Membrány a lipidy (modulace cytokinetiky)

Laboratory of Cytokinetics

Institute of Biophysics, Brno
Academy of Sciences
Czech Republic

The four families of small organic molecules in cells

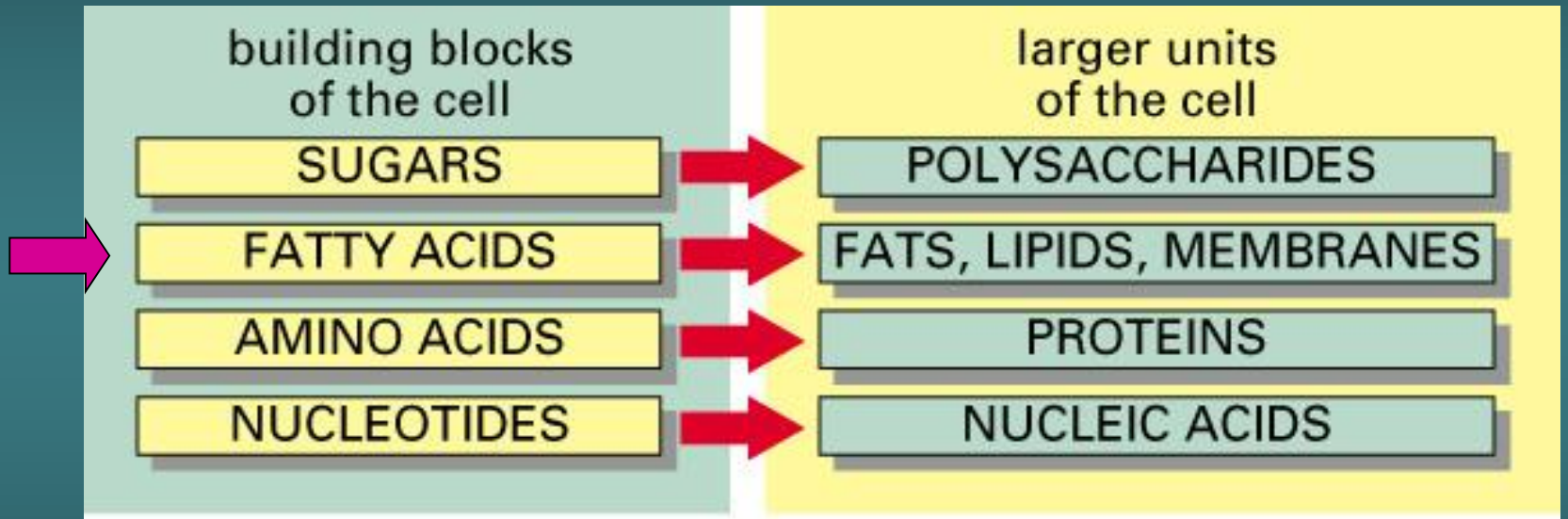


Figure 2–17. Molecular Biology of the Cell, 4th Edition.

TABLE 2–3 The Approximate Chemical Composition of a Bacterial Cell

	PERCENT OF TOTAL CELL WEIGHT	NUMBER OF TYPES OF EACH MOLECULE
Water	70	1
Inorganic ions	1	20
Sugars and precursors	1	250
Amino acids and precursors	0.4	100
Nucleotides and precursors	0.4	100
Fatty acids and precursors	1	50
Other small molecules	0.2	~300
Macromolecules (proteins, nucleic acids, and polysaccharides)	26	~3000

STRUCTURÁLNÍ ÚLOHA

FOSFOPIDŮ v BUŇKÁCH

MEMBRANOVÉ SYSTÉMY a buněčné kompartmenty

Protientropické důsledky

NEODMYSLITELNÉ od BUNĚČNÝCH FUNKCÍ

Kompartmenty:

Funkně nebo prostorově oddělené soubory prvků (složek)

Důsledek kompartmentace (existence jednotlivých kompartmentů) prvky (např. látky nebo buňky) jsou nerovnoměrně rozděleny.

Příklady:

Všechny membránami ohraničené struktury mají (z hlediska rozdělení látek) „své vnitřní prostředí“ a selektivně akumulují nebo zadržují určité látky proti koncentračnímu spádu.

Už tímto prostým faktem jsou některé reakce umožněny, jiným může být zabráněno.

Tato **protientropická distribuce molekul** v buňce směřující proti neuspořádanosti má velký význam pro buněčný metabolismus a regulace.

Umožňuje ji právě

existence buněčných membrán – jeden ze základů biologických systémů

A fatty acid

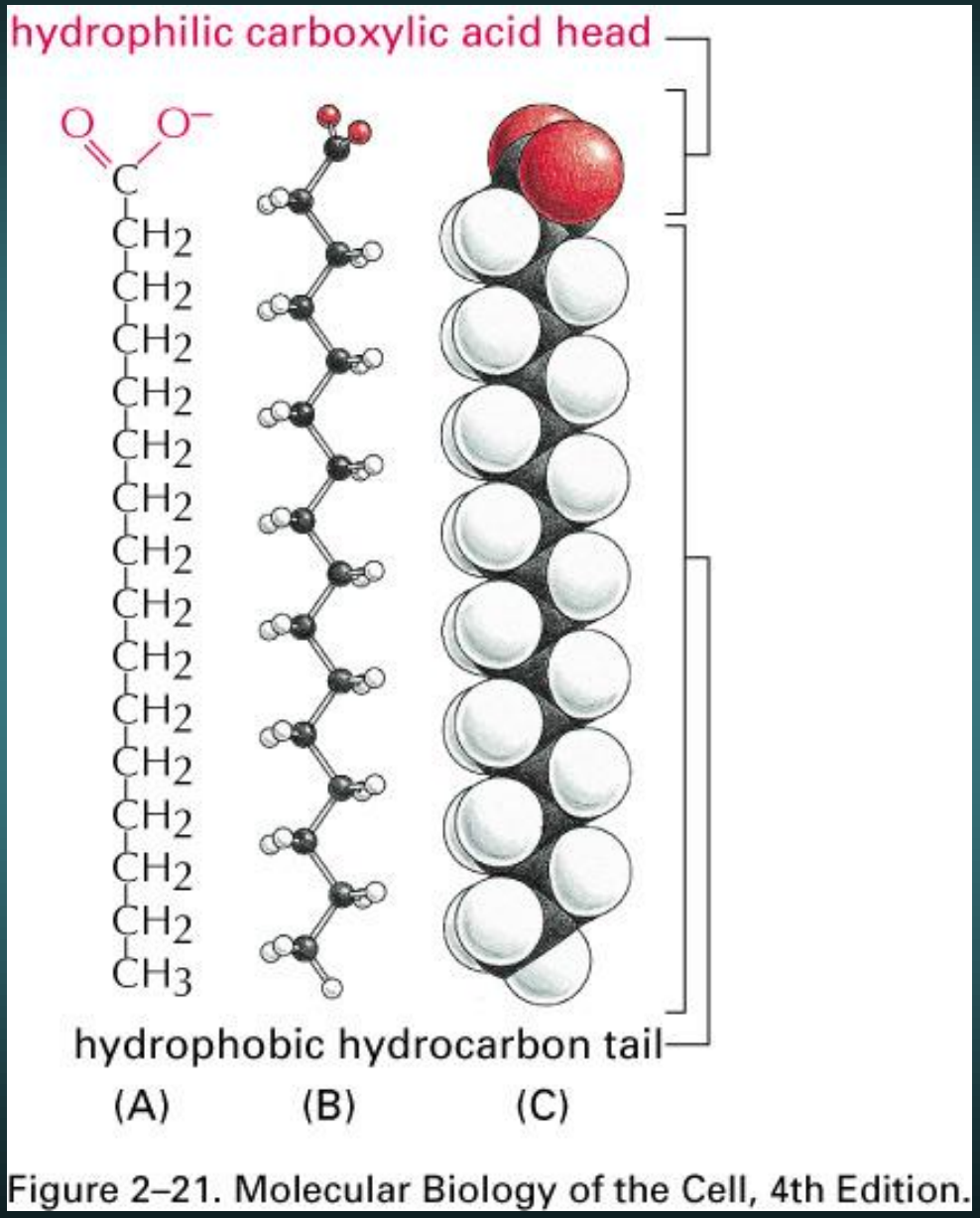


Figure 2–21. Molecular Biology of the Cell, 4th Edition.

C-16
(k. palmitová)

Phospholipid structure and the orientation of phospholipids in membrane

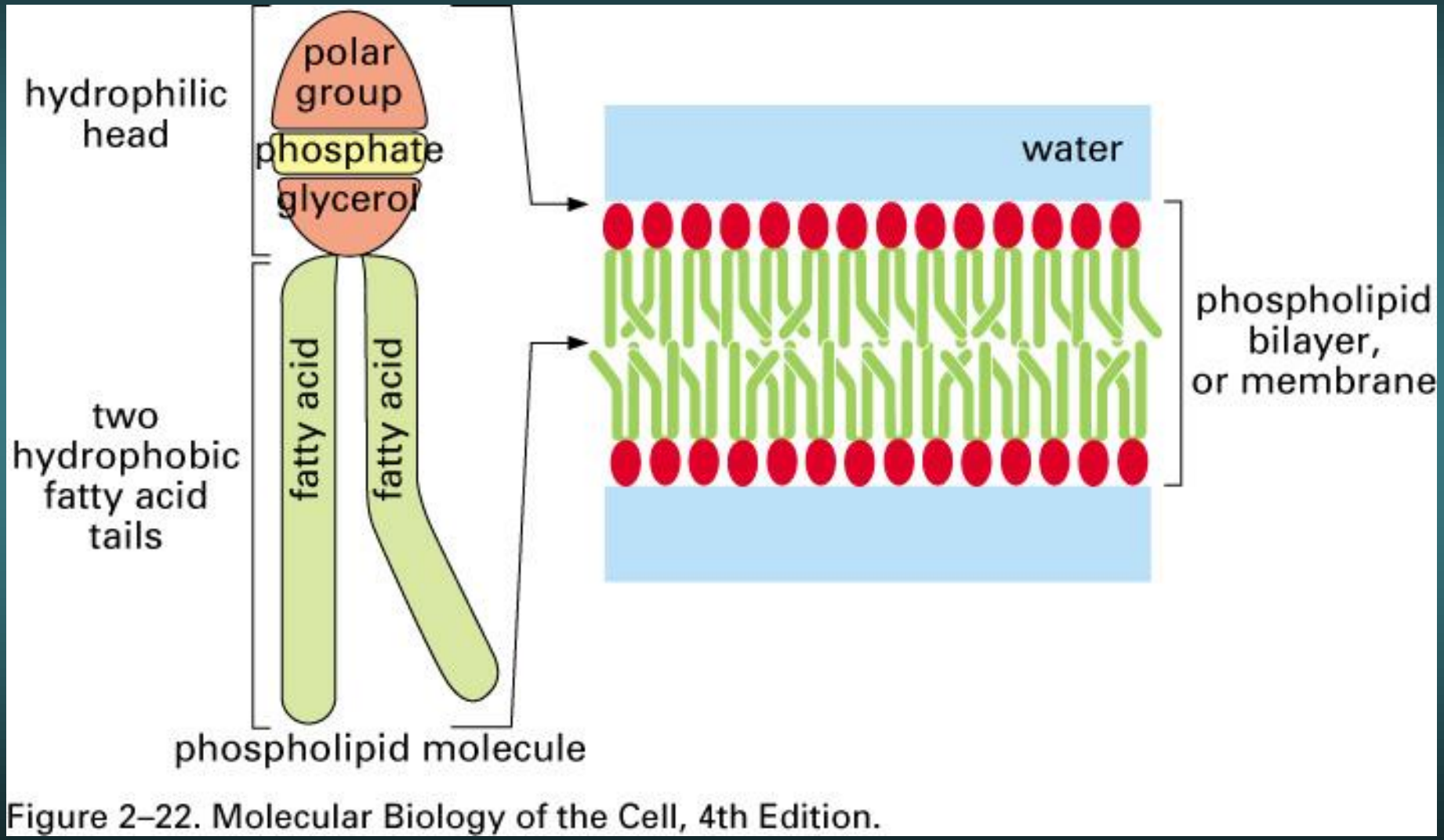
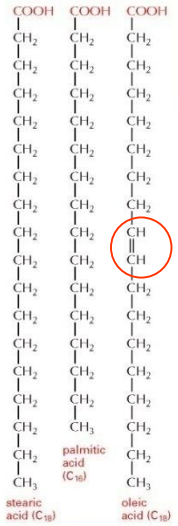


