resolvins
blocks prostanoids
docosapentaenoic acid
22:5 ω-6

20:4n6 (arachidonic acid)

↑ Δ5

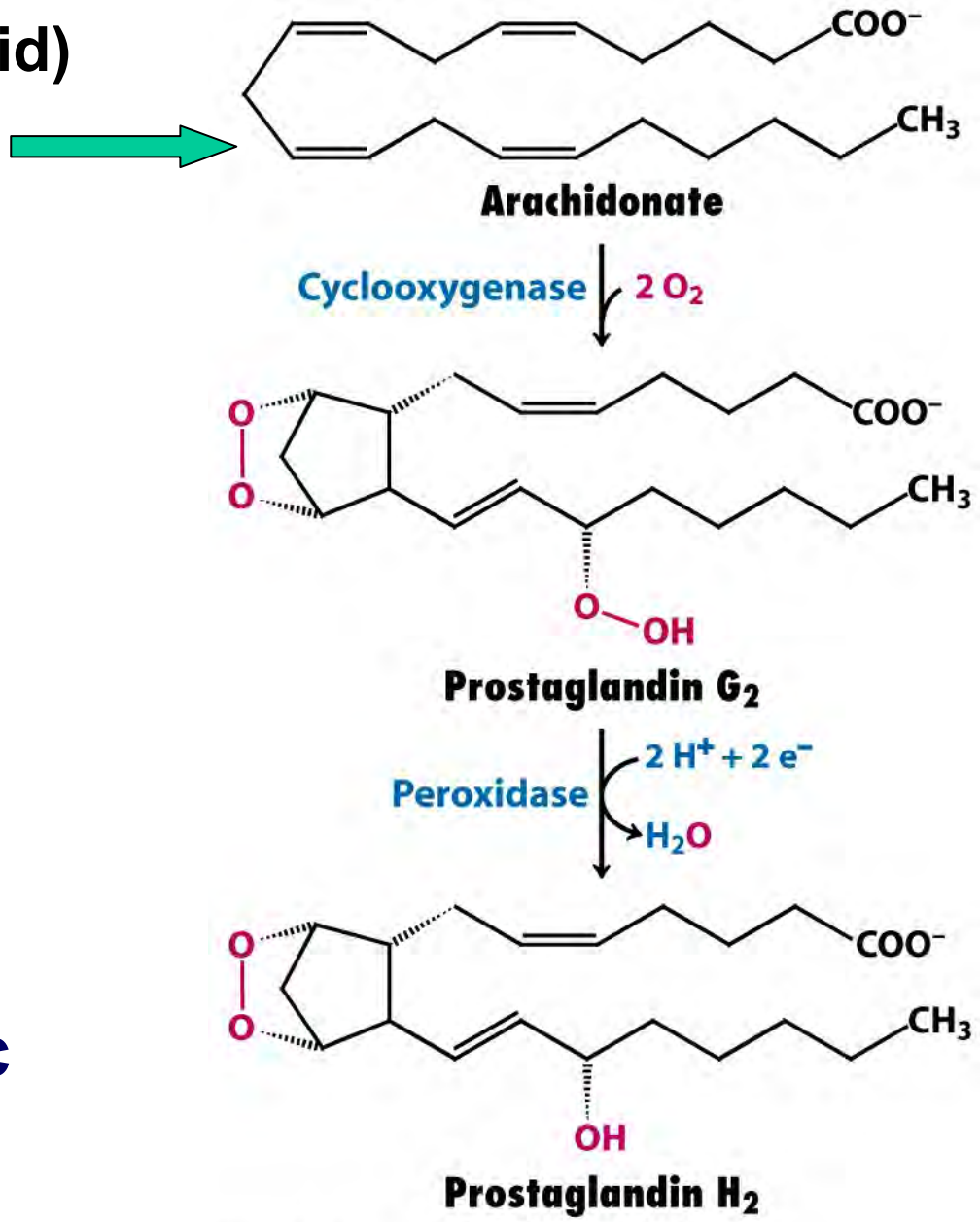
20:3n6

↑ Elongase

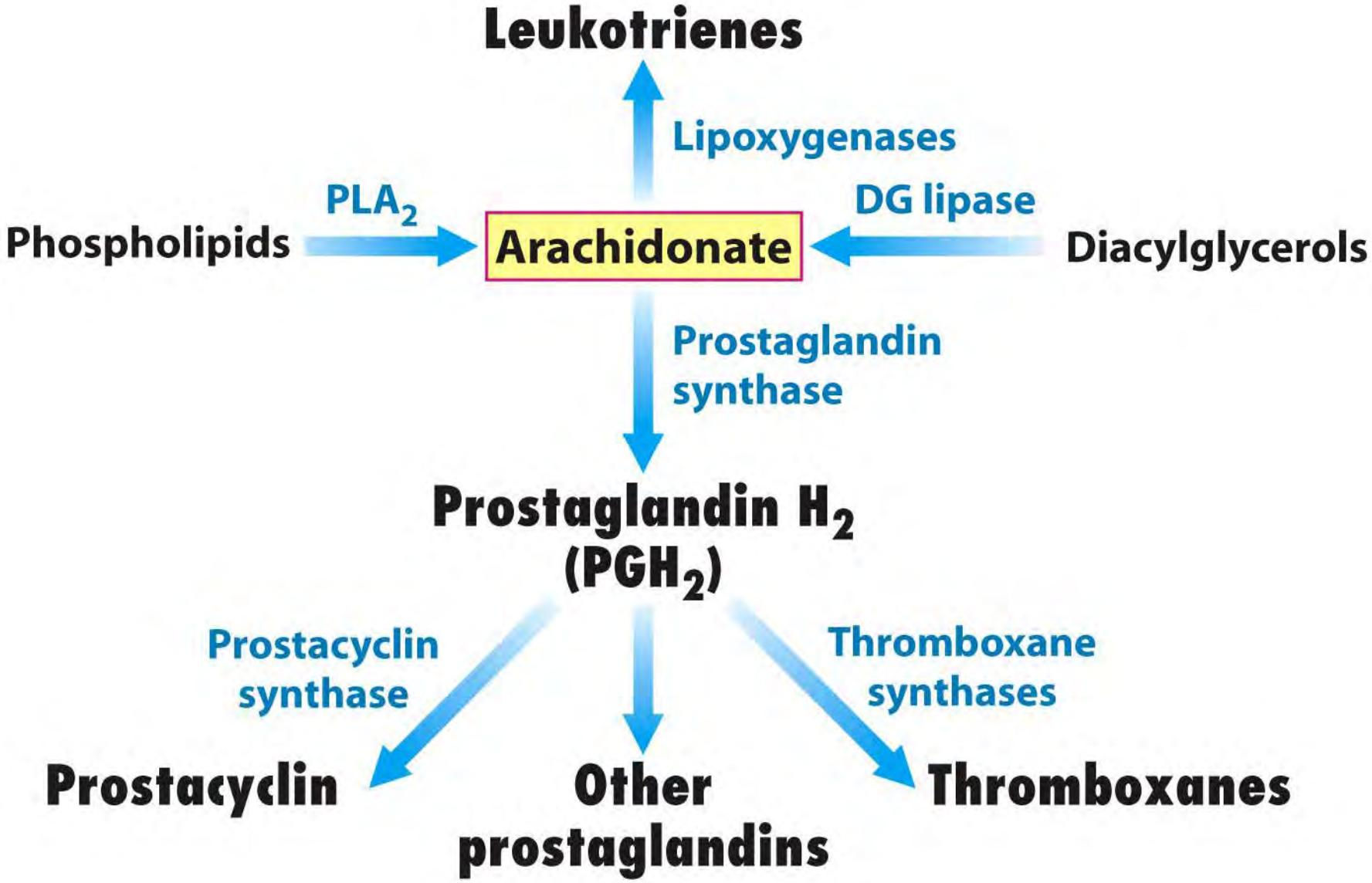
18:3n6

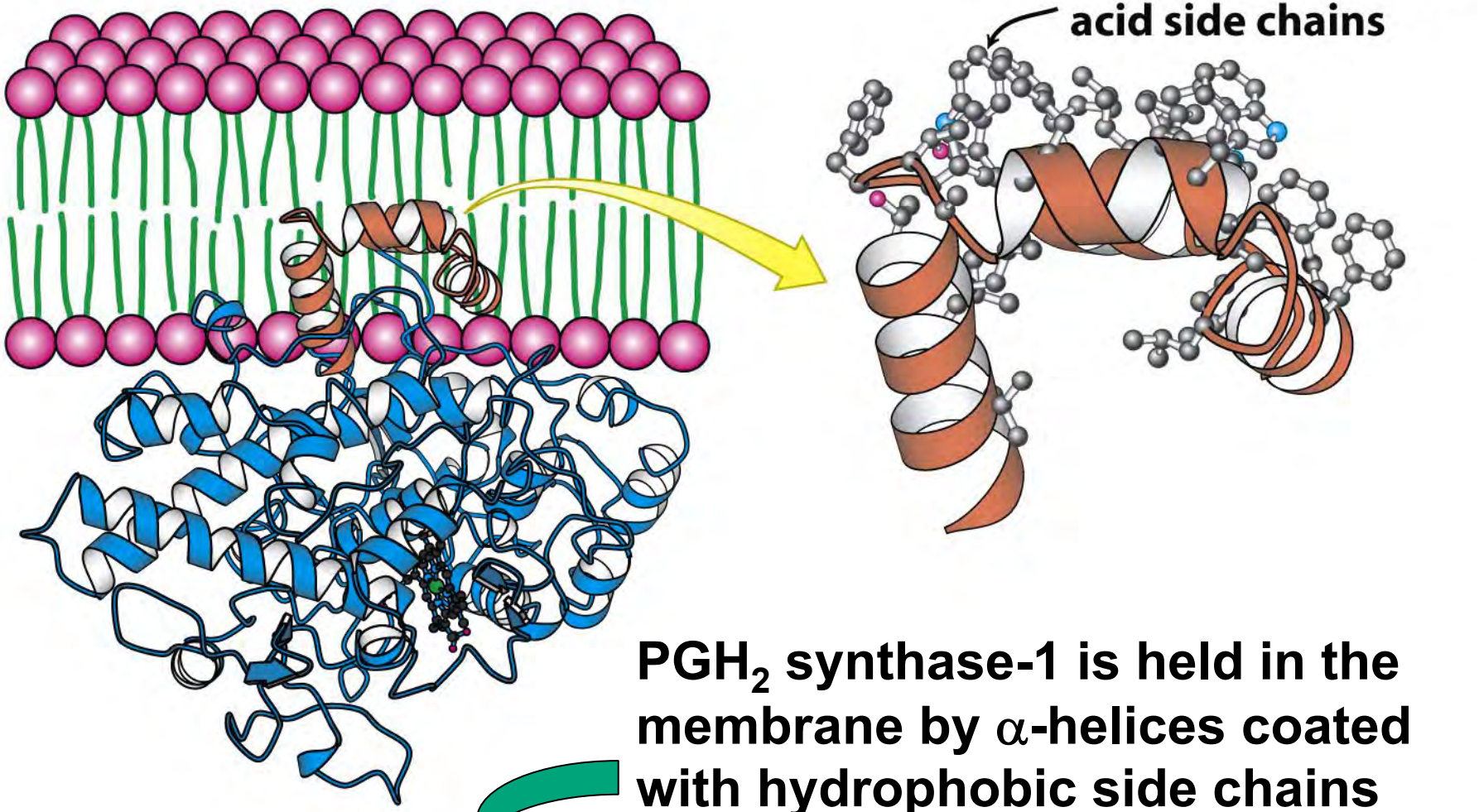
↑ Δ6

18:2n6 (linoleic acid)



PGH_2 promotes inflammation and modulates gastric acid secretion

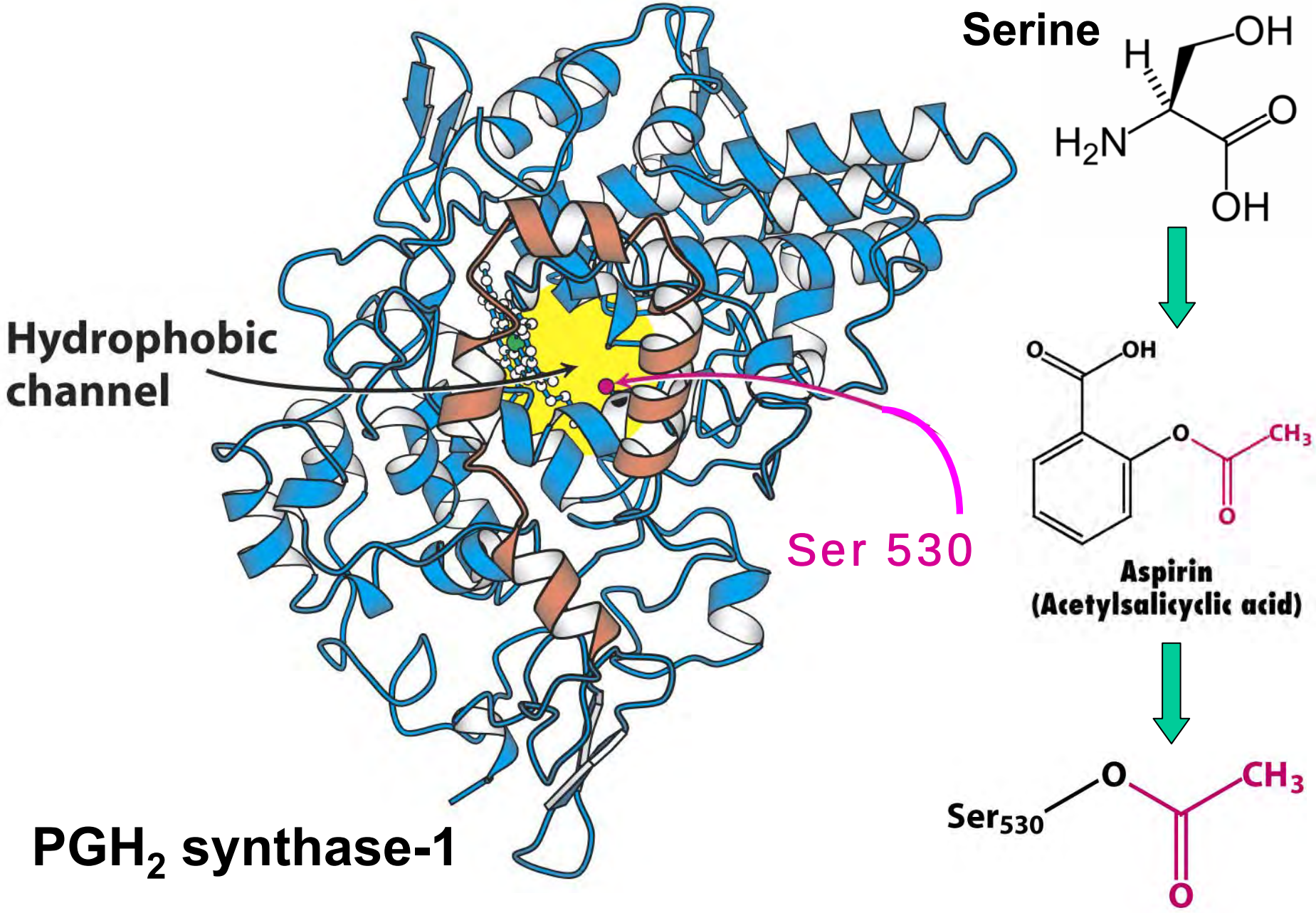

Leukotrienes
Lipoxygenases
PLA2
Phospholipids
Arachidonate
DG lipase
Diacylglycerols
Prostaglandin synthase
Prostaglandin H2 (PGH2)
Prostacyclin synthase
Thromboxane synthases
Prostacyclin
Other prostaglandins
Thromboxanes

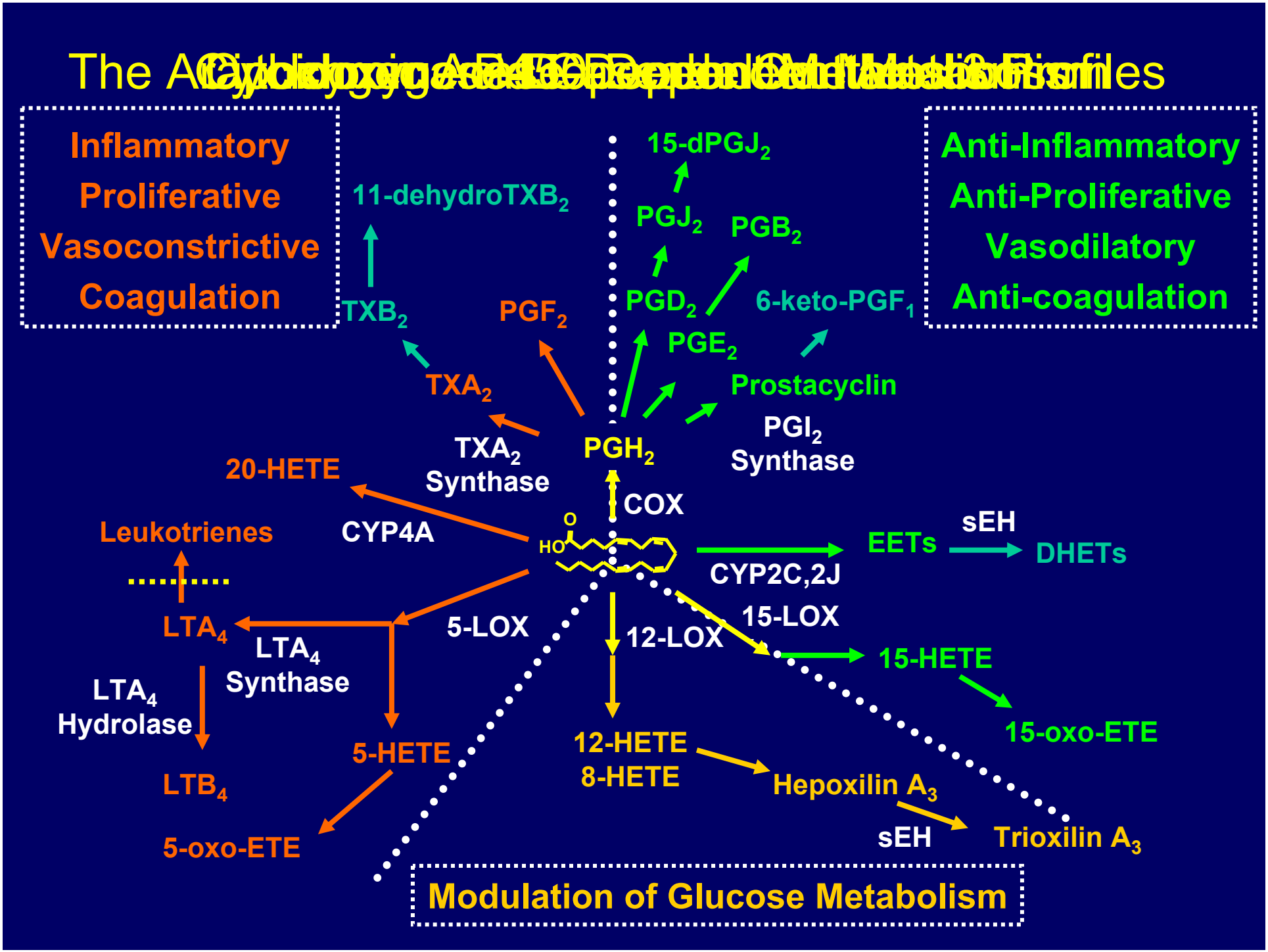


PGH_2 synthase-1 is held in the membrane by α-helices coated with hydrophobic side chains

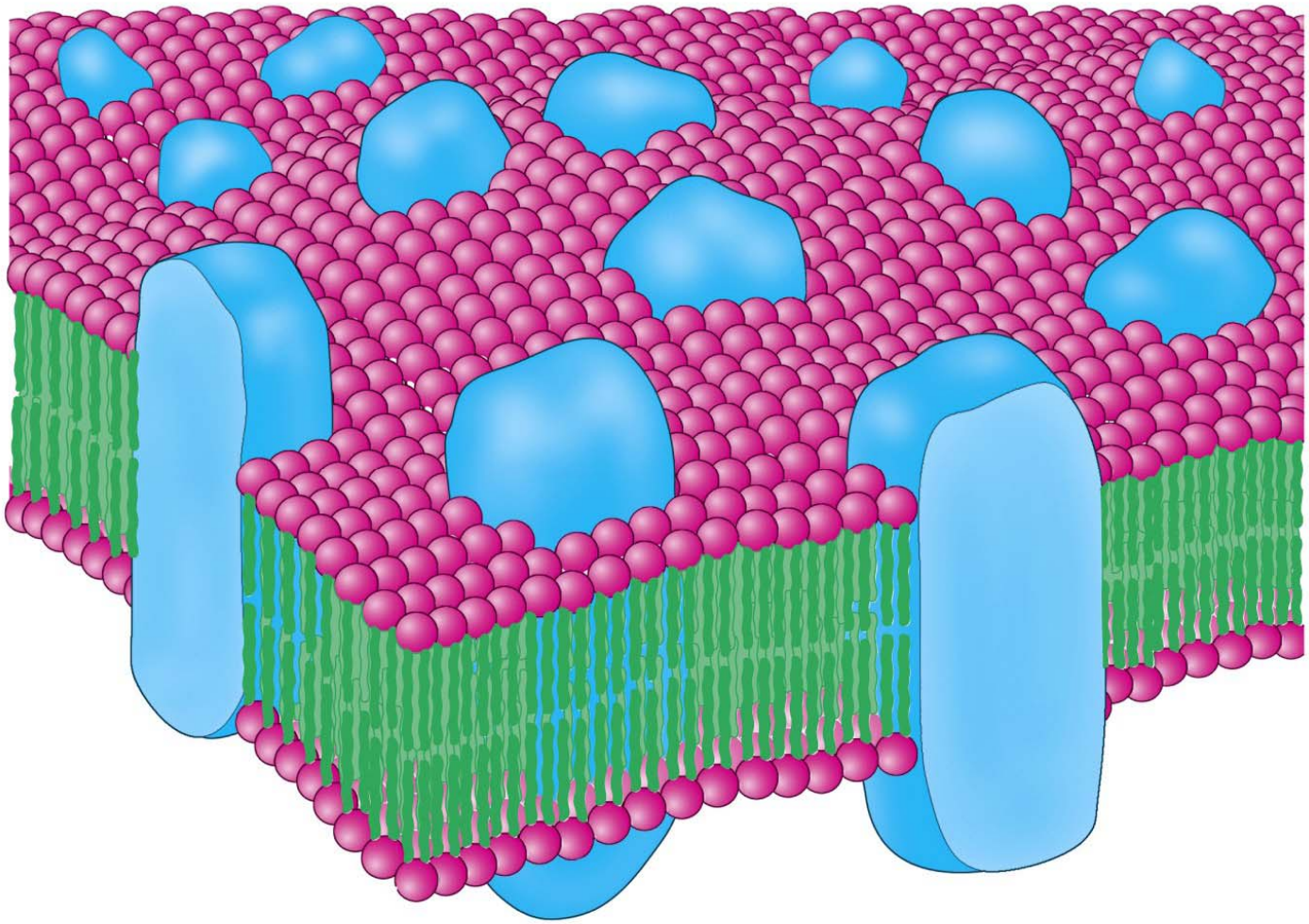
Integral membrane protein

AA is hydrophobic and is funneled thru protein channel


Hydrophobic channel
Ser 530
Serine
Aspirin
(Acetylsalicyclic acid)
PGH2 synthase-1

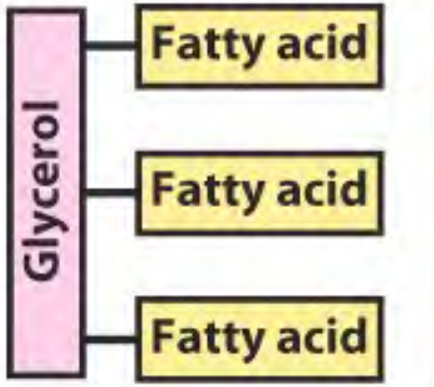

Inflammatory
Proliferative
Vasoconstrictive
Coagulation
Anti-Inflammatory
Anti-Proliferative
Vasodilatory
Anti-coagulation
11-dehydroTXB2
TXB2
PGF2
15-dPGJ2
PGJ2
PGB2
PGD2
6-keto-PGF1
PGE2
Prostacyclin
PGI2 Synthase
TXA2
TXA2 Synthase
PGH2
COX
20-HETE
CYP4A
Leukotrienes
HO
O
EETs
sEH
DHETs
CYP2C,2J
LTA4
LTA4 Synthase
LTA4 Hydrolase
5-LOX
12-LOX
15-LOX
15-HETE
15-oxo-ETE
5-HETE
LTB4
5-oxo-ETE
12-HETE
8-HETE
Hepoxilin A3
sEH
Trioxilin A3
Modulation of Glucose Metabolism

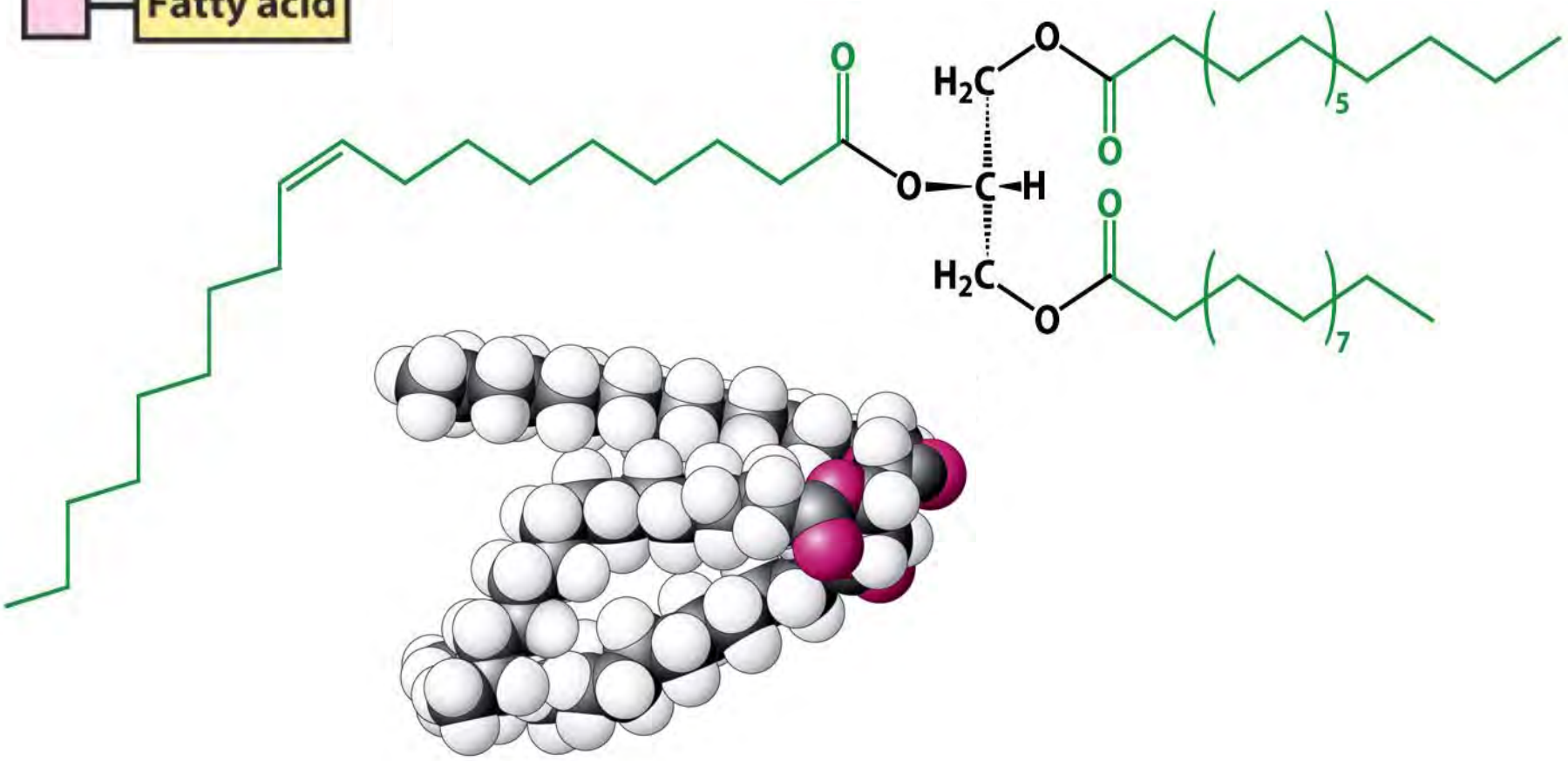
Biosynthesis of membrane lipids and steroids



Triacylglycerol (TAG)

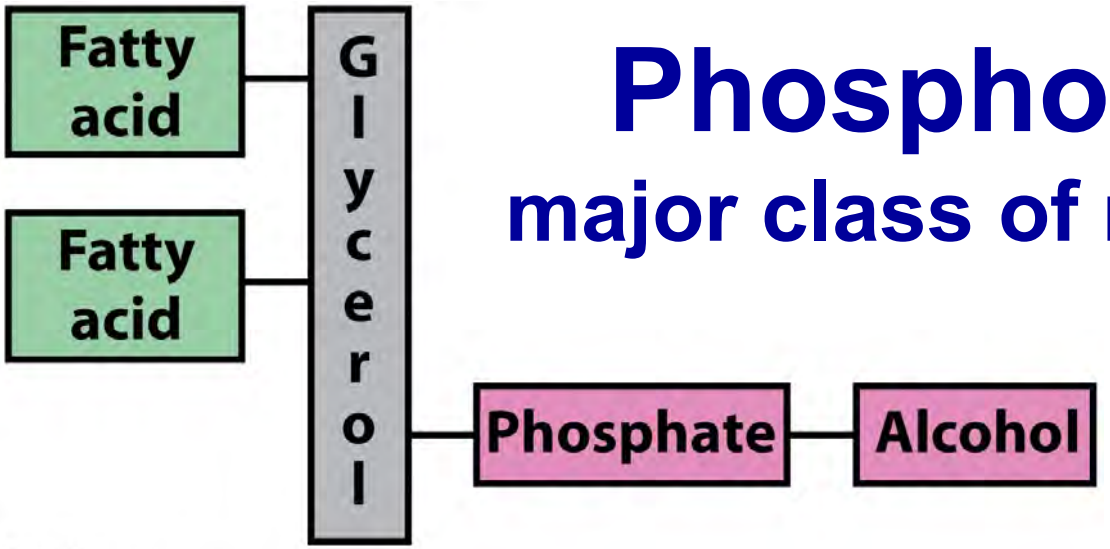
= ester of glycerol + 3 FA

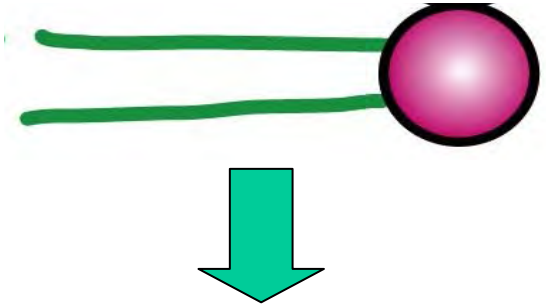




Phospholipids (PL)