Figure 2–22. Molecular Biology of the Cell, 4th Edition.

PANEL 2–5 Fatty Acids and Other Lipids

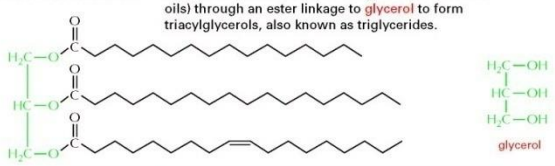
COMMON FATTY ACIDS

These are carboxylic acids with long hydrocarbon tails.

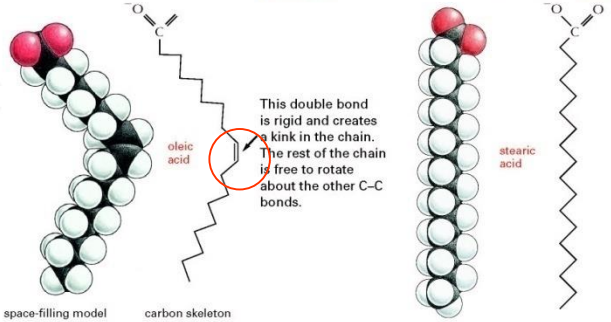


TRIACYLGLYCEROLS

Fatty acids are stored as an energy reserve (fats and oils) through an ester linkage to glycerol to form triacylglycerols, also known as triglycerides.

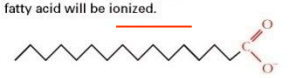


Hundreds of different kinds of fatty acids exist. Some have one or more double bonds in their hydrocarbon tail and are said to be unsaturated. Fatty acids with no double bonds are saturated.

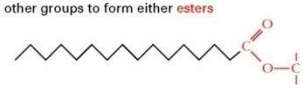


CARBOXYL GROUP

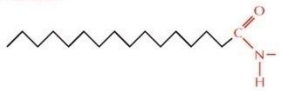
If free, the carboxyl group of a fatty acid will be ionized.



But more usually it is linked to other groups to form either esters

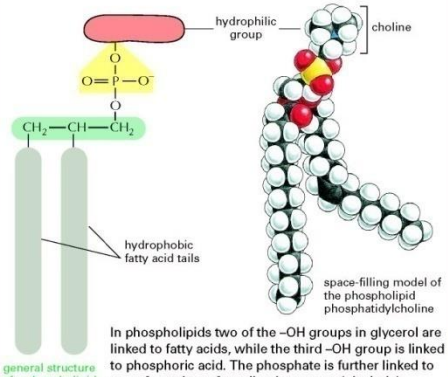


or amides.



PHOSPHOLIPIDS

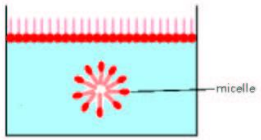
Phospholipids are the major constituents of cell membranes



In phospholipids two of the –OH groups in glycerol are linked to fatty acids, while the third –OH group is linked to phosphoric acid. The phosphate is further linked to one of a variety of small polar groups (alcohols).

LIPID AGGREGATES

Fatty acids have a hydrophilic head and a hydrophobic tail.

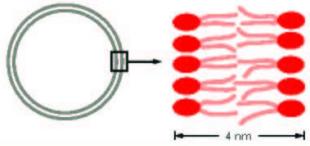


In water they can form a surface film or form small micelles.

Their derivatives can form larger aggregates held together by hydrophobic forces:

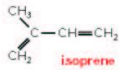
Triglycerides can form large spherical fat droplets in the cell cytoplasm.

Phospholipids and glycolipids form self-sealing lipid bilayers that are the basis for all cell membranes.



OTHER LIPIDS

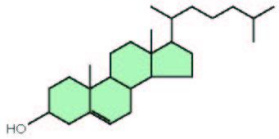
Lipids are defined as the water-insoluble molecules in cells that are soluble in organic solvents. Two other common types of lipids are steroids and polyisoprenoids. Both are made from isoprene units.



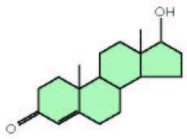
isoprene

STEROIDS

Steroids have a common multiple-ring structure.



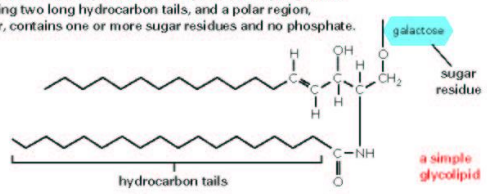
cholesterol—found in many membranes



testosterone—male steroid hormone

GLYCOLIPIDS

Like phospholipids, these compounds are composed of a hydrophobic region, containing two long hydrocarbon tails, and a polar region, which, however, contains one or more sugar residues and no phosphate.



POLYISOPRENOIDS

long-chain polymers of isoprene

dolichol phosphate—used to carry activated sugars in the membrane-associated synthesis of glycoproteins and some polysaccharides