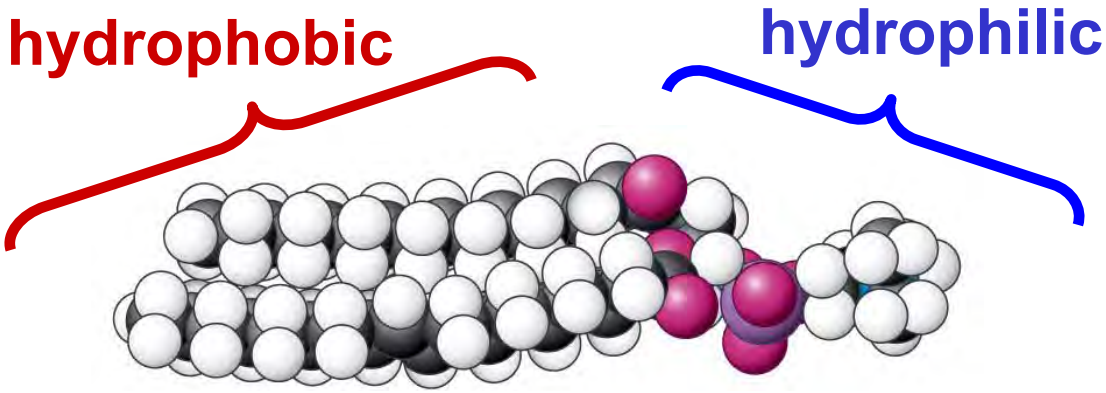
major class of membrane lipids

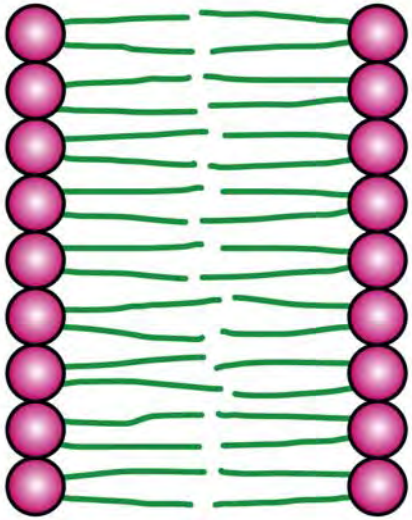




Glycerophospholipid

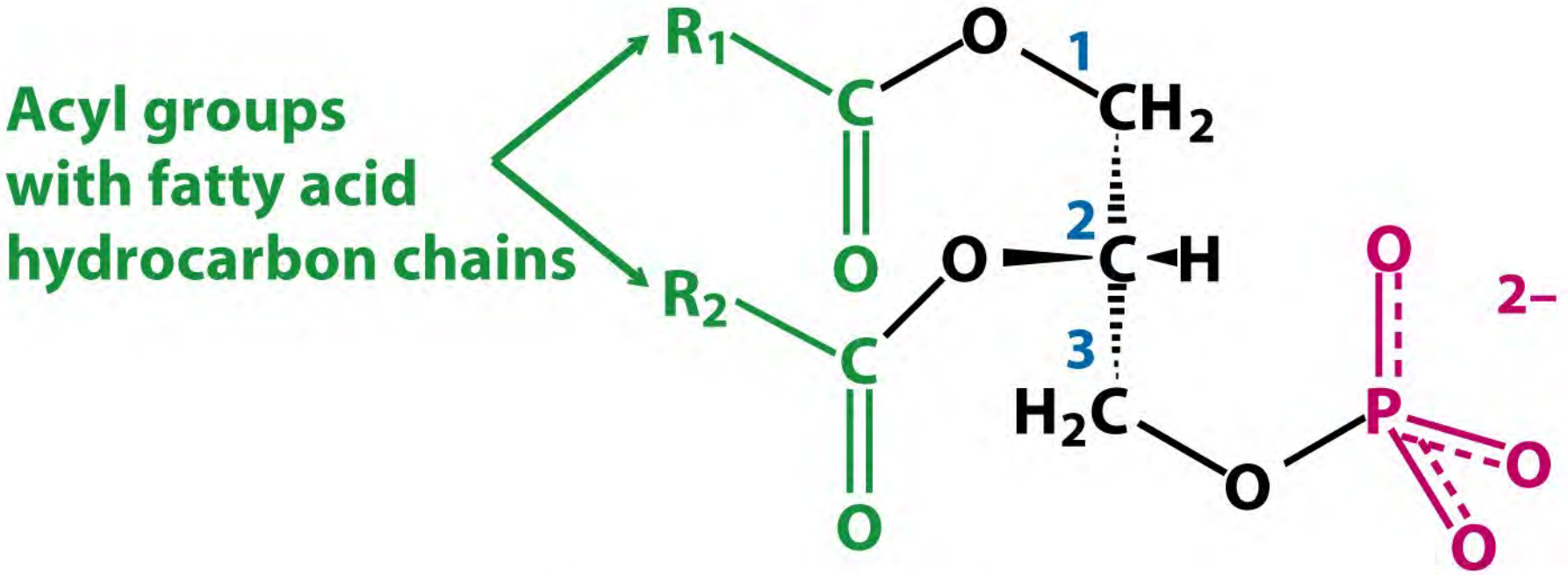
constructed of 4 components



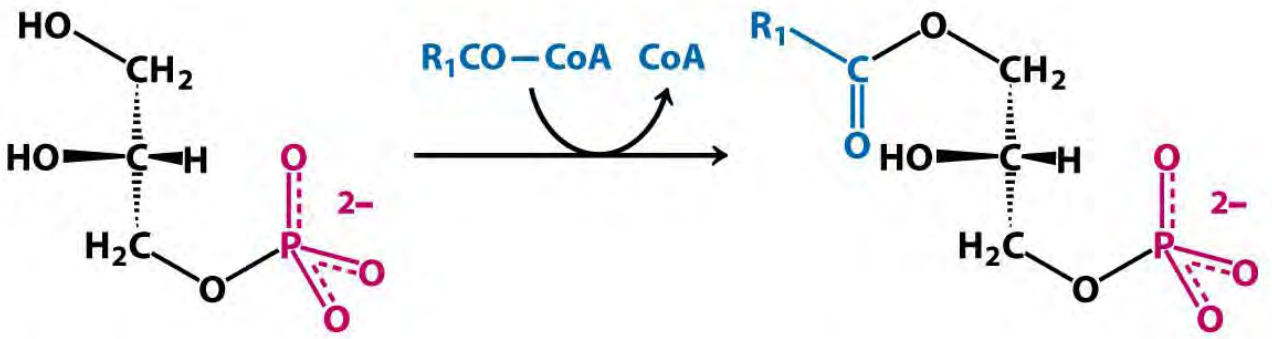


Membrane

1st step in synthesis of phospholipids (PLs) and triacylglycerols (TAGs) is the synthesis of phosphatidate



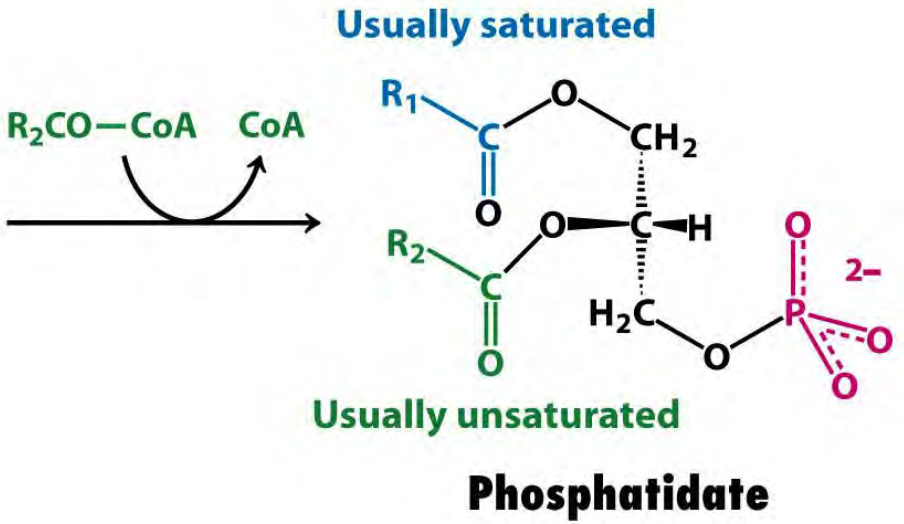
Phosphatidate (Diacylglycerol 3-phosphate)



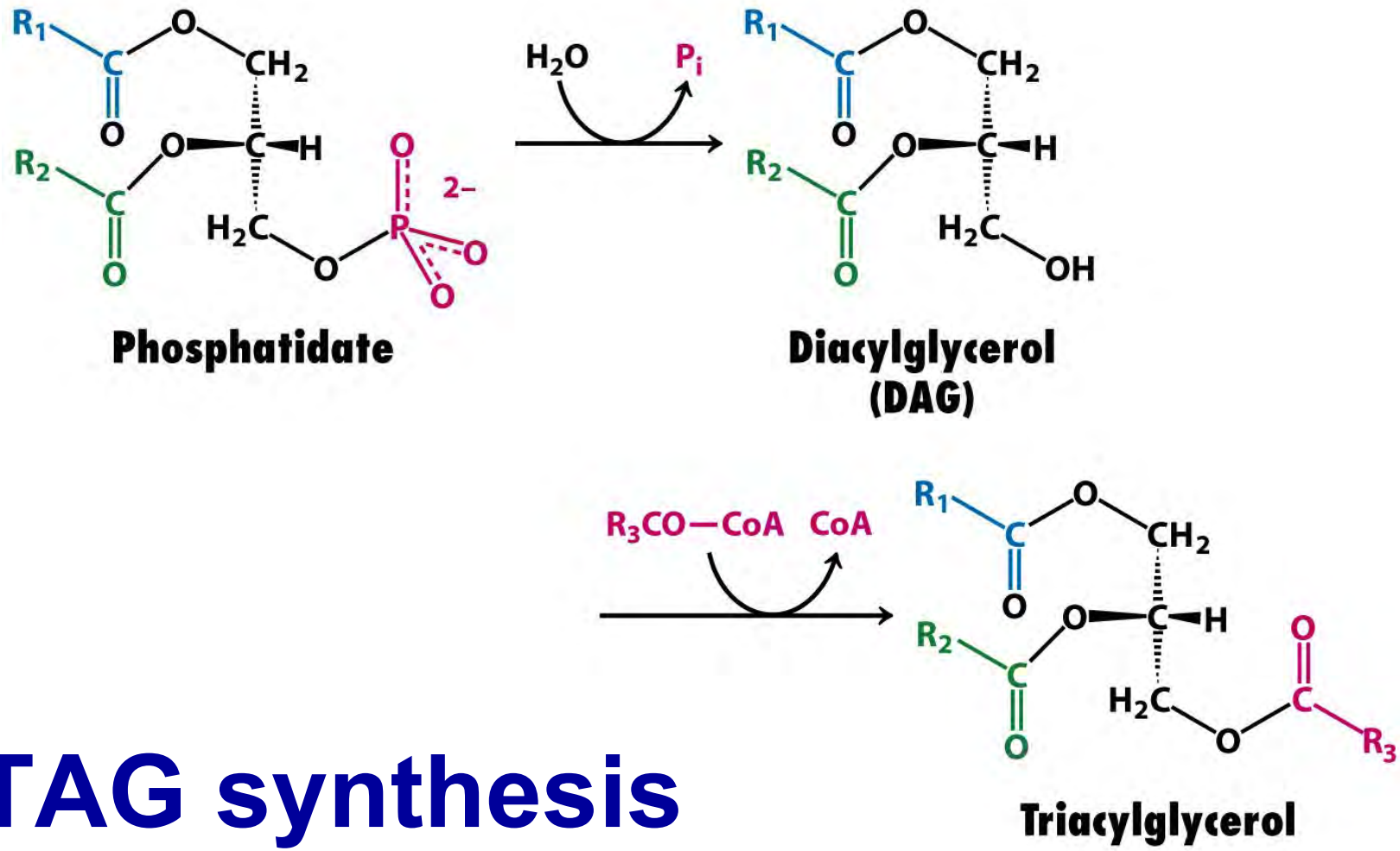
Glycerol 3-phosphate

Lysophosphatidate

Phosphatidate is built from L-glycerol-3-phosphate and activated fatty acids

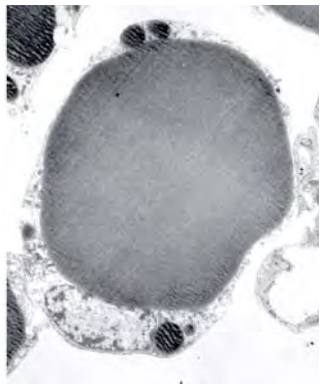


Phosphatidate



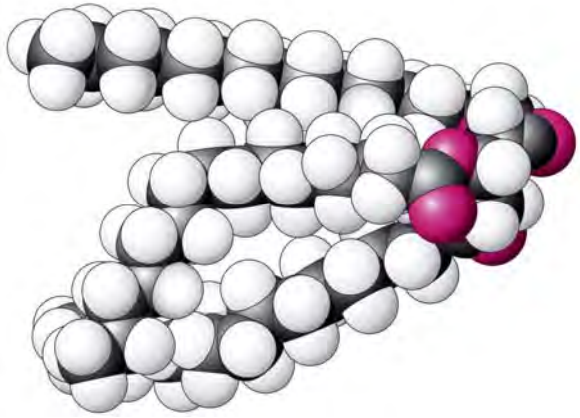
TAG synthesis proceeds via DAG

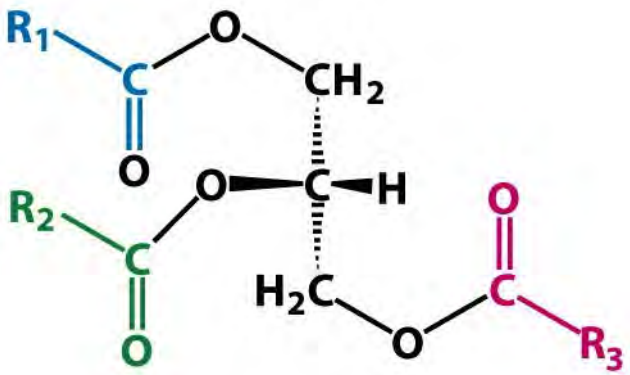
Triacylglycerols (TAG)



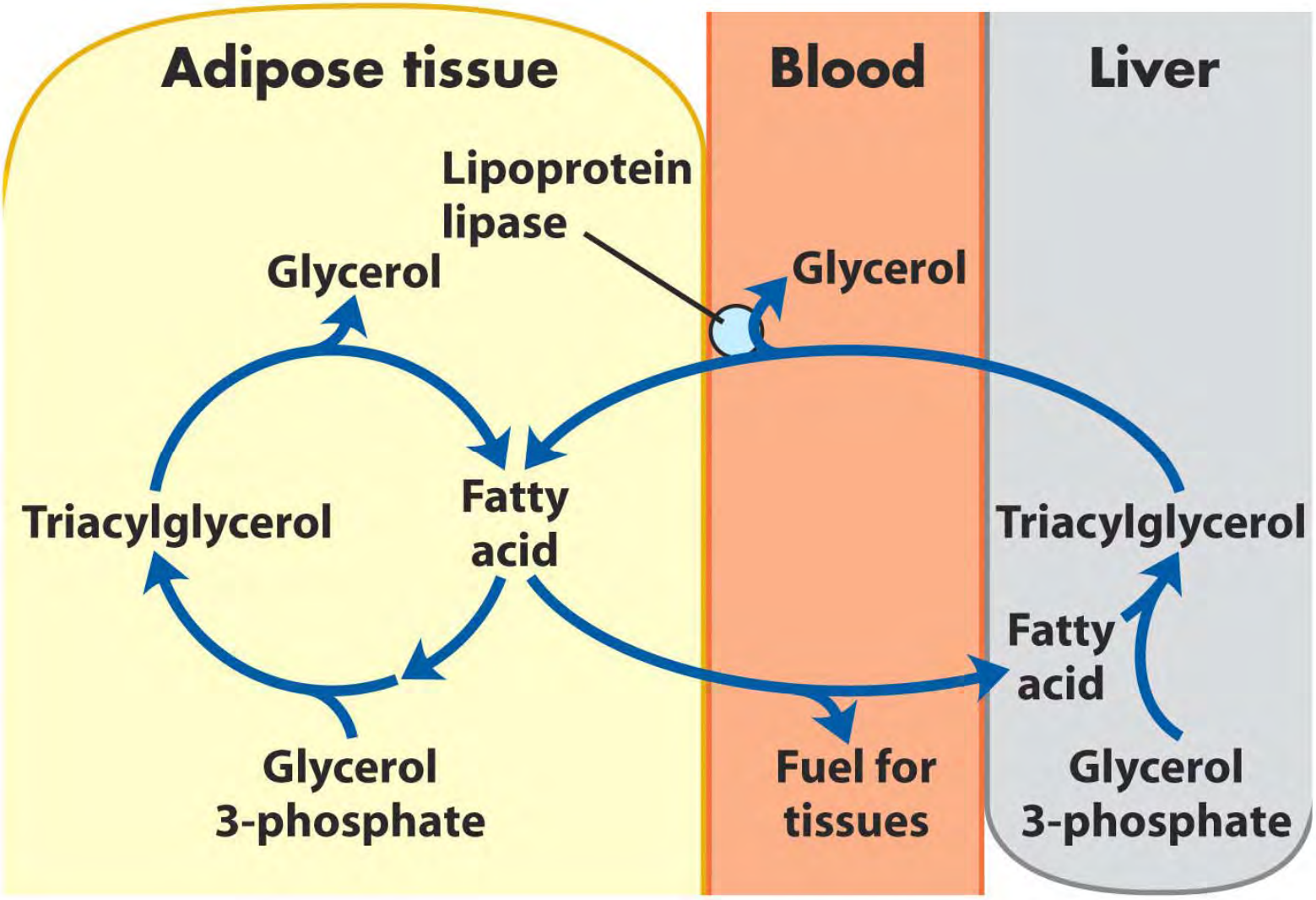
- **Stored energy in fat cells**
  - **adipose cells**
- **More energy/gram than carbohydrates**
  - **9 kcal/g compared to 4 kcal/g**
  - **stored in anhydrous form (carbs 2g H_2O/g)**

=> fat has 6.75x > energy than hydrated glycogen



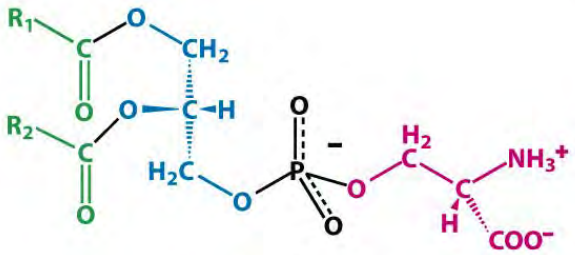


TAG cycle

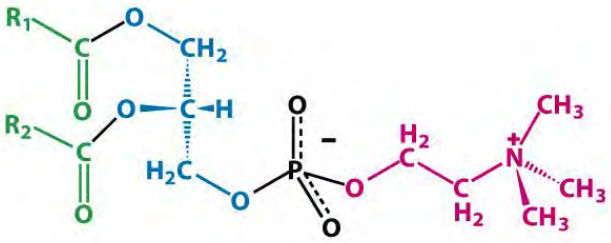

Adipose tissue
Blood
Liver
Lipoprotein lipase
Glycerol
Glycerol
Triacylglycerol
Fatty acid
Triacylglycerol
Fatty acid
Glycerol 3-phosphate
Fuel for tissues
Glycerol 3-phosphate

Glycerophospholipids (phosphoglycerides)

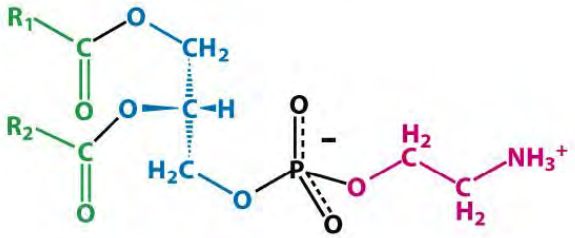
- **glycerol-based PLs – main component of biological membranes**



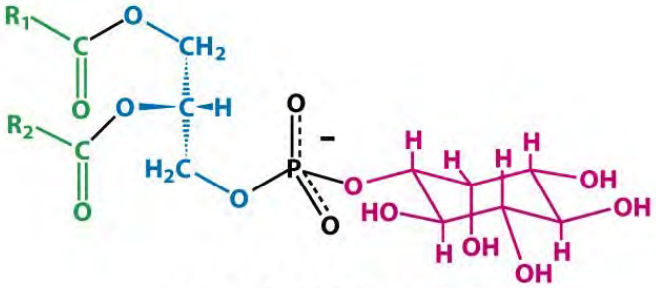
Phosphatidylserine



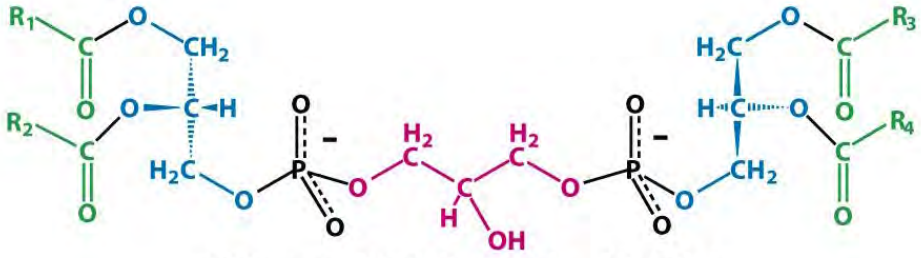
Phosphatidylcholine



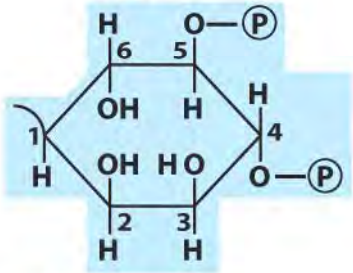
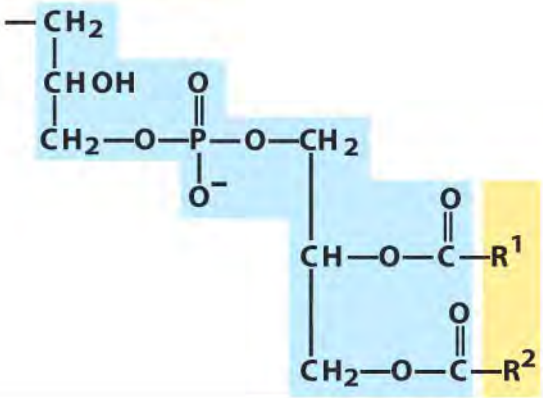
Phosphatidylethanolamine



Phosphatidylinositol



Diphosphatidylglycerol (cardiolipin)

	Name of glycerophospholipid	Name of X	Formula of X	Net charge (at pH 7)
PA	Phosphatidic acid	—	— H	− 1
PE	Phosphatidylethanolamine	Ethanolamine	— CH_2—CH_2—$\overset{+}{N}H_3$	0
PC	Phosphatidylcholine	Choline	— CH_2—CH_2—$\overset{+}{N}(CH_3)_3$	0
PS	Phosphatidylserine	Serine	—CH_2—$CH(\overset{+}{N}H_3)$—COO^-	− 1
PG	Phosphatidylglycerol	Glycerol	—CH_2—$CH(OH)$—CH_2—OH	− 1
PIP_2	Phosphatidylinositol 4,5-bisphosphate	*myo*-Inositol 4,5-bisphosphate		− 4
CL	Cardiolipin	Phosphatidyl-glycerol		− 2

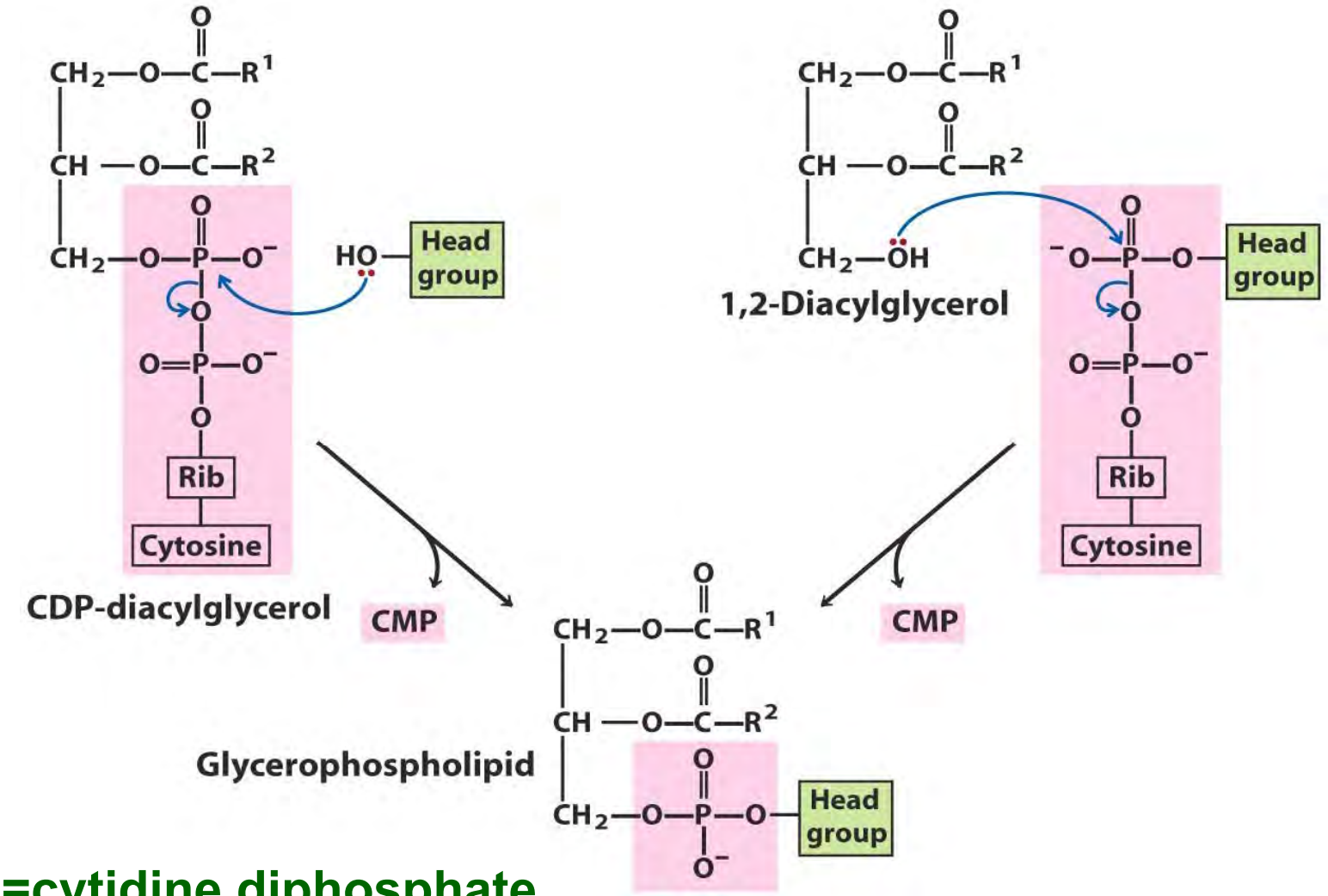
Biological role of PLs

- PC most common lipid in mammals
- PS is 10% of total PLs in mammals
- CL located in inner mitochondrial membrane (role in oxidative phosphorylation)
- Ampipathic = possesses both hydrophilic and hydrophobic properties

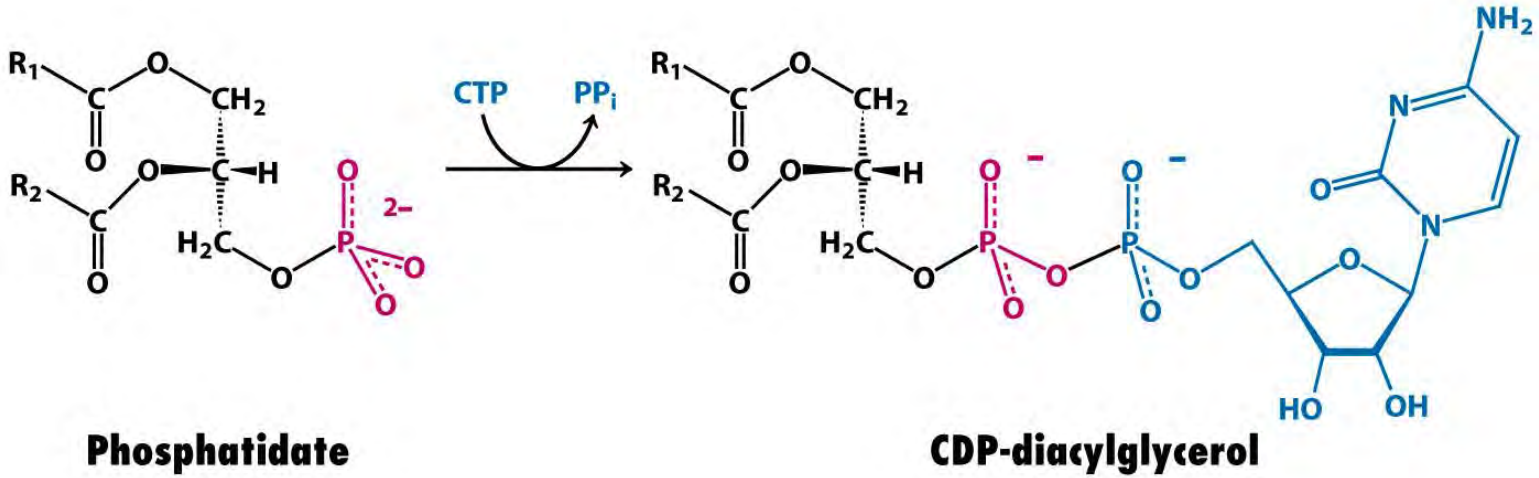
PL synthesis requires an activated intermediate