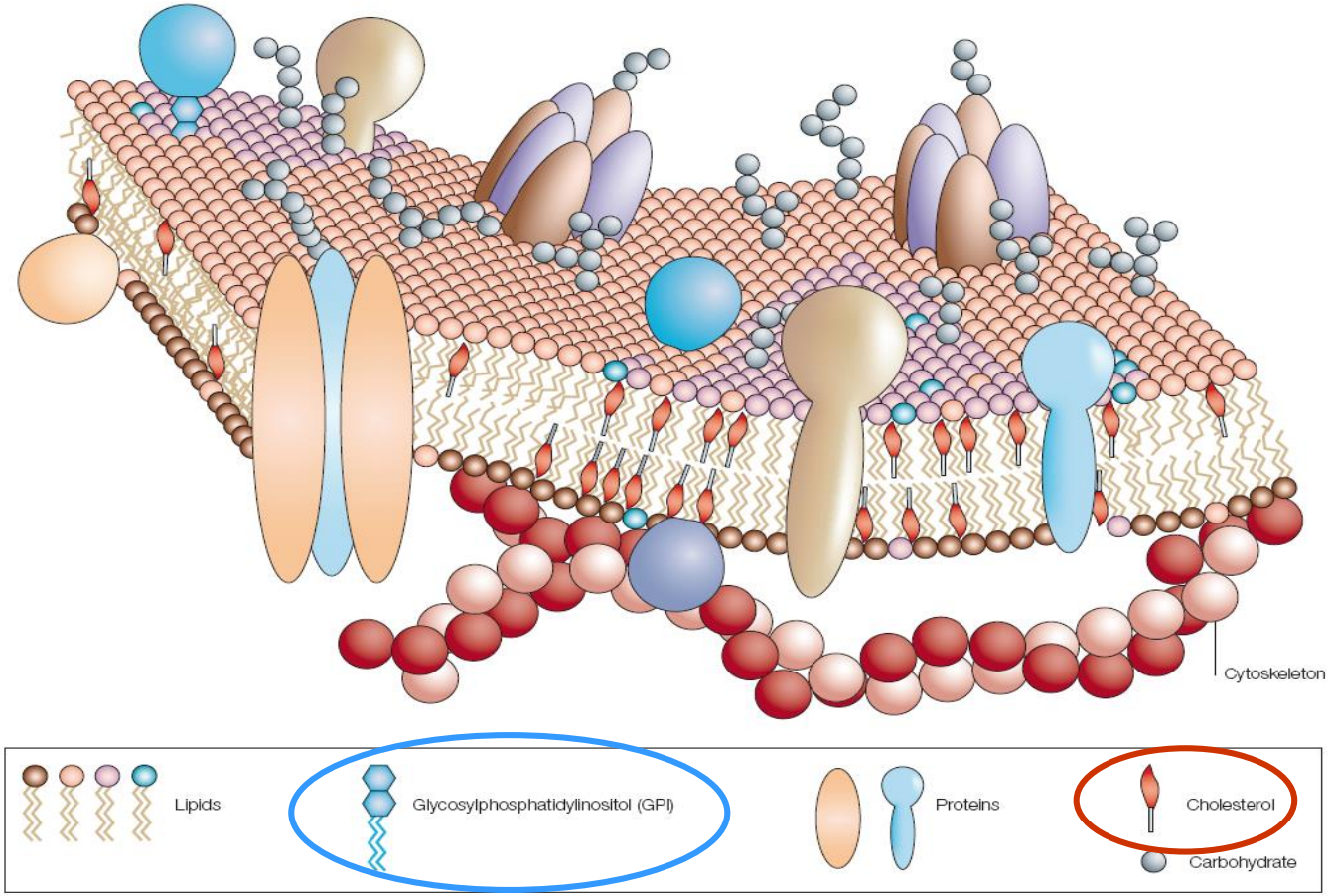


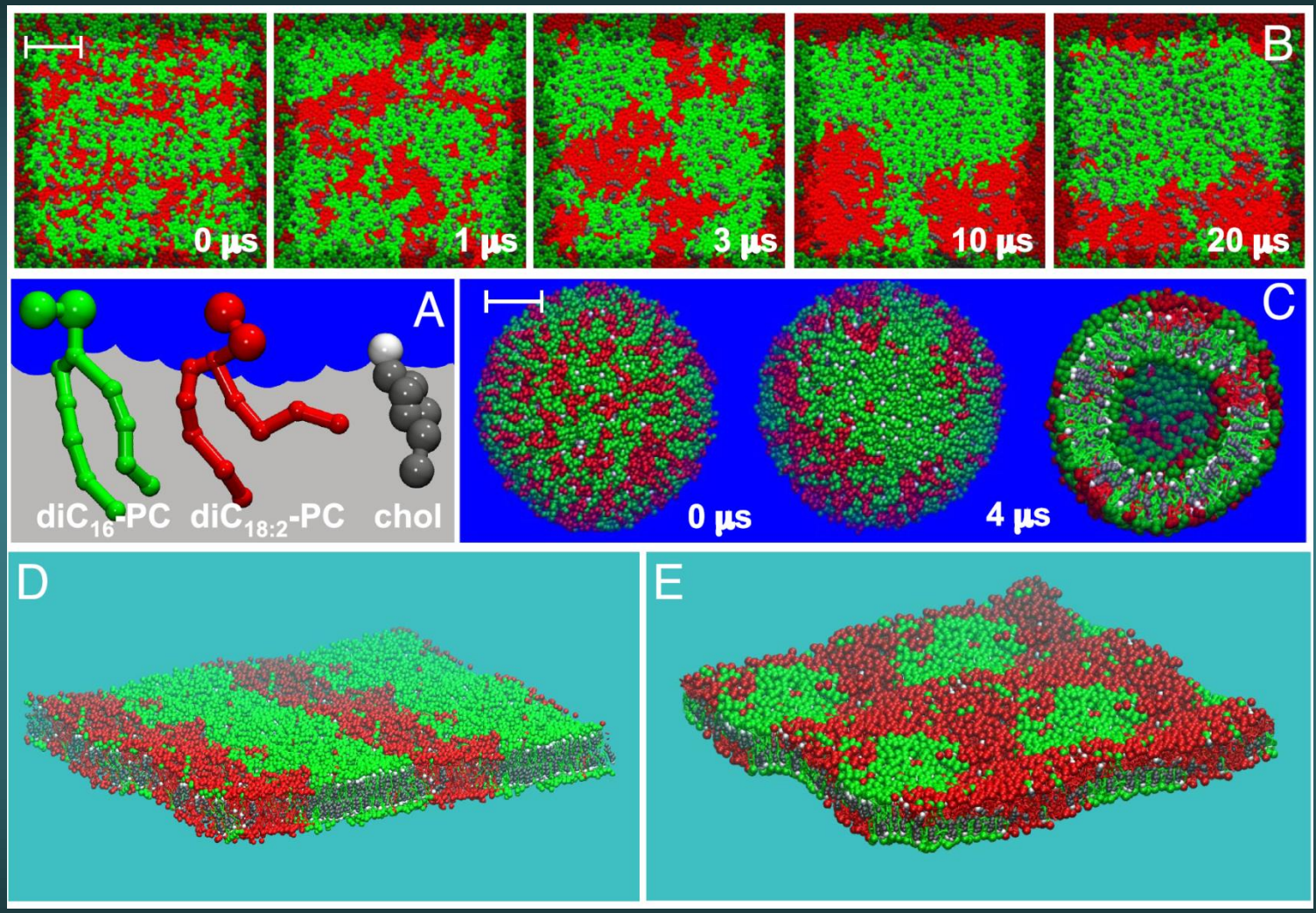
Figure 2 | **The Fluid-Mosaic-Model of the cell membrane.** Like a mosaic, the cell membrane is a complex structure made up of many different parts, such as proteins, phospholipids and cholesterol. The relative amounts of these components vary from membrane to membrane, and the types of lipids in membranes can also vary.

Pietzsch J et al., Nature Reviews, October 2004

Zajištění většiny biologických funkcí se neobejde bez unikátních interakcí lipidových komponent [1] s dalšími biologicky významnými molekulami. Jejich modulace mohou významně měnit intenzitu a také směr sign. transdukce

1) např. tzv. lipidových raftů – membránových lipidových mikrodomén obohacených o glykosfingolipidy a cholesterol

Dynamický charakter biologických membrán (model)



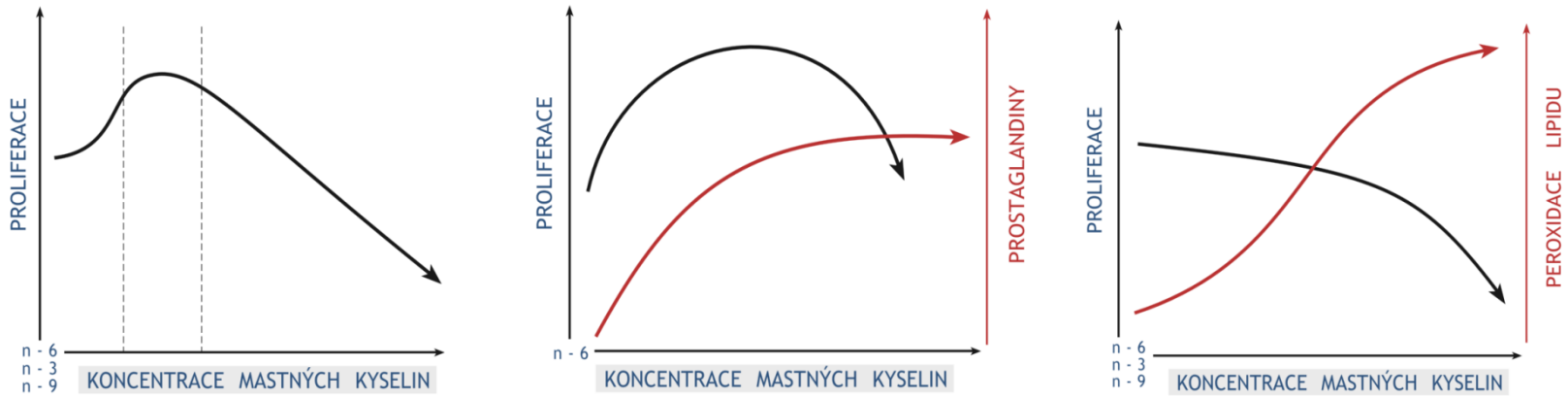
PNAS | November 11, 2008 | vol. 105 | no. 45 | 17367–17372

Spektrum eikosanoisů

Efekty závisí na koncentraci – <u>další důkazy</u> z oblasti <u>nádorové</u> problematiky:

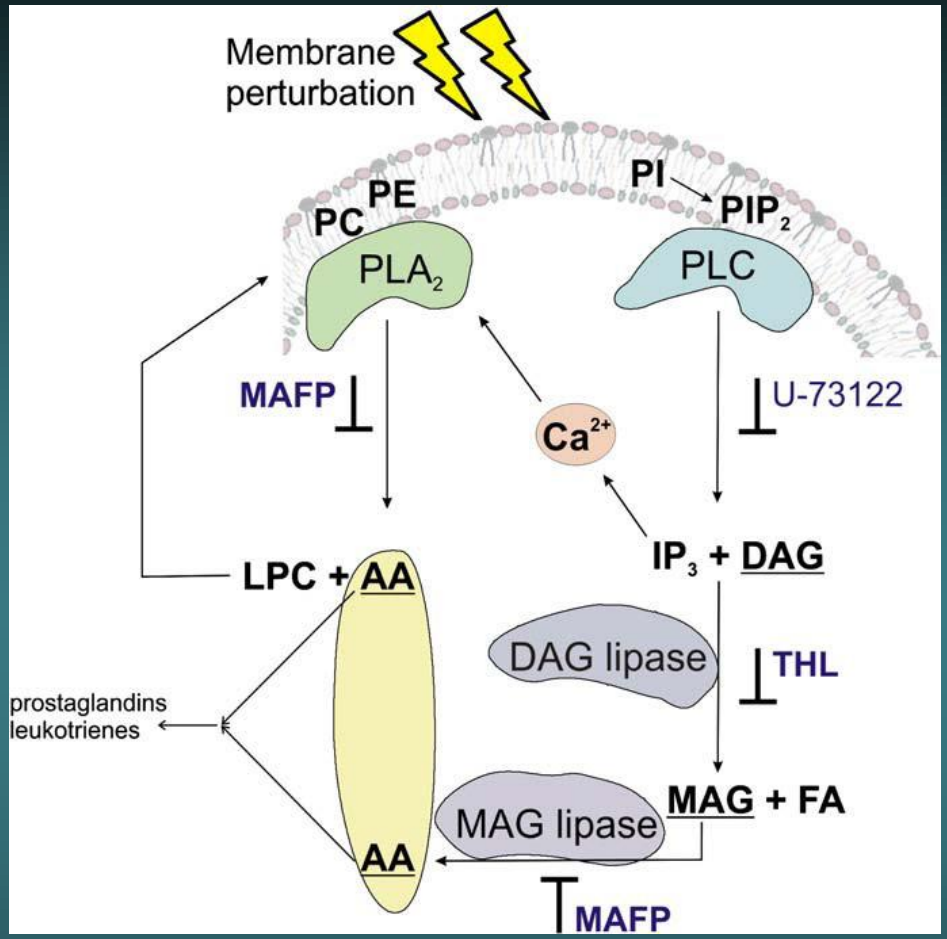
VLIV KONCENTRACE NENASYCENÝCH MASTNÝCH KYSELIN NA PROLIFERACI NÁDOROVÝCH BUNĚK – shrnutí (do r. 1985)

(„FATTY ACID PARADOXES“)



(VNMK mohou generovat jak +, tak – signál na proliferaci)