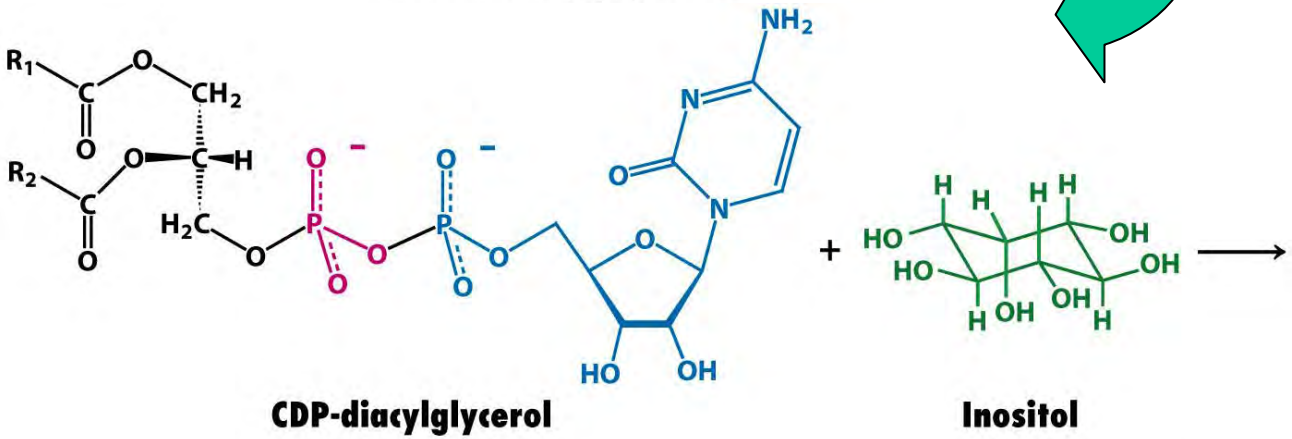
Strategy 1
Alcohol activation of CDP

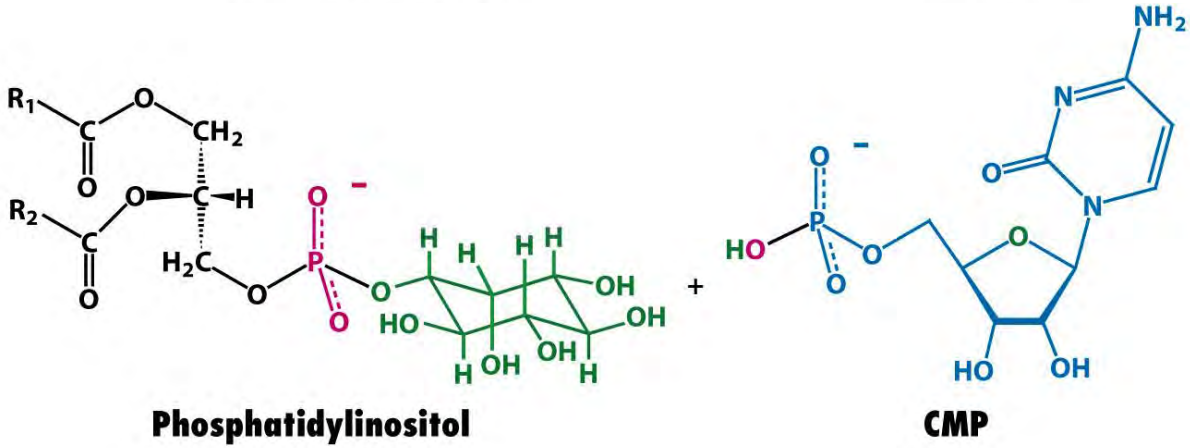
Strategy 2
DAG activation of CDP



CDP=cytidine diphosphate







Strategy 1

PL synthesis from activated alcohol

CDP=cytidine diphosphate

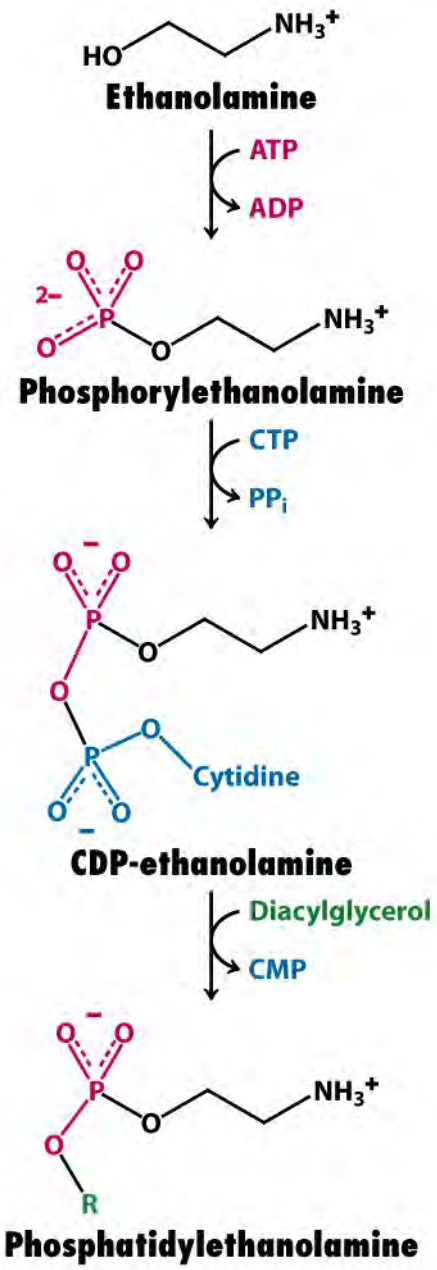
Strategy 2

PL synthesis from activated DAG

CTP=cytidine triphosphate

CDP=cytidine diphosphate

CMP=cytidine monophosphate



Glycerophospholipid synthesis

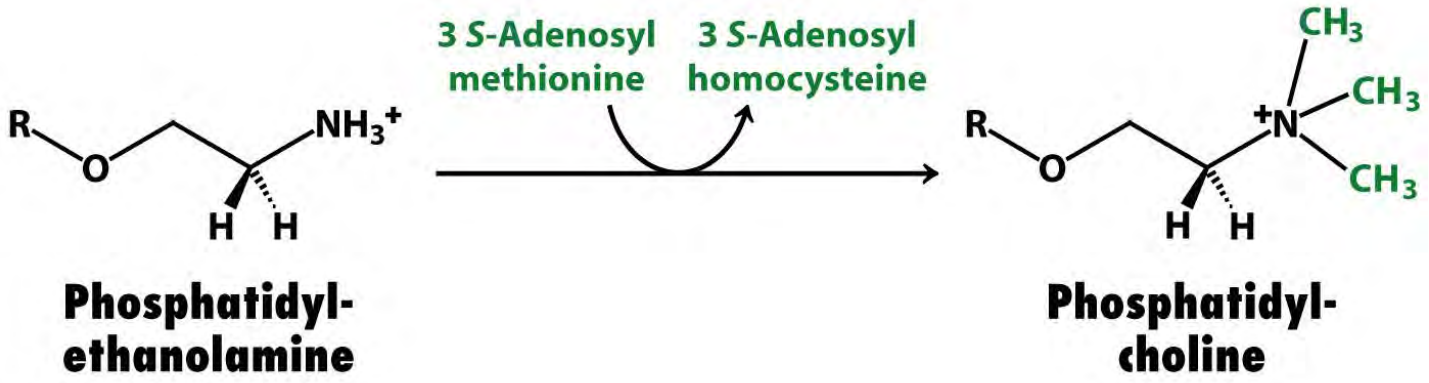
PE and PC: Strategy 1

PI, PG, cardiolipin (CL): Strategy 2

PS, PE, PC are "coupled"

PS from PE or PC

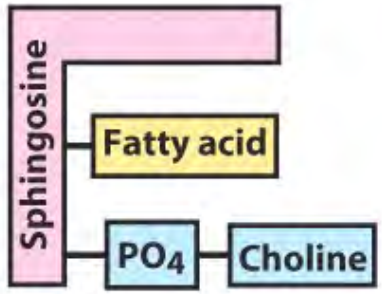
PC from PE (+ 3 adoMet)

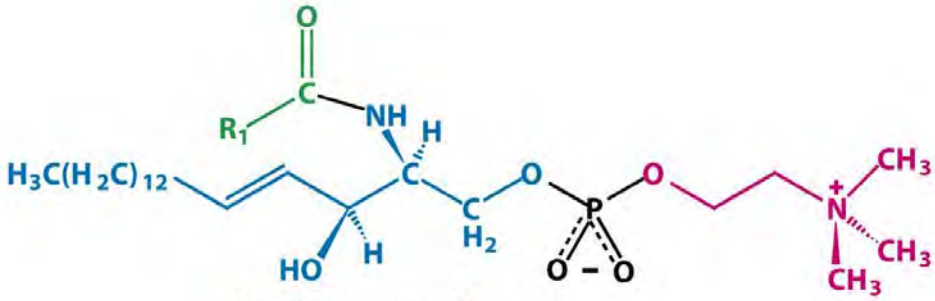


Sphingolipids

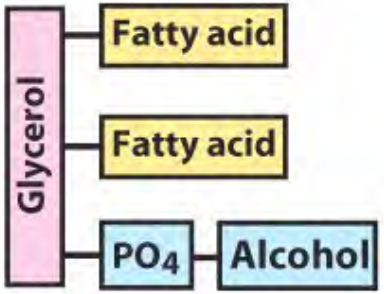
contain sphingosine backbone (not glycerol)

Sphingosine

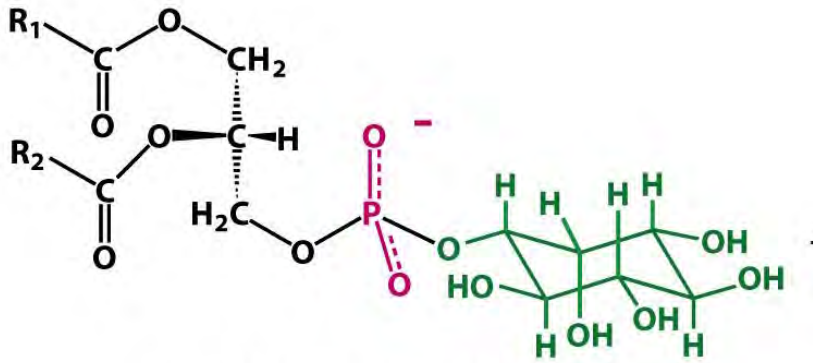




Sphingomyelin

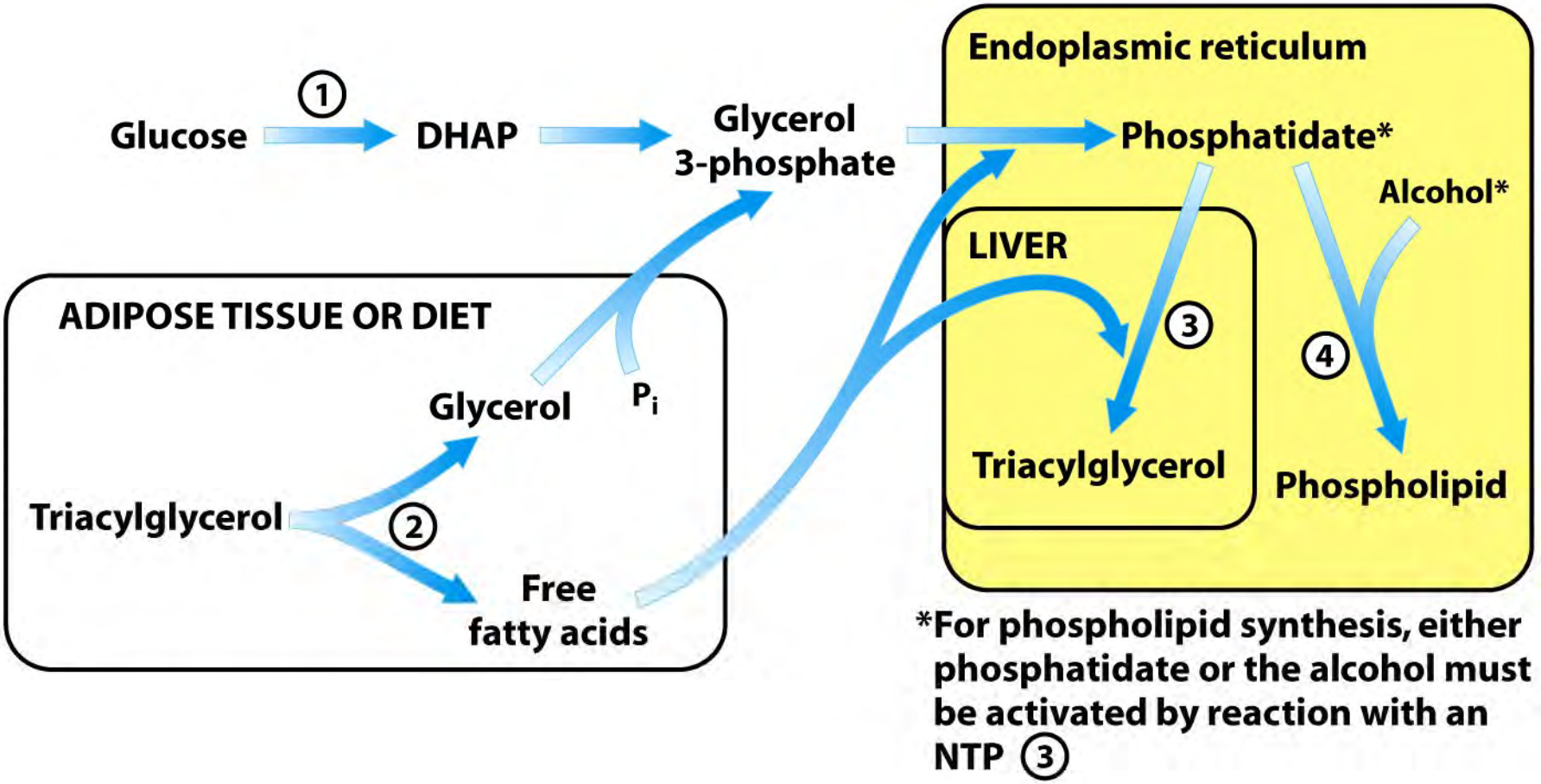


glycerophospholipid



Phosphatidylinositol

Membrane lipid = concentration ↑ in central nervous system

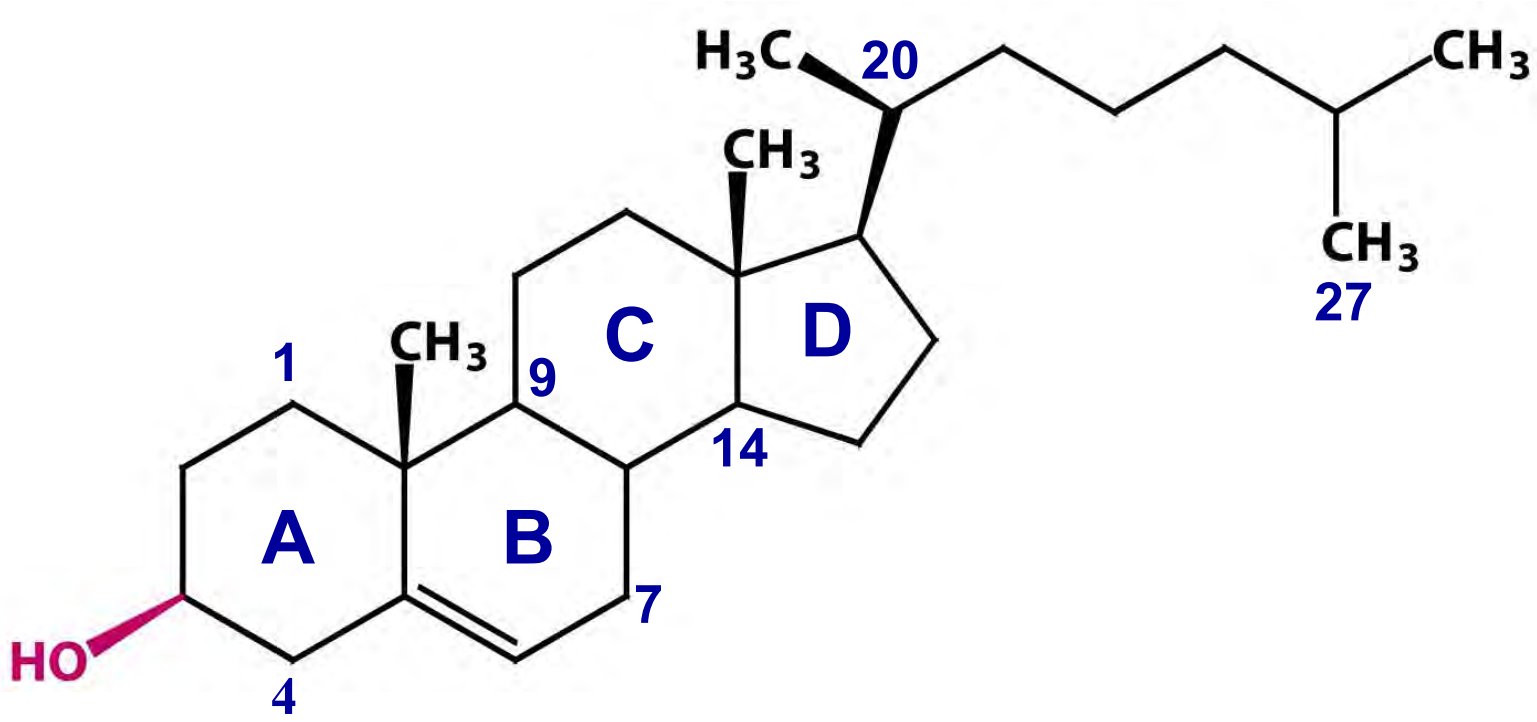


Pathway integration for TAG and PL synthesis

phosphatidate is produced from multiple pathways and is further incorporated into TAGs or PLs

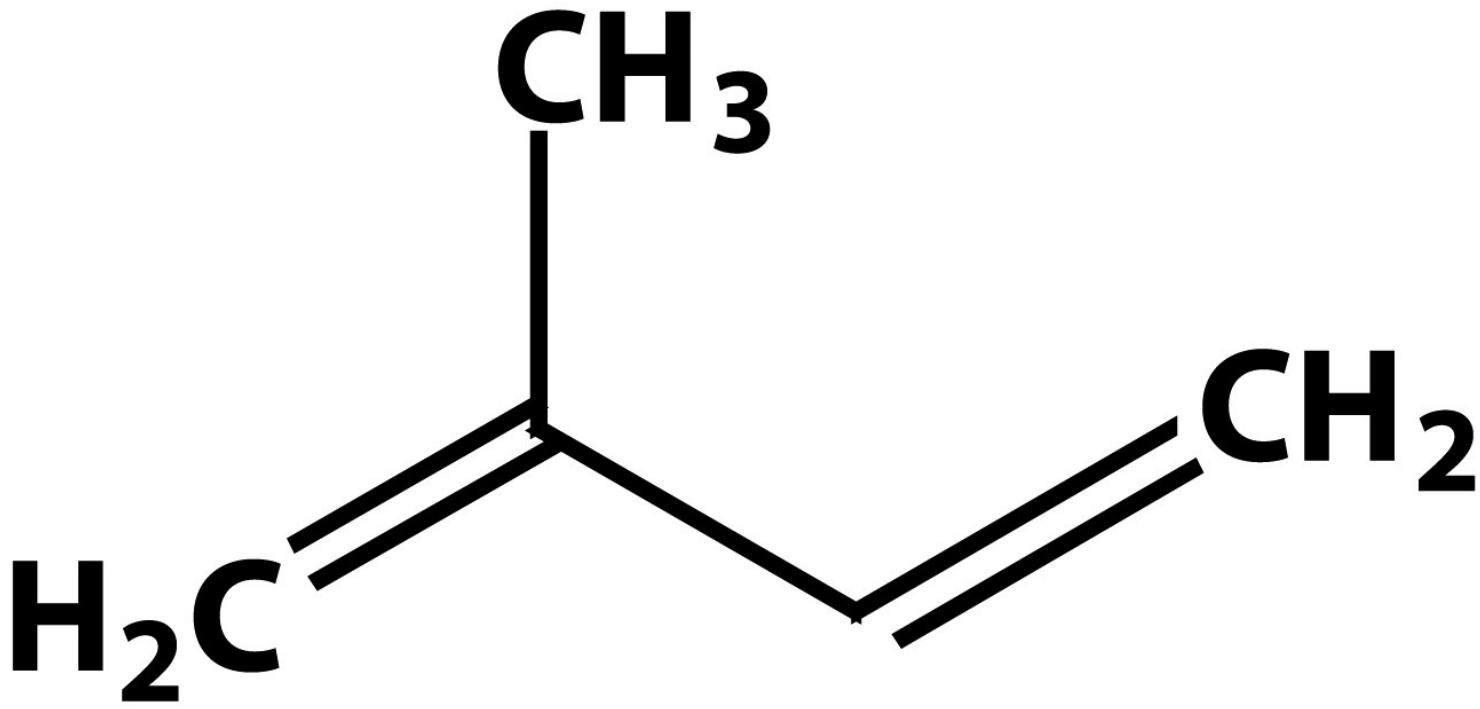
Cholesterol biosynthesis

modulates fluidity in animal membranes and is precursor of steroid hormones

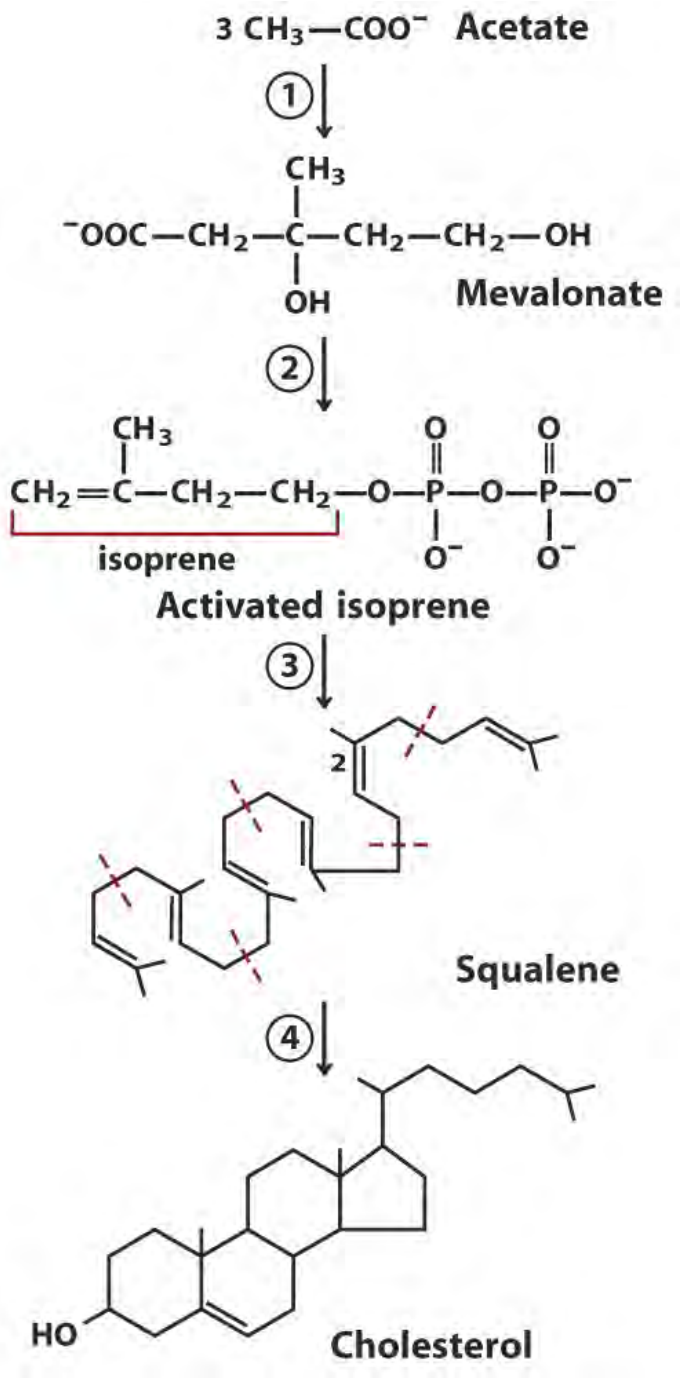


In 4 steps ....

where isoprene is the key intermediate



Isoprene



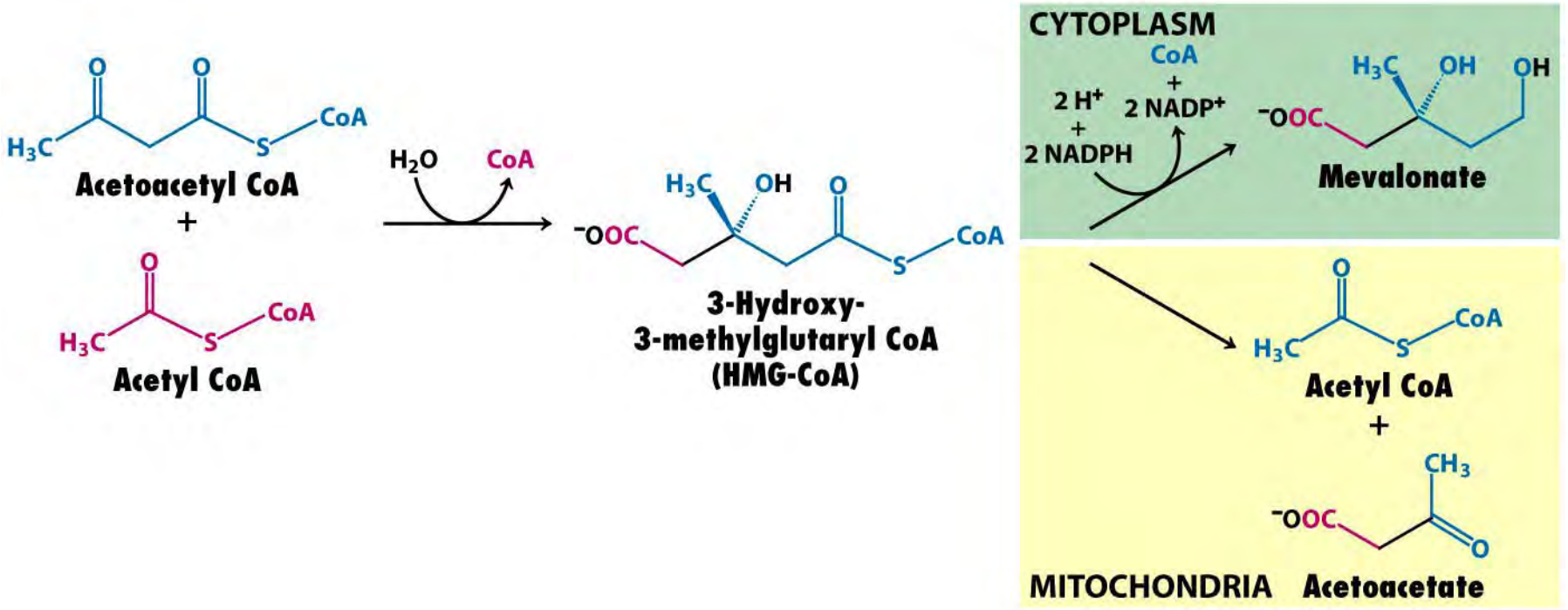
1. Condensation of 3 Ac-CoA to mevalonate

2. Conversion of mevalonate to activated isoprene (3-isopentenyl pyrophosphate)

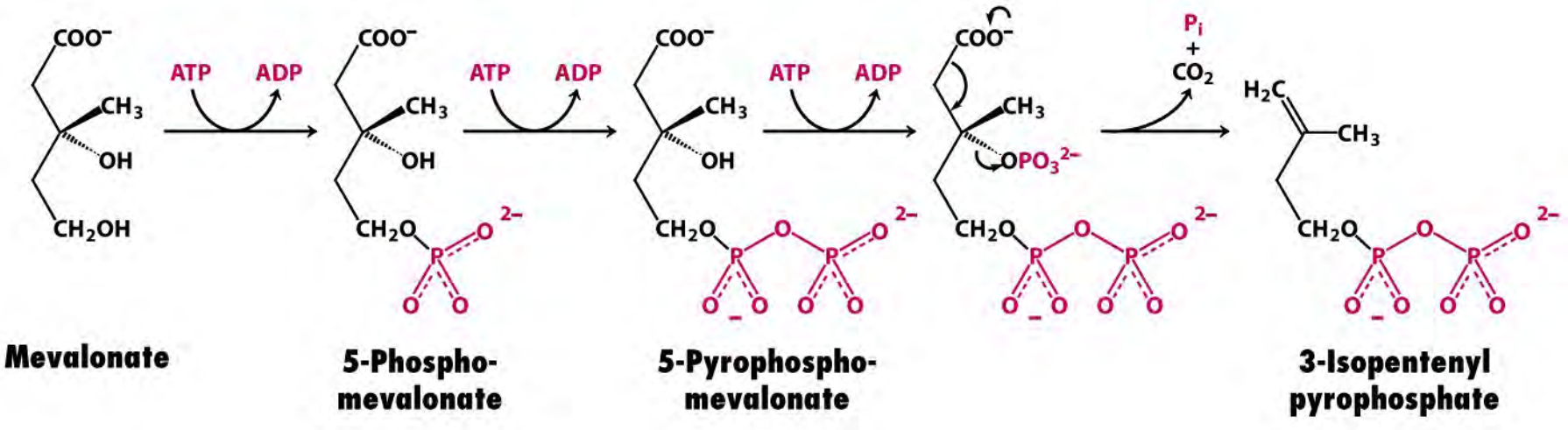
3. Condensation of 6 activated isoprene units to squalene

4. Cyclization

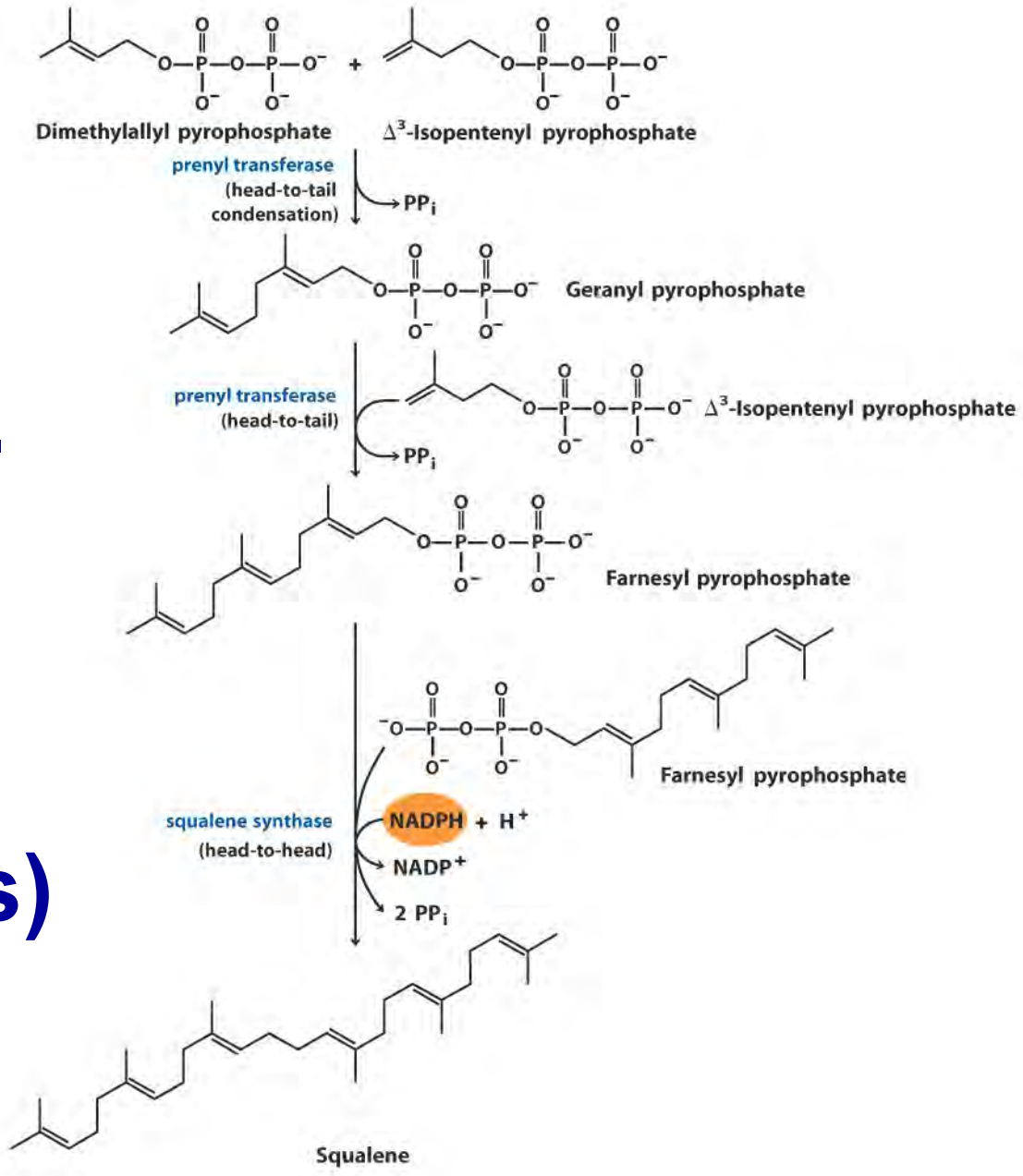
Step 1: Condensation of 3 Ac-CoA to mevalonate (6 carbons)