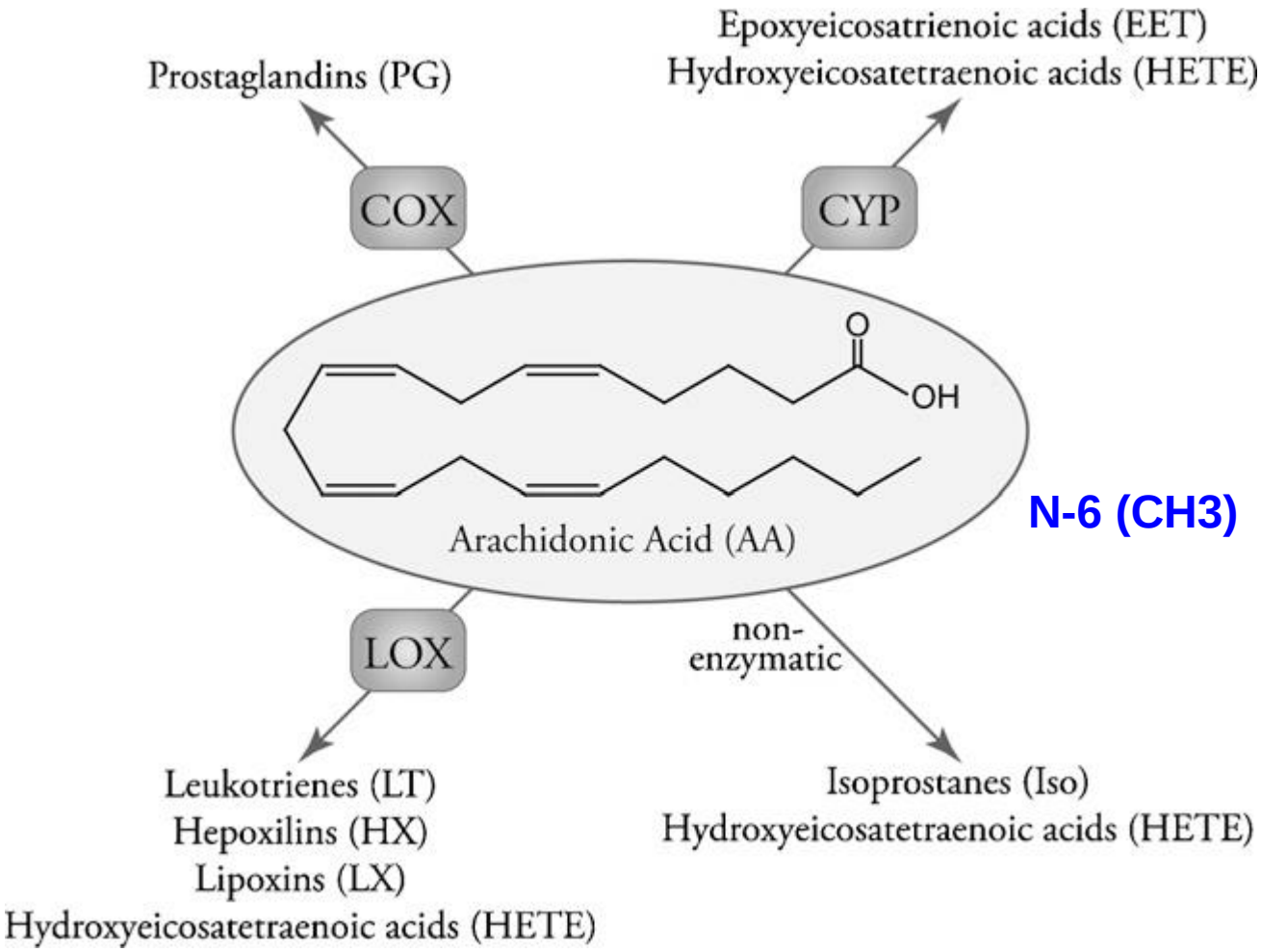
D.G.Cornwell and N.Morisaki, Free Radicals in Biology. Vol.6, 1984



Overview of the potential arachidonic acid releasing pathways, applied inhibitors
and detected lipid intermediates (underlined). Note that DAG, AA and Ca2+ are known
Hsp upregulators.

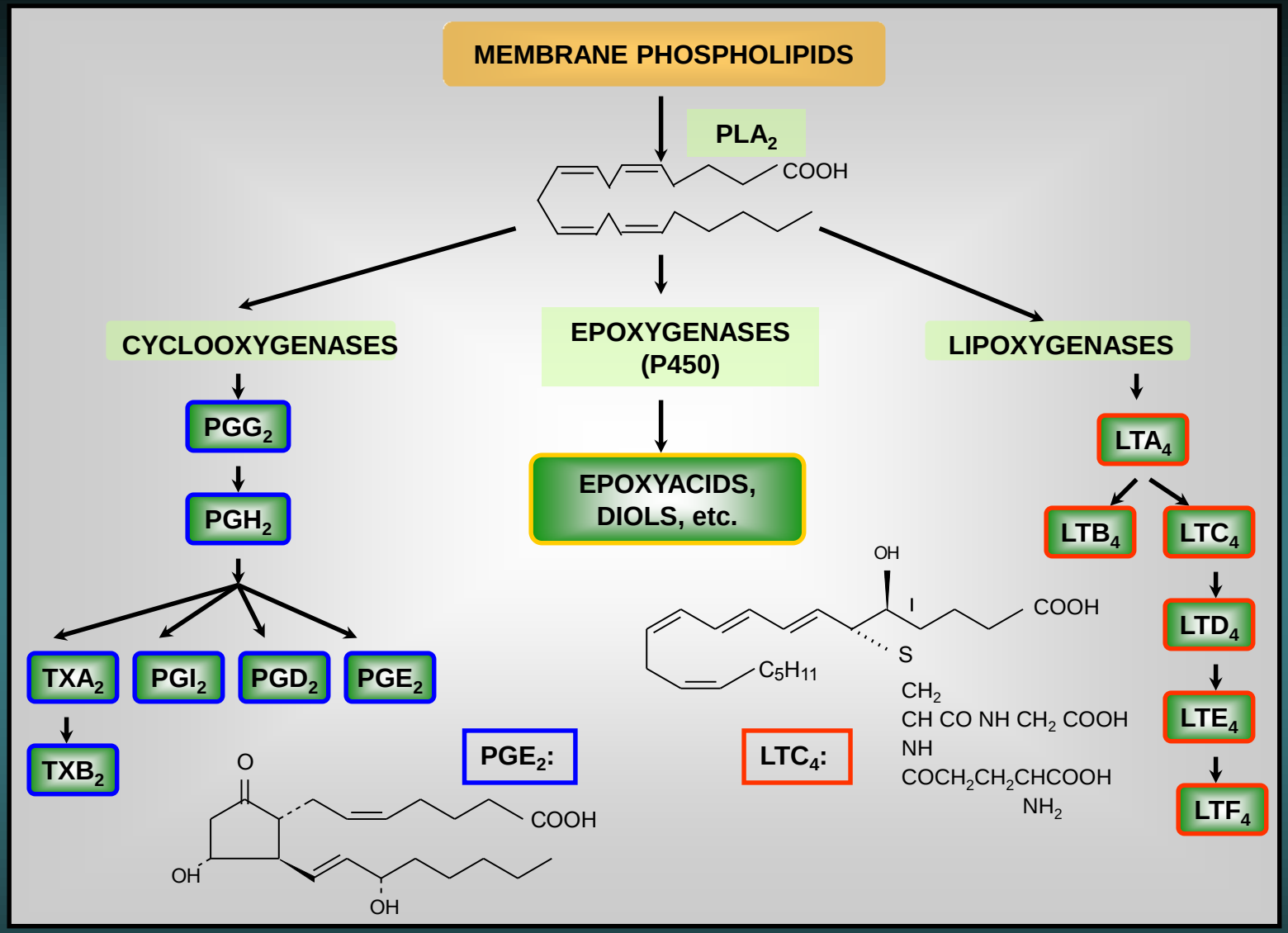
Lipidomics reveals membrane lipid remodelling and release of potential lipid mediators during early stress responses in a murine melanoma cell line

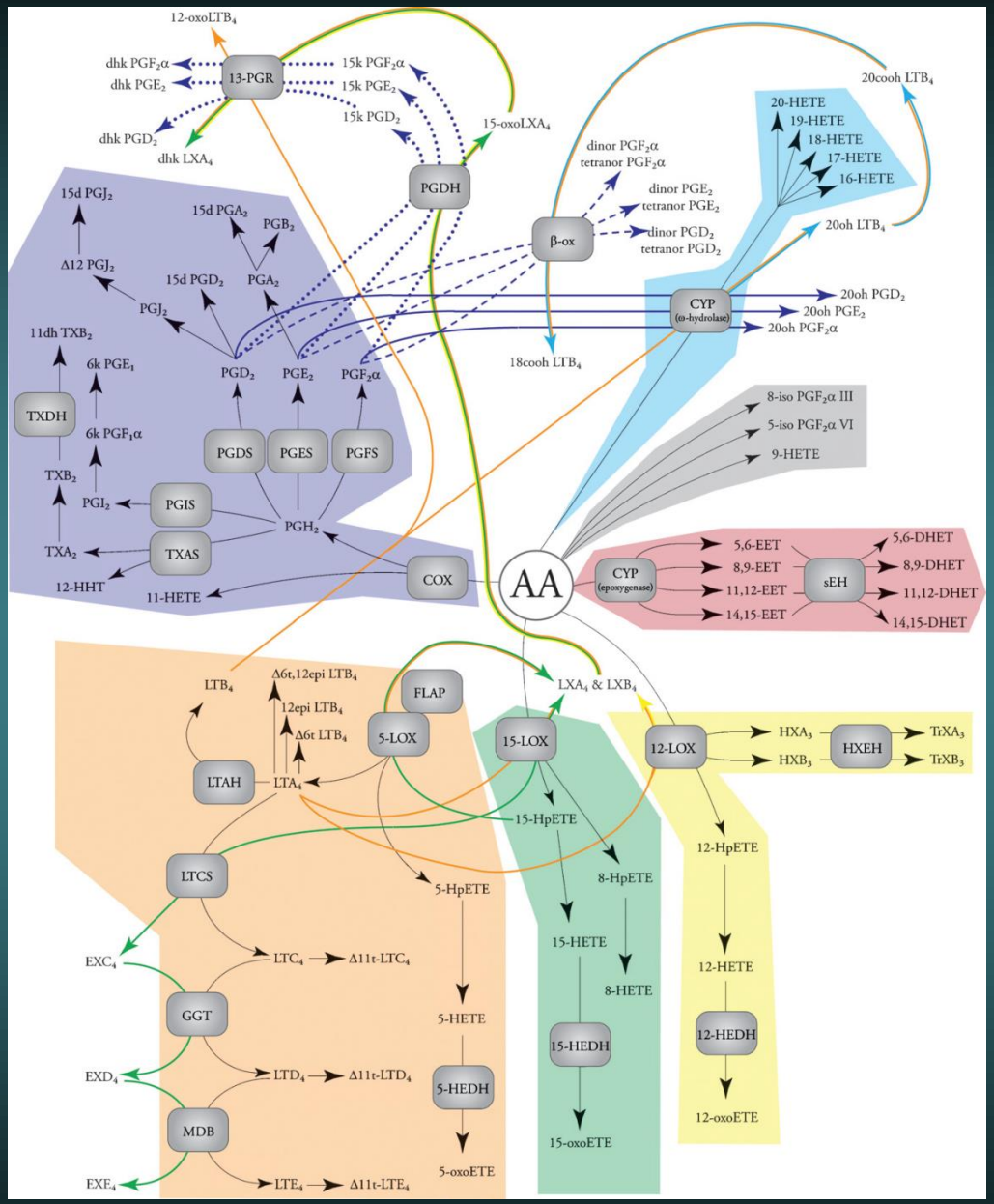
**Gábor Balogh a, Mária Péter a, Gerhard Liebisch b, Ibolya Horváth a, Zsolt Török a, Enikő Nagy a,
Andriy Maslyanko a, Sándor Benkő c, Gerd Schmitz b, John L. Harwood d,□, László Vígh a,□****Biochimica et Biophysica Acta xxx (2010) xxx–xxx**



N-6 (CH3)

J Lipid Res. 2009 June; 50(6): 1015–1038.
doi: 10.1194/jlr.R900004-JLR200.