Step 2: Conversion of mevalonate to activated isoprenes (5 carbons)



Step 3: Cond. of isoprene-units to squalene (linear, 30 carbons)



5 + 5

=10

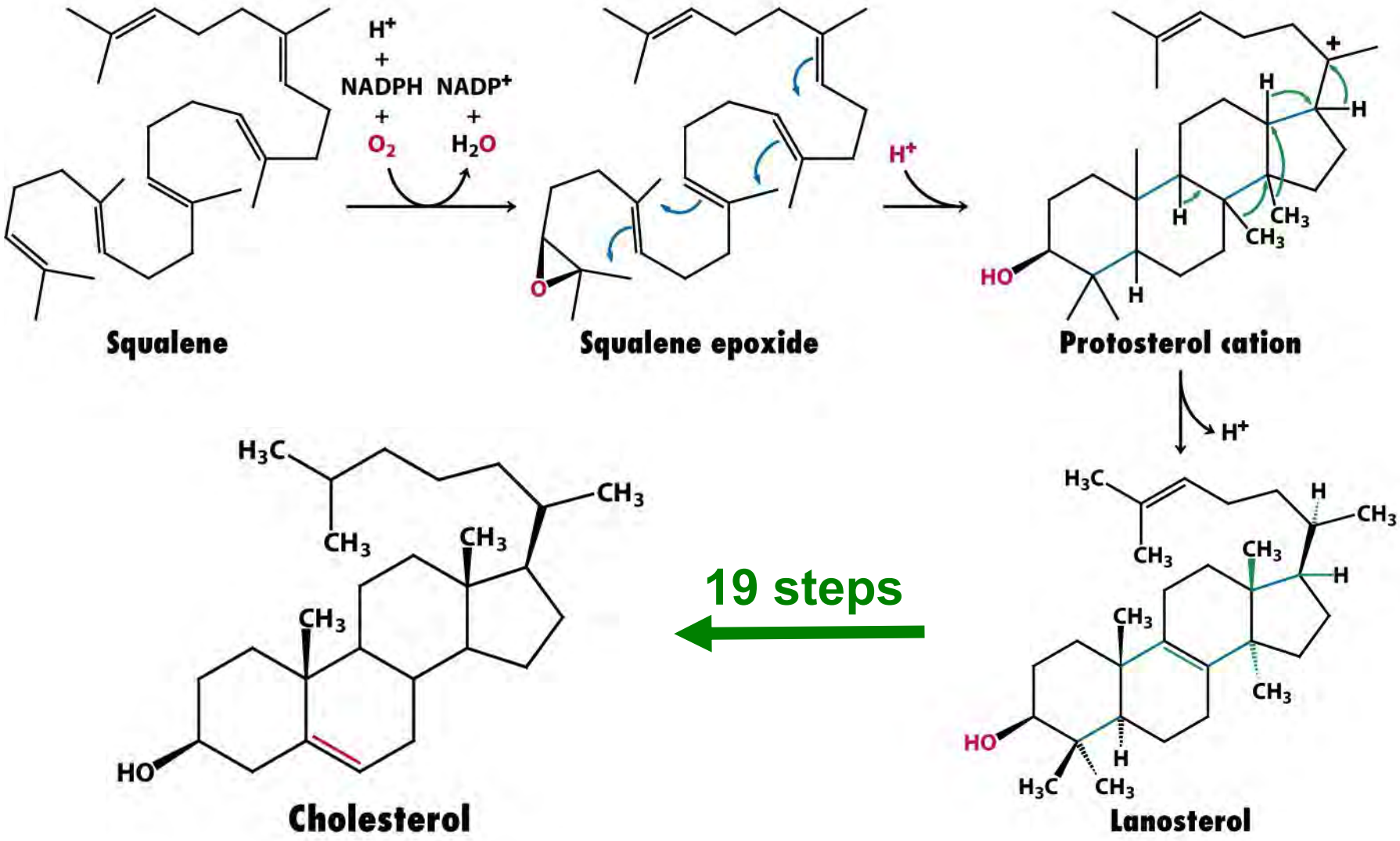
+5

= 15

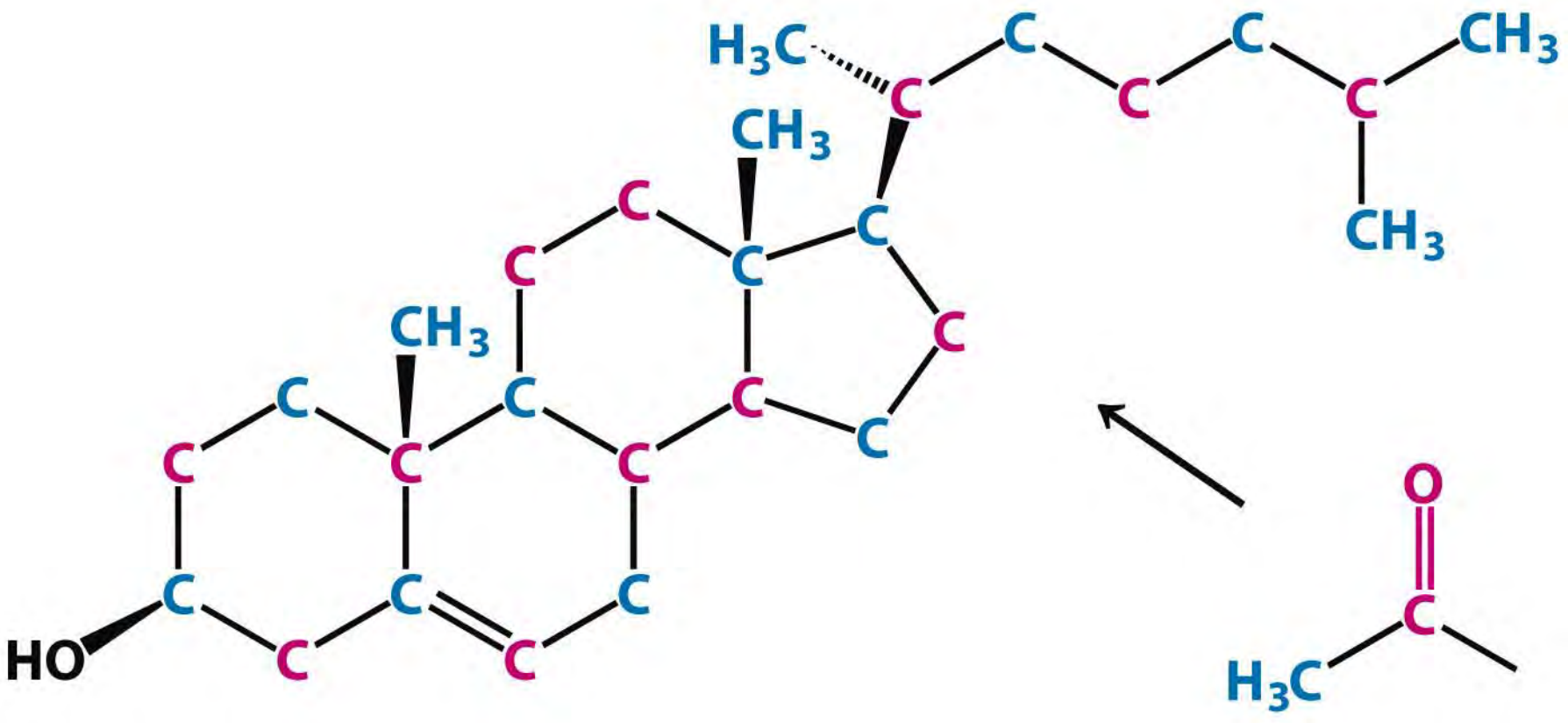
+ 15

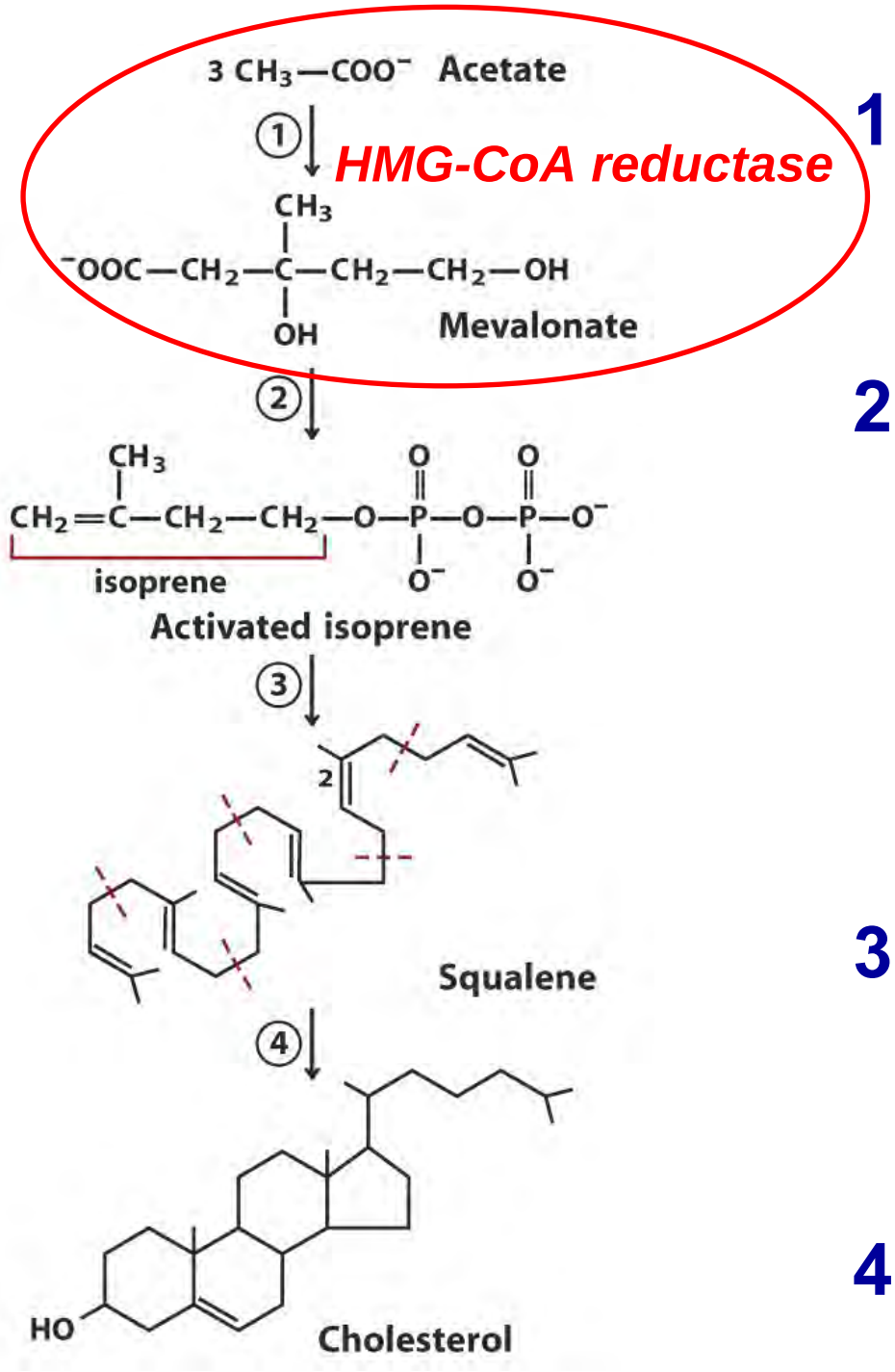
= 30

Step 4: Cyclization (4 rings)



All 27 carbons in cholesterol are dervied from Ac-CoA





1. Condensation of 3 Ac-CoA to mevalonate
   limiting step!!
2. Conversion of mevalonate to activated isoprene (3-isopoentenyl pyrophosphate)
3. Condensation of 6 activated isoprene units to squalene
4. Cyclization

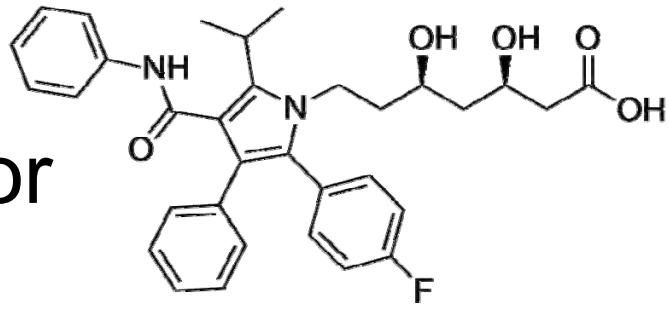
Regulation of HMG-CoA-reductase
(integral membrane protein in ER)

1. Feedback – cholesterol stimulates proteolysis
2. Hormonal – inactivated by phosphorylation, activated by dephosphorylation
3. Transcription - via SREBP (rate of synthesis)