MEMBRANE PHOSPHOLIPIDS
PLA2
COOH
CYCLOOXYGENASES
EPOXYGENASES (P450)
LIPOXYGENASES
PGG2
PGH2
EPOXYACIDS, DIOLS, etc.
LTA4
LTB4
LTC4
LTD4
LTE4
LTF4
TXA2
PGI2
PGD2
PGE2
TXB2
OH
I
COOH
S
C5H11
CH2
CH CO NH CH2 COOH
NH
COCH2CH2CHCOOH
NH2
LTC4:
PGE2:
O
COOH
OH
OH



Major eicosanoid biosynthetic pathways. The metabolites of the major pathways are indicated in color:

COX (purple),
5-LOX (orange),
15-LOX (green),
12-LOX (yellow),
CYP epoxygenase (red),
CYP ω-hydroxylase (cyan),
and nonenzymatic oxidation (gray)

J Lipid Res. 2009 June; 50(6): 1015–1038.

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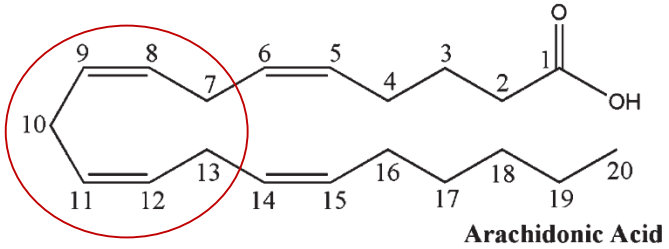
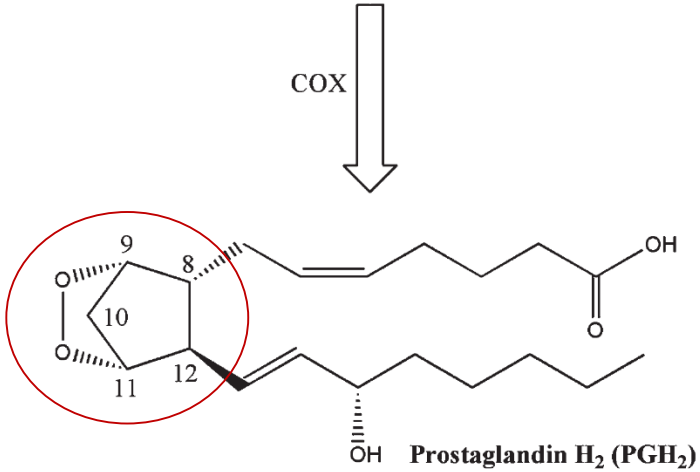
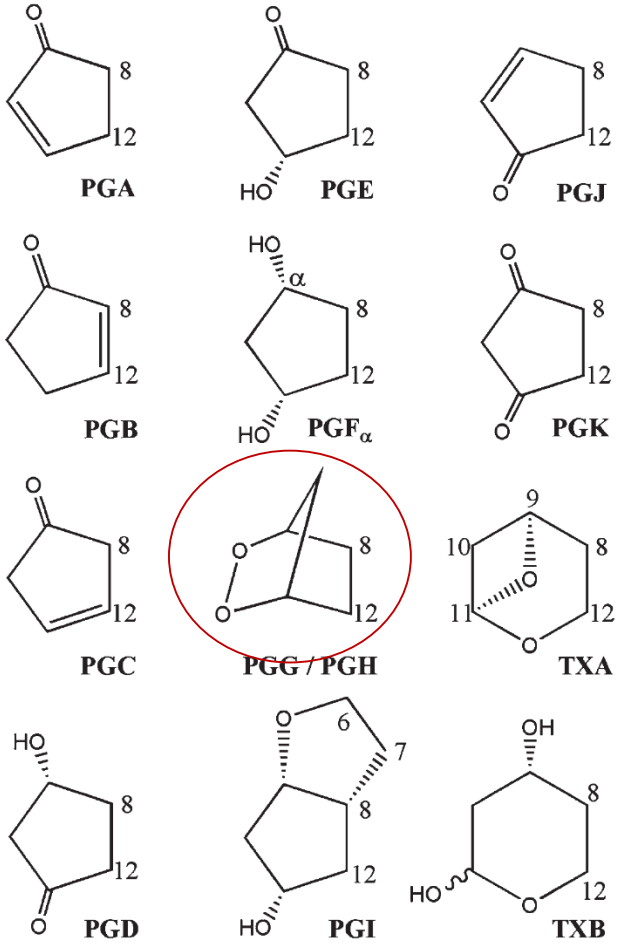
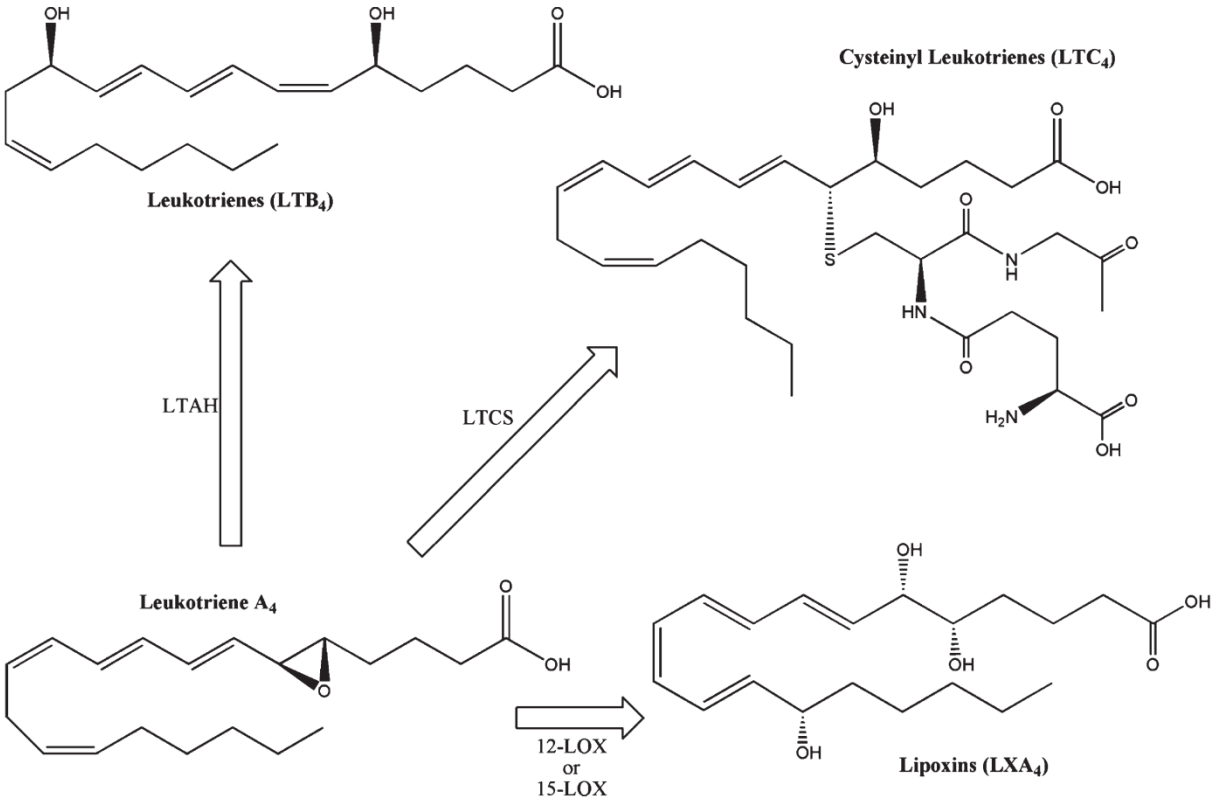




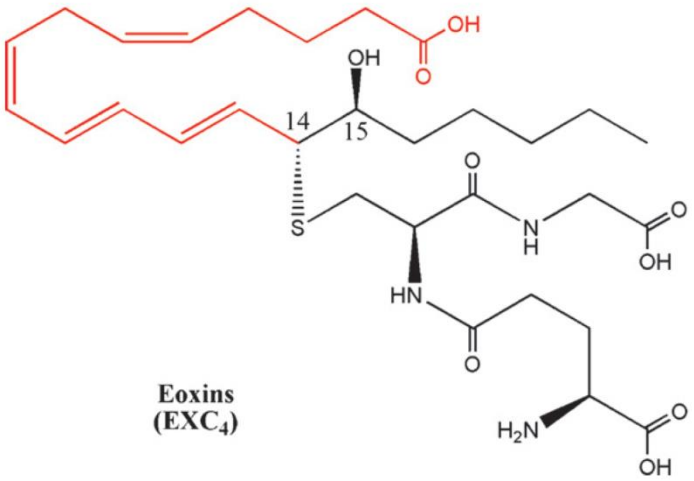


J Lipid Res. 2009 June; 50(6): 1015–1038.

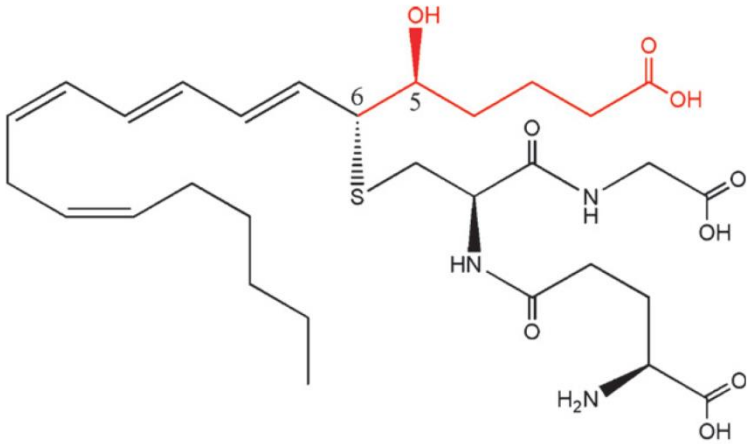


(cystein)

Structures of 5-lipoxygenase metabolites. 5-Lipoxygenase creates the labile epoxide LTA_4, which can be enzymatically converted into LTB_4, LTC_4, and LXA_4.
From:
J Lipid Res. 2009 June; 50(6): 1015–1038.
doi: 10.1194/jlr.R900004-JLR200.



Eoxins
(EXC_4)



Cysteinyl Leukotrienes
(LTC_4)

Structure of eoxin C_4. Eoxins are the 15-LOX analogs of the cysteinyl leukotrienes, where the thiol attachment occurs at C-14.

From:
J Lipid Res. 2009 June; 50(6): 1015–1038.
doi: 10.1194/jlr.R900004-JLR200.

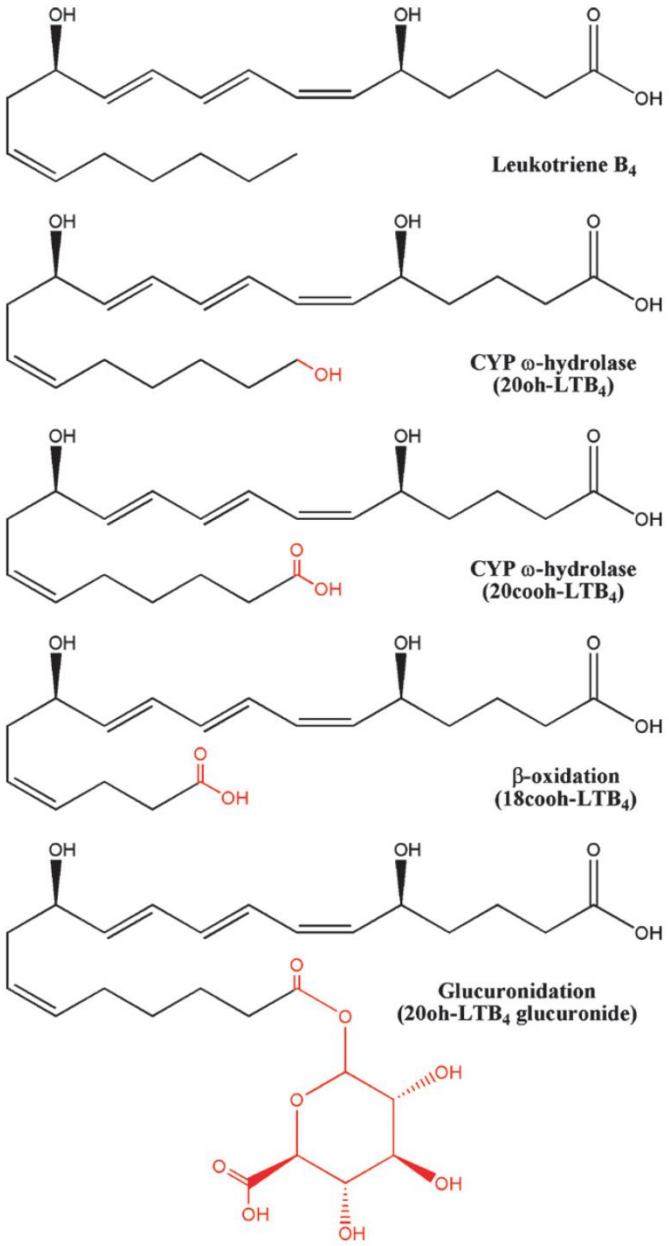
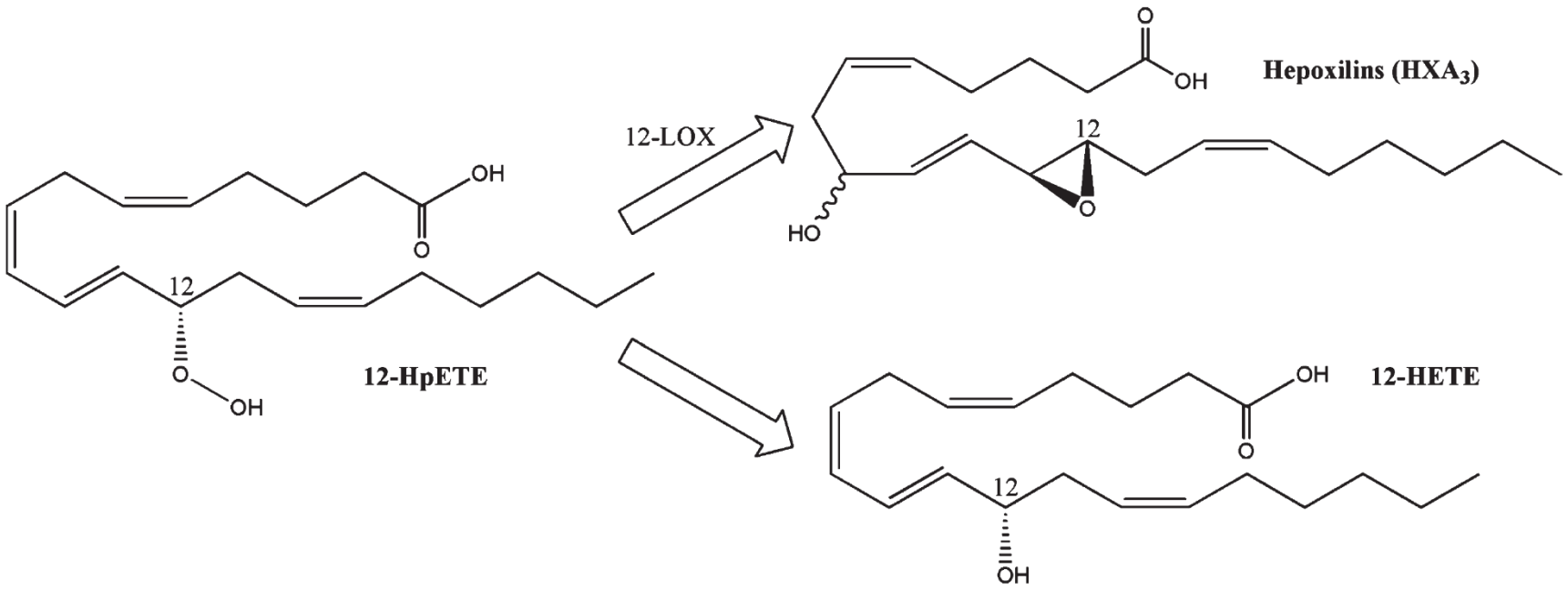


Fig. 8. Examples of LTB_4 metabolism by β-oxidation, CYP ω-hydrolases, and glucuronidation.

J Lipid Res. 2009 June; 50(6): 1015–1038.



Structures of 12-lipoxygenase metabolites. 12-Lipoxygenase creates 12-HpETE, which can further isomerize to form HXA_3.

J Lipid Res. 2009 June; 50(6): 1015–1038.

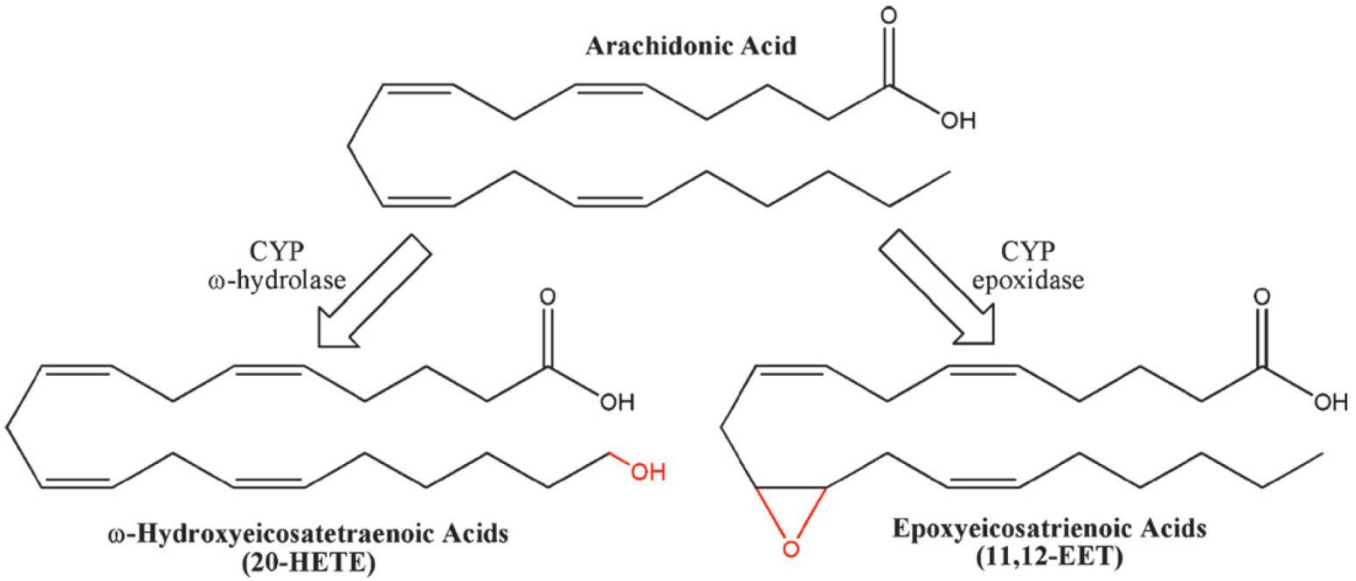
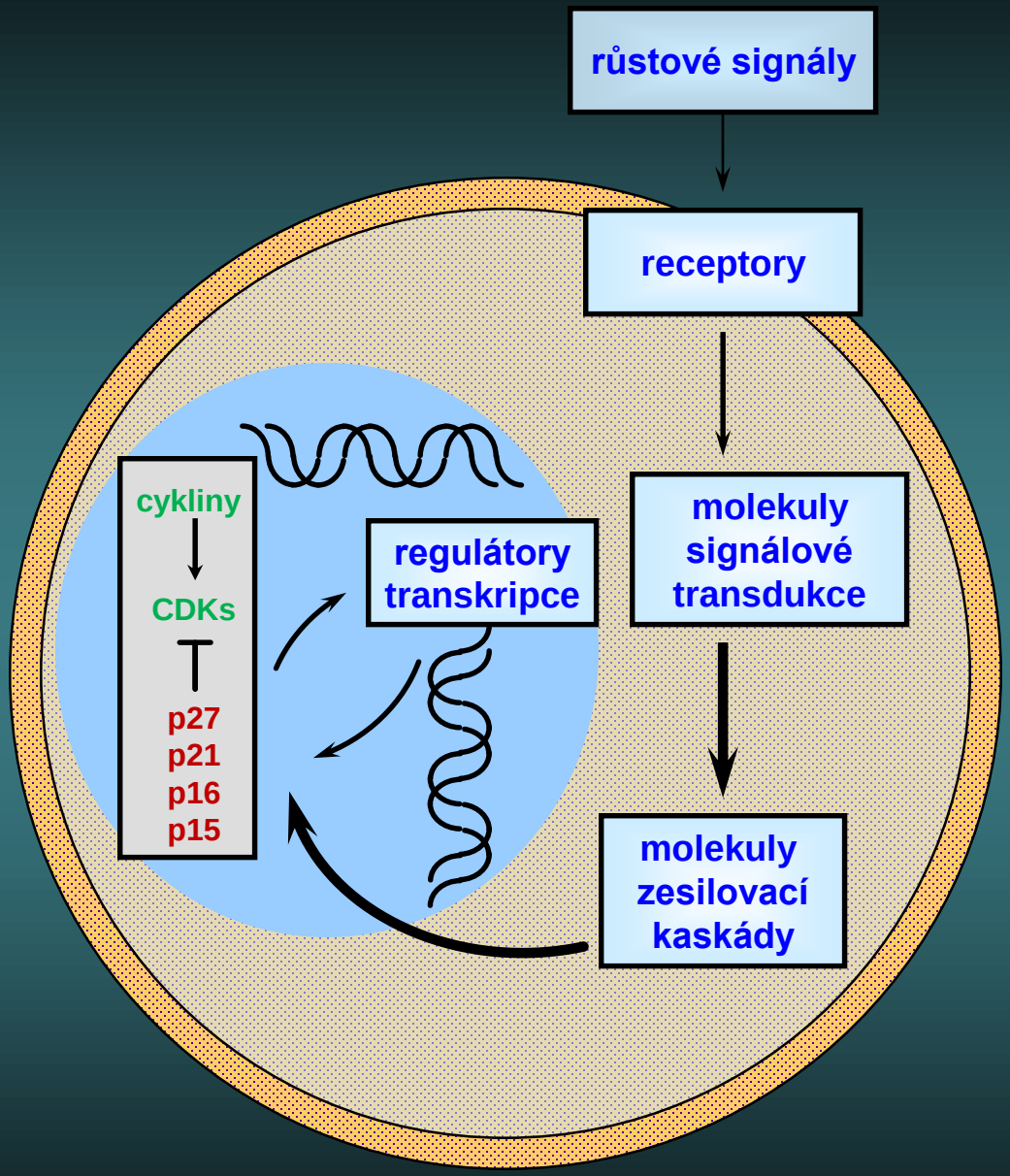
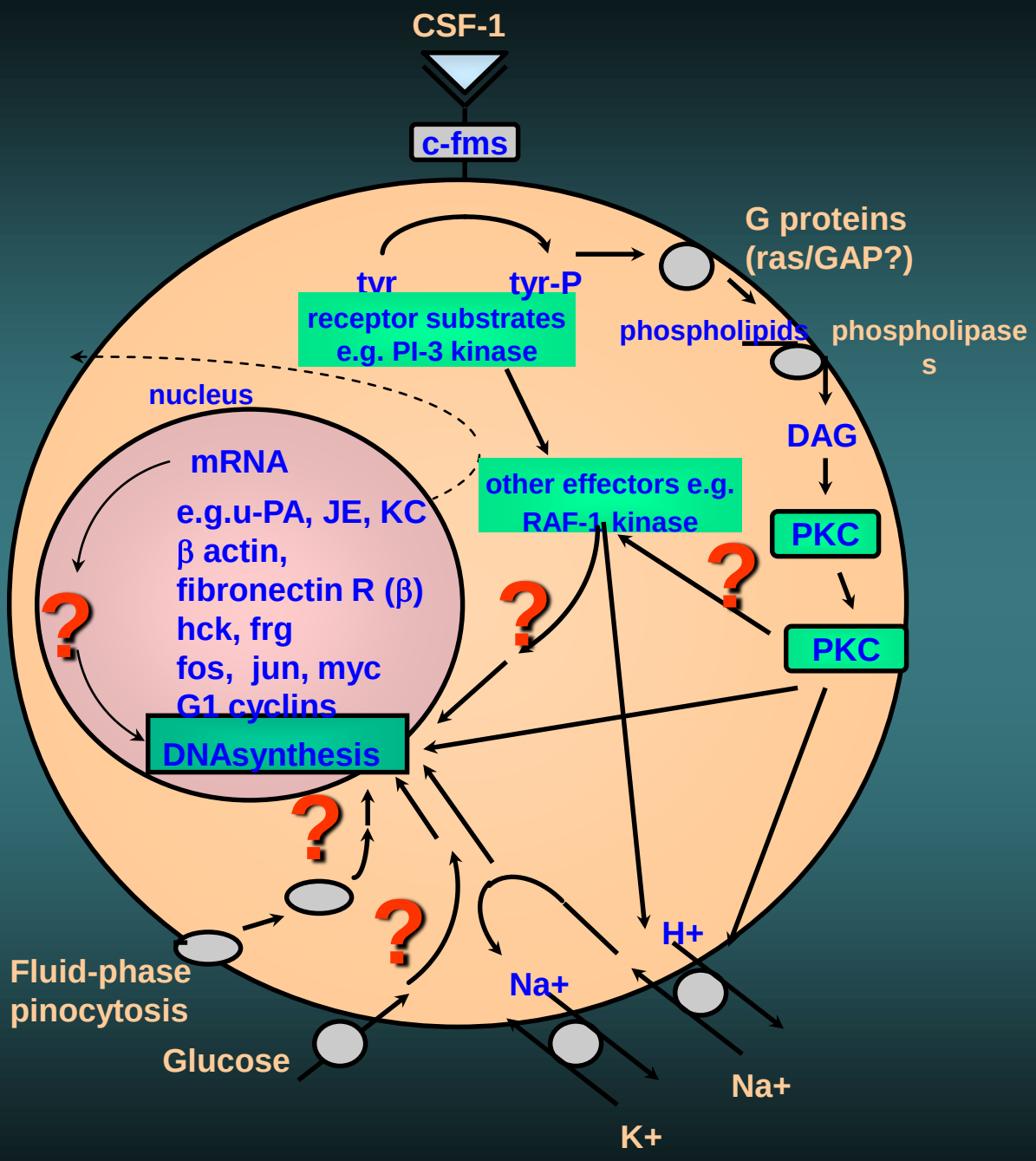