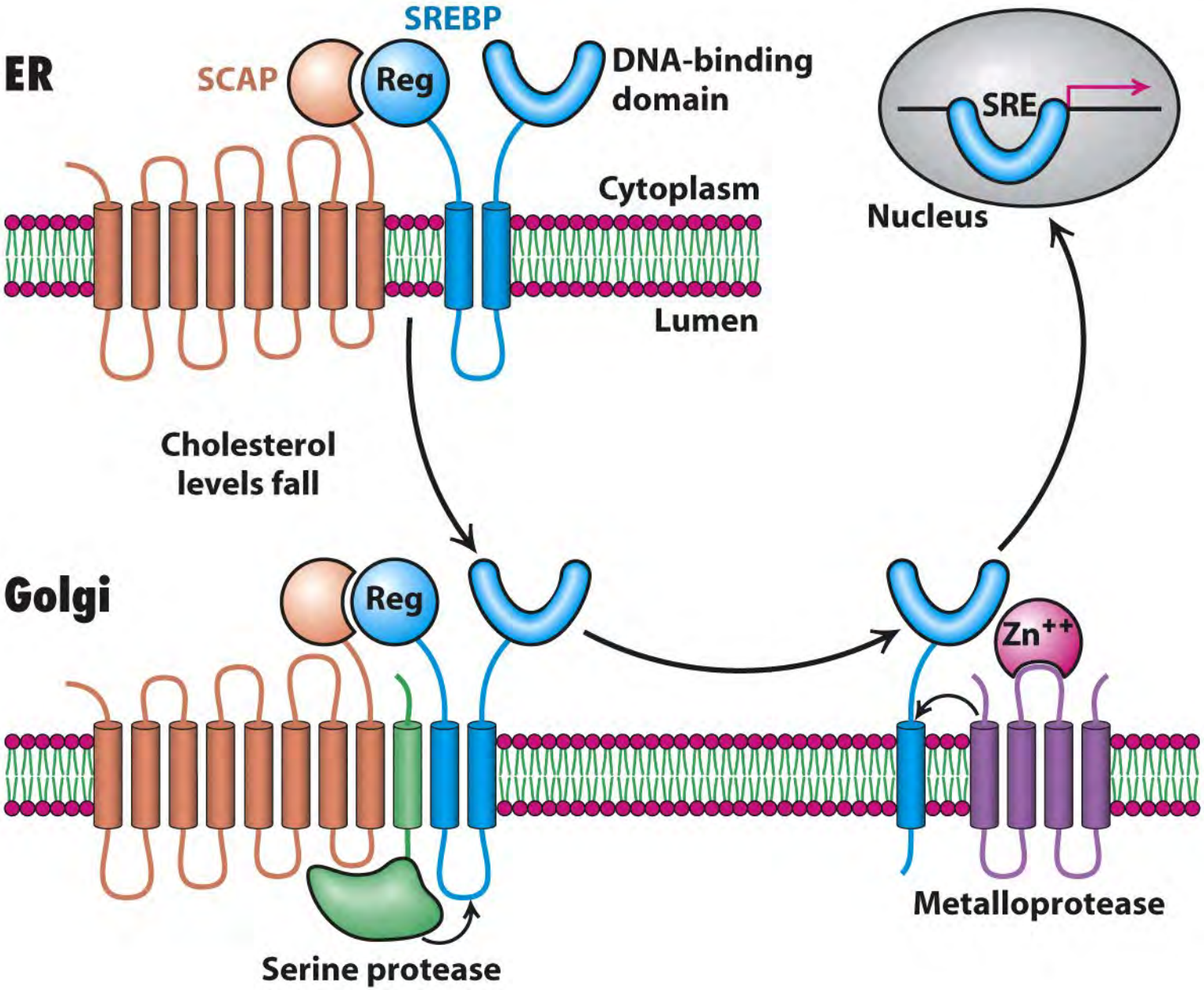
   sterol regulatory element binding protein
4. Therapeutics - mevalonate analogs

   competitive inhibitor – statins

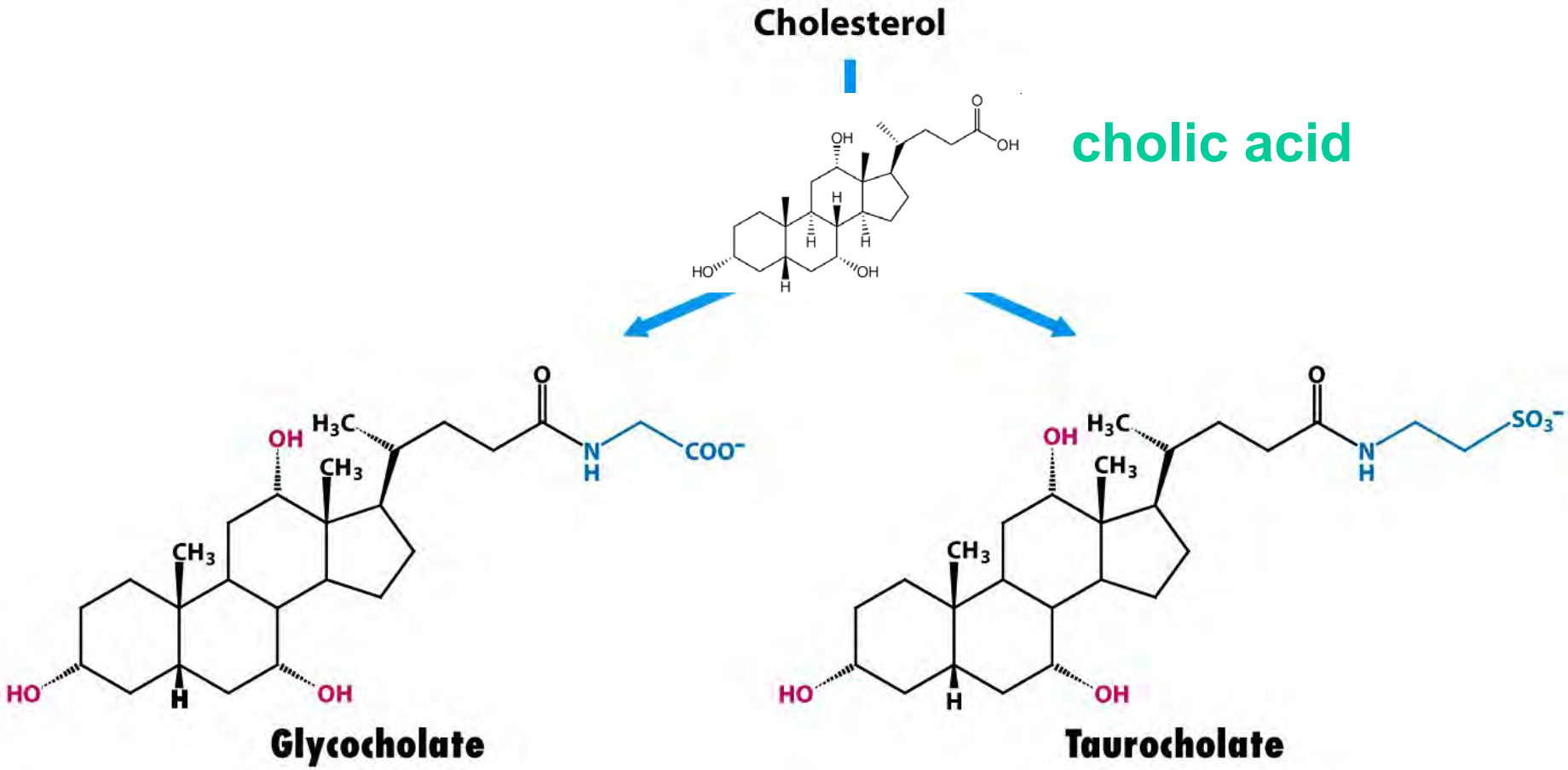
   lovastatin, atorvastatin - Lipitor



SREBP pathway = sterol regulatory binding element protein



Cholesterol is a precursor to bilesalts (and to steroid hormones and vitamin D)



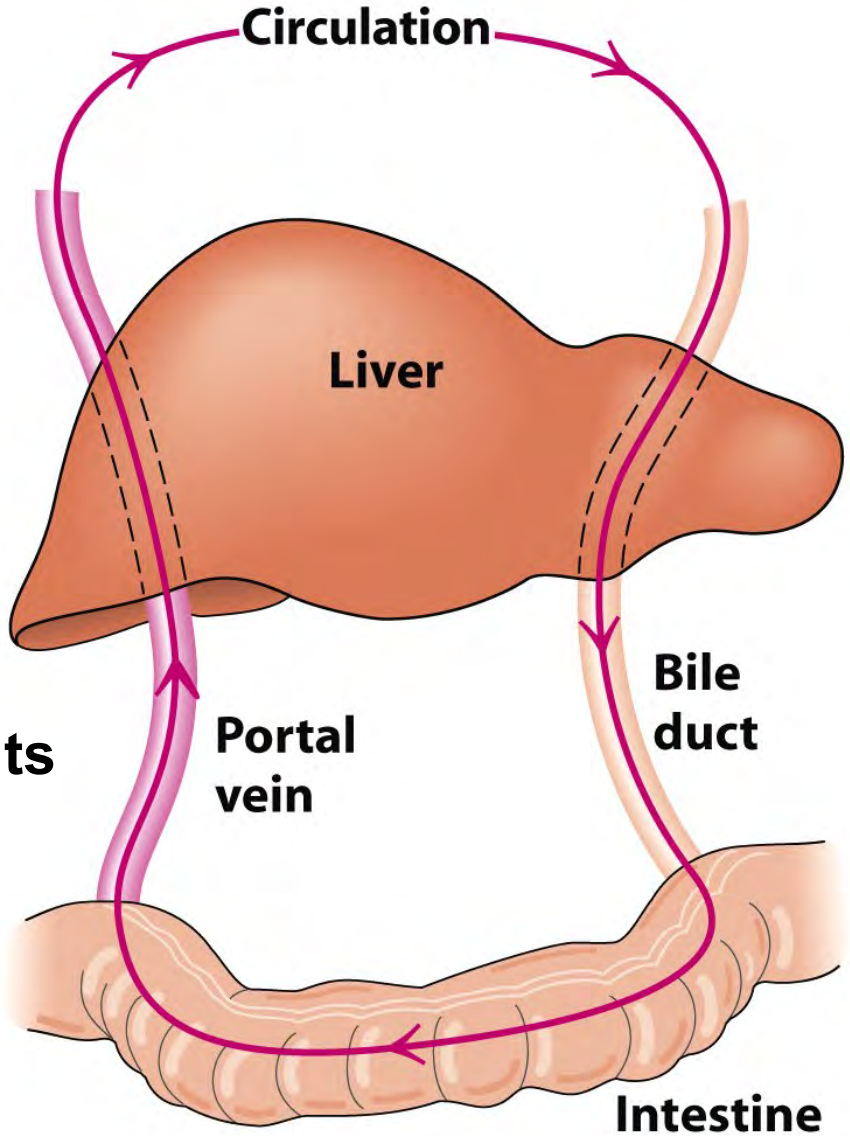
Enterohepatic circulation

circulation of bile from the liver, to the small intestine where it aids in fat digestion

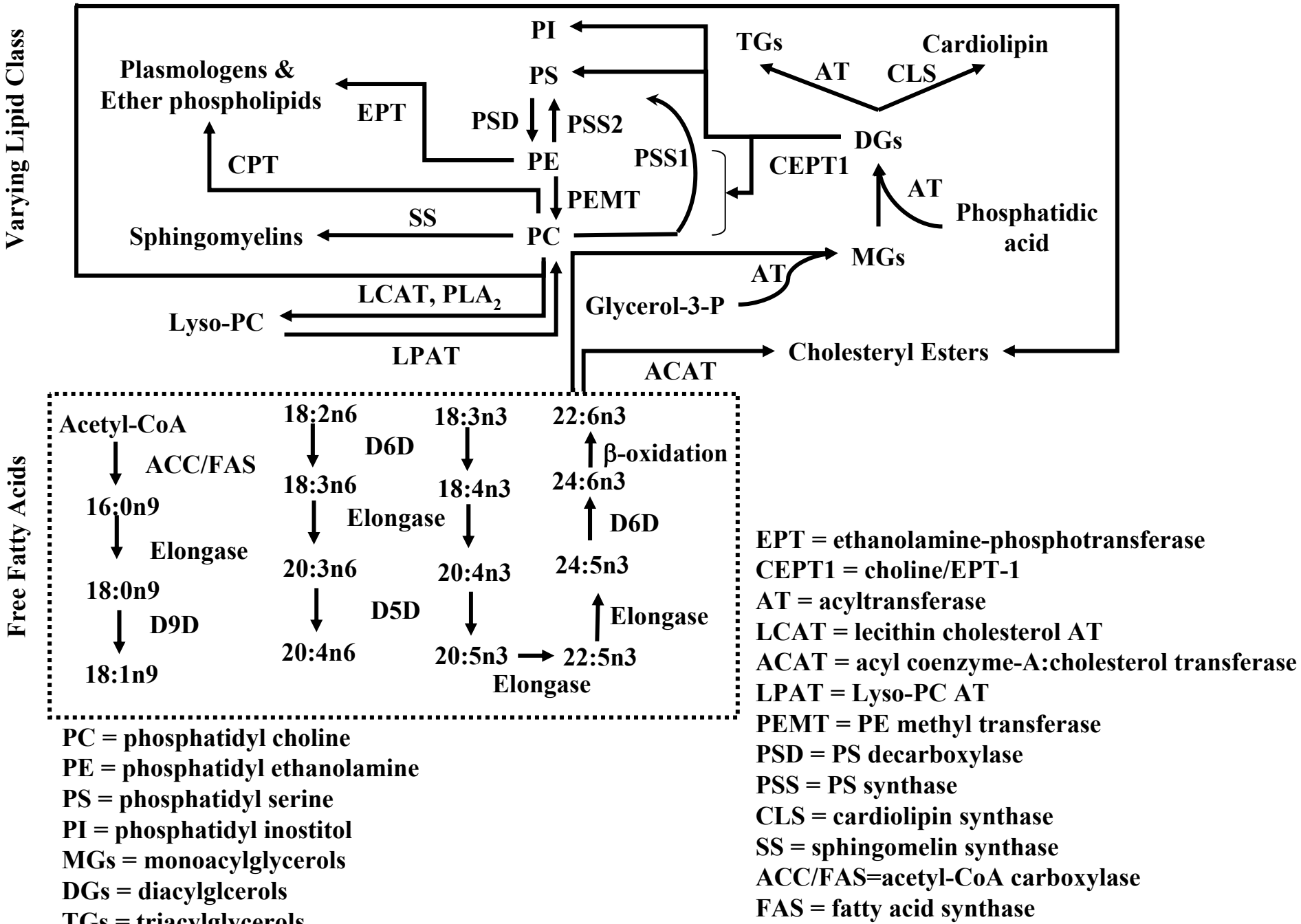
hepatocytes metabolize cholesterol to lipid-soluble bile acids → bile salts

conjugated to glycine or taurine

Glycocholate



the enterohepatic circulation of bile acids may be disrupted as a way to lower cholesterol


Varying Lipid Class
PI
PS
TGs
Cardiolipin
AT
CLS
Plasmologens &
Ether phospholipids
EPT
PSD
PSS2
DGs
CPT
PE
PSS1
CEPT1
AT
PEMT
Phosphatidic
acid
SS
Sphingomyelins
PC
MGs
AT
LCAT, PLA2
Glycerol-3-P
Lyso-PC
LPAT
Cholesteryl Esters
ACAT
Free Fatty Acids
Acetyl-CoA
ACC/FAS
16:0n9
Elongase
18:0n9
D9D
18:1n9
18:2n6
D6D
18:3n6
Elongase
20:3n6
D5D
20:4n6
18:3n3
18:4n3
20:4n3
20:5n3
Elongase
22:5n3
22:6n3
β-oxidation
24:6n3
D6D
24:5n3
Elongase
PC = phosphatidyl choline
PE = phosphatidyl ethanolamine
PS = phosphatidyl serine
PI = phosphatidyl inostitol
MGs = monoacylglycerols
DGs = diacylglcerols
TGs = triacylglycerols
EPT = ethanolamine-phosphotransferase
CEPT1 = choline/EPT-1
AT = acyltransferase
LCAT = lecithin cholesterol AT
ACAT = acyl coenzyme-A:cholesterol transferase
LPAT = Lyso-PC AT
PEMT = PE methyl transferase
PSD = PS decarboxylase
PSS = PS synthase
CLS = cardiolipin synthase
SS = sphingomelin synthase
ACC/FAS=acetyl-CoA carboxylase
FAS = fatty acid synthase

What is a lipid?

Classical definition:

biological molecule that is soluble in organic solvent, but insoluble in water

Modern (specific) definition:

fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds

More specific definition:

Hydrophobic small molecules that originate by carbanion-based condensations of thioesters (fatty acids, polyketides, etc.) and/or by carbocation-based condensations of isoprene units (prenols, sterols, etc)

Specific structural-based definition

Lipid Biosynthesis - summary

- **Lipids overview** classification, structure, synthesis
- **Fatty acids** in liver (fat) and cyotosol; Mal-CoA; multifunctional enzyme; modified in ER
- **Eicosanoids** important signaling molecules; play roles in pain and inflammation
- **Triacylglycerols** in liver, fat, and intestine; energy storage; phosphatidate; dynamic equilibrium
- **Phospholipids** in almost all cells; phosphatidate, 2 strategies for synthesis, membrane components
- **Cholesterol** in all cells; mostly liver, 4 steps, from Ac-CoA via isoprene, HMG-CoA reductase
- **Bile acids** important in fat digestion, enterohepatic circulation

Whew…….

- **http://www.cyberlipid.org/**
- **http://www.lipidlibrary.co.uk/**
- **http://www.lipidmaps.org/**
- **http://www.metabolomics.se/**
  - **(contains downloadable file of today's lecture under the section "Courses")**