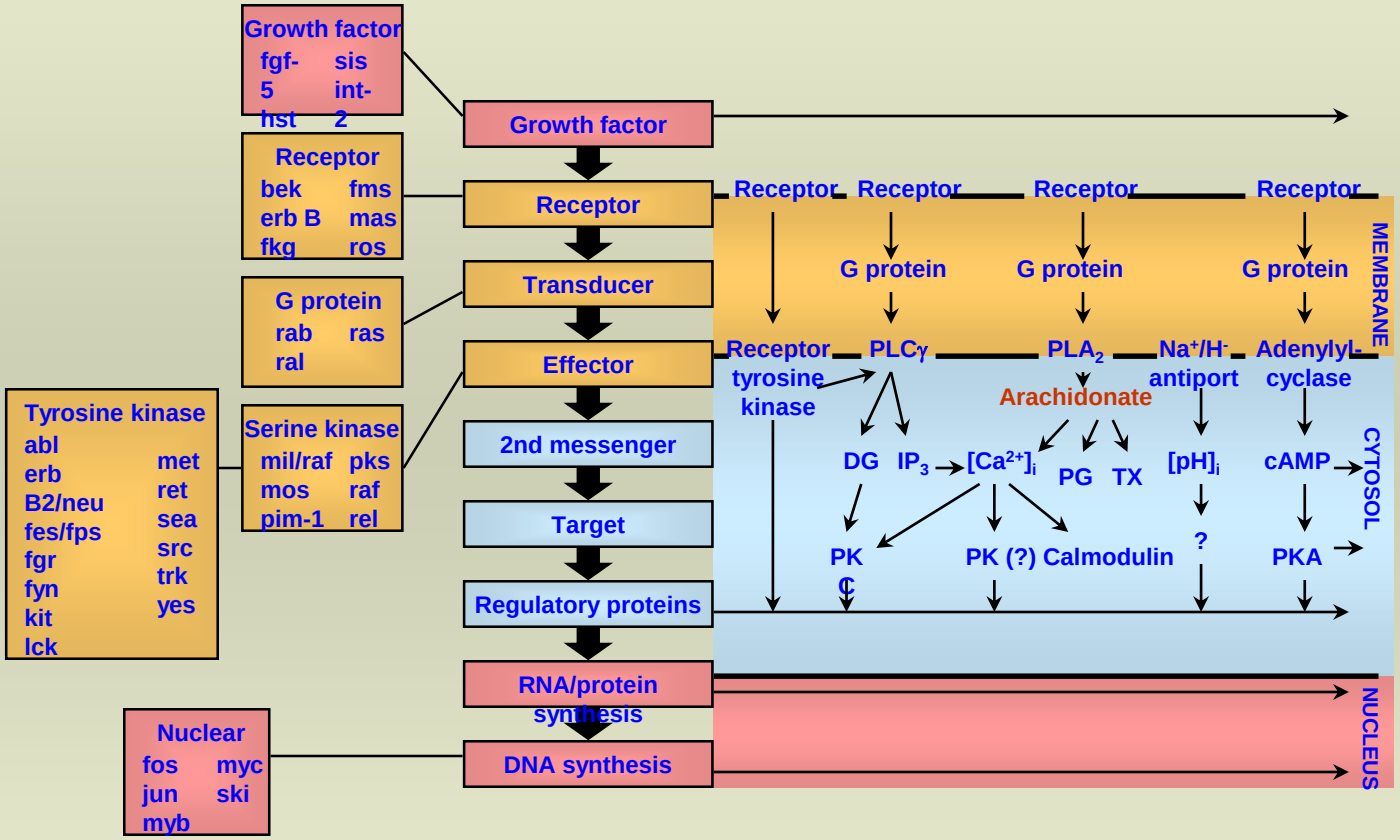
Fig. 7. Structures of cytochrome P450 metabolites. Cytochrome P450 enzymes can catalyze ω-oxidation (example: 20-HETE) and epoxidation (11,12-EET) reactions.

From:
J Lipid Res. 2009 June; 50(6): 1015–1038.


růstové signály
receptory
molekuly signálové transdukce
molekuly zesilovací kaskády
regulátory transkripce
cykliny
CDKs
p27
p21
p16
p15


CSF-1
c-fms
G proteins
(ras/GAP?)
tyr
tyr-P
receptor substrates
e.g. PI-3 kinase
phospholipids
phospholipase
s
nucleus
DAG
mRNA
e.g.u-PA, JE, KC
β actin,
fibronectin R (β)
hck, frg
fos, jun, myc
G1 cyclins
other effectors e.g.
RAF-1 kinase
PKC
PKC
?
?
?
?
?
DNAsynthesis
H+
Na+
Na+
K+
Glucose
Fluid-phase
pinocytosis

Oncogenes



According to: G.Powis: TiPS; 12: 188 -194, 1991

Modulace cytokinetiky látkami tukové povahy

Lipidy a zejména jejich složky *vysoce nenasycené kyseliny* (PUFA), včetně jejich metabolitů *eikosanoidů*,

patří mezi významné epigeneticky působící faktory schopné ovlivnit jak dělení a zánik normálních,

ale i transformovaných buněčných populací, tak proces maligní transformace.

Faktory, které mohou modulovat rychlost dělení, diferenciaci anebo zánik buněk

Faktory, které mohou ovlivnit cytokinetiku změnami

---

1) exprese anebo funkce molekul zapojených v přenosu signálů přímo regulujících proliferaci, diferenciaci a buněčnou smrt (apoptózou),

včetně exprese protoonkogenů a nádorově-supresorových genů

---

2) signálů, které tyto funkce ovlivňují do určité míry nepřímo,

jako jsou inhibice mezibuněčných spojení, ovlivnění funkce enzymů reparujících DNA, metylace DNA apod.

Hlavní mechanismy působení PUFAs

1) přímé ovlivnění aktivity transkripčních faktorů regulujících expresi genů významných z hlediska cytokinetiky

2) produkce eikosanoidů působících na přenos signálů cytokinů a imunitní systém

3) produkce reaktivních kyslíkových metabolitů vznikajících peroxidací lipidů.

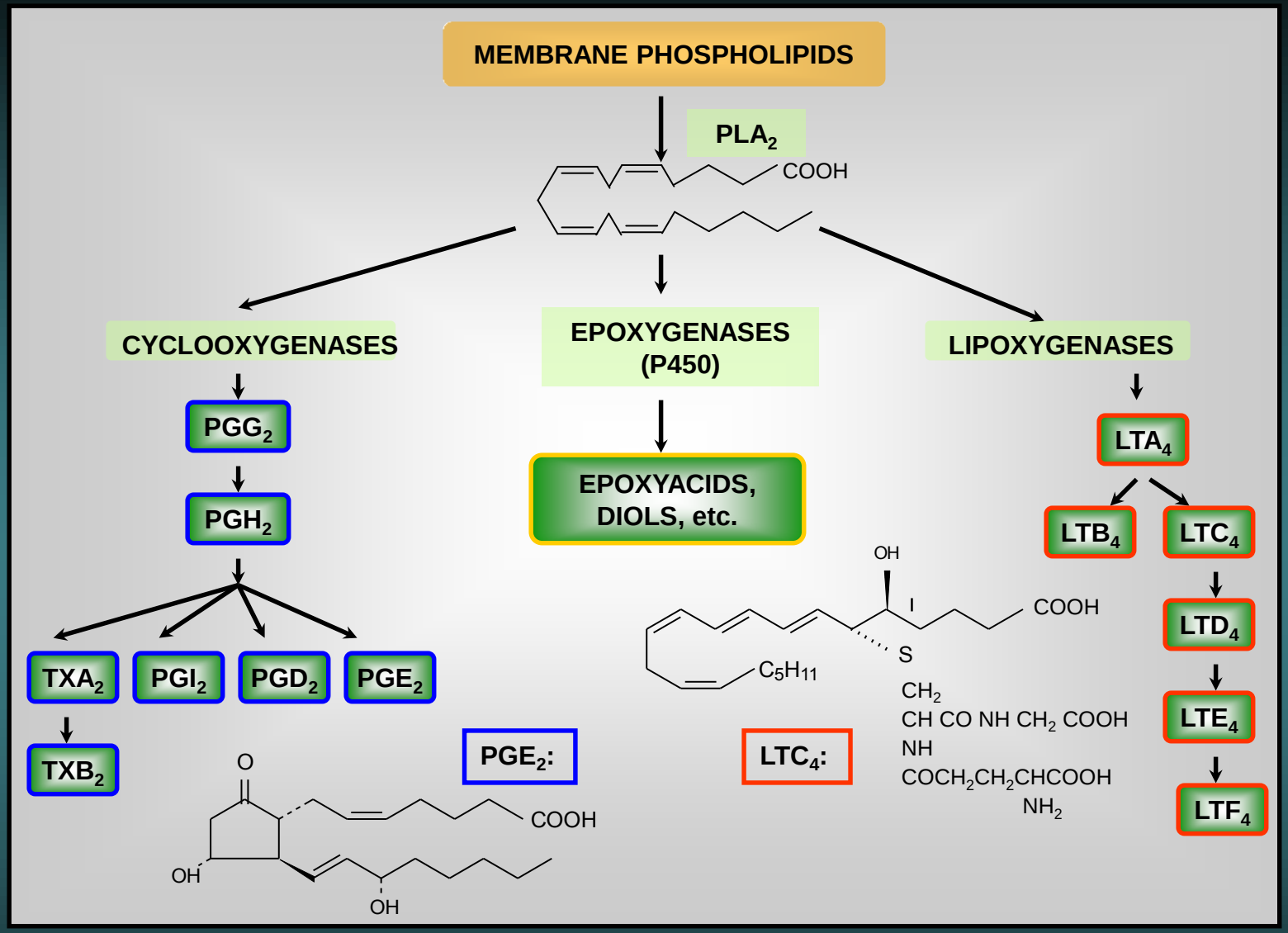
Význam rovnováhy v přísunu prekursorových PUFAs

a

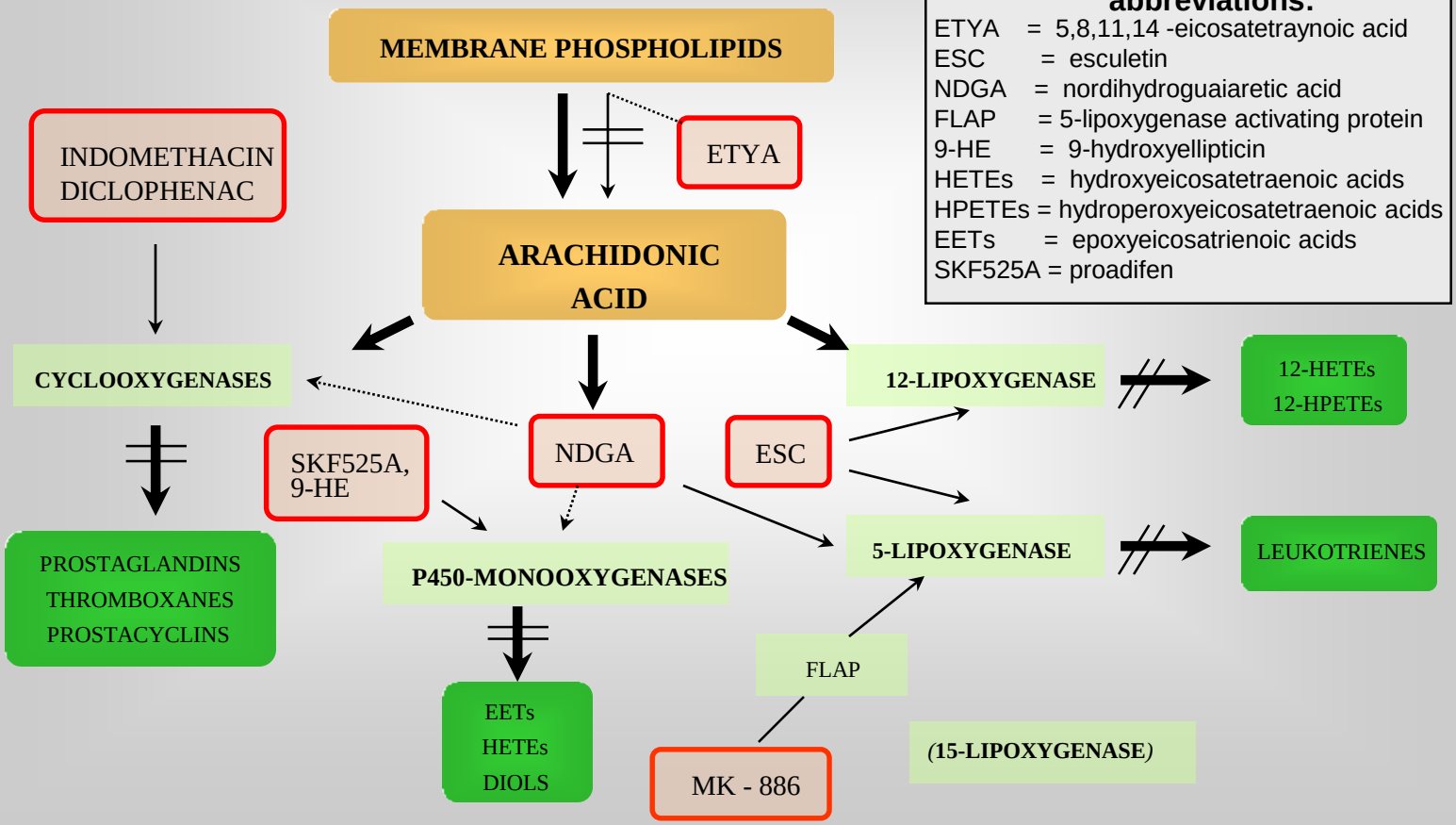
v produkci jednotlivých jejich metabolitů

Efekty inhibitorů metabolismu AA

význam rovnováhy
v přísunu prekursorových PUFAs
a
v produkci jednotlivých jejich metabolitů


MEMBRANE PHOSPHOLIPIDS
PLA2
COOH
CYCLOOXYGENASES
EPOXYGENASES (P450)
LIPOXYGENASES
PGG2
PGH2
EPOXYACIDS, DIOLS, etc.
LTA4
LTB4
LTC4
LTD4
LTE4
LTF4
TXA2
PGI2
PGD2
PGE2
TXB2
OH
I
COOH
S
C5H11
CH2
CH CO NH CH2 COOH
NH
COCH2CH2CHCOOH
NH2
LTC4:
PGE2:
O
COOH
OH
OH

Arachidonic acid: metabolic pathways and its possible modulations



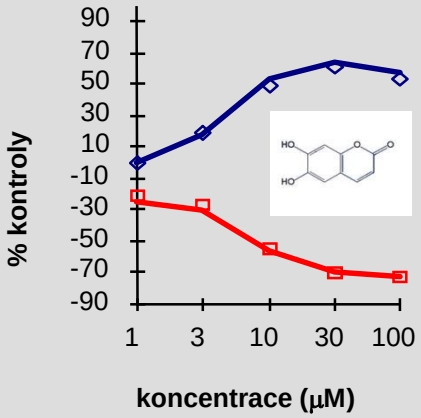
abbreviations:

ETYA = 5,8,11,14 -eicosatetraynoic acid
ESC = esculetin
NDGA = nordihydroguaiaretic acid
FLAP = 5-lipoxygenase activating protein
9-HE = 9-hydroxyellipticin
HETEs = hydroxyeicosatetraenoic acids
HPETEs = hydroperoxyeicosatetraenoic acids
EETs = epoxyeicosatrienoic acids
SKF525A = proadifen

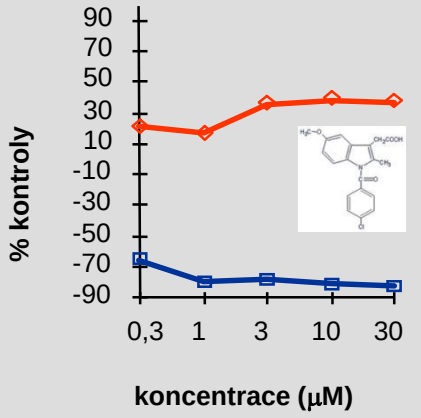
PRODUKTY
LIPOXYGENÁZ A CYKLOOXYGENÁZ

VORE et al., J. Immunol. : 11, 435 - 442, 1989

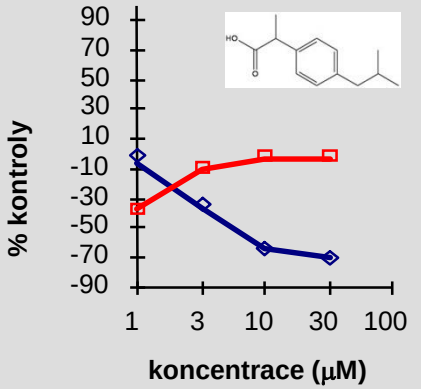
Esculetin



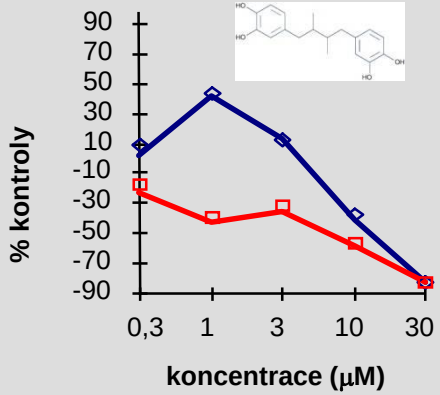
Indomethacin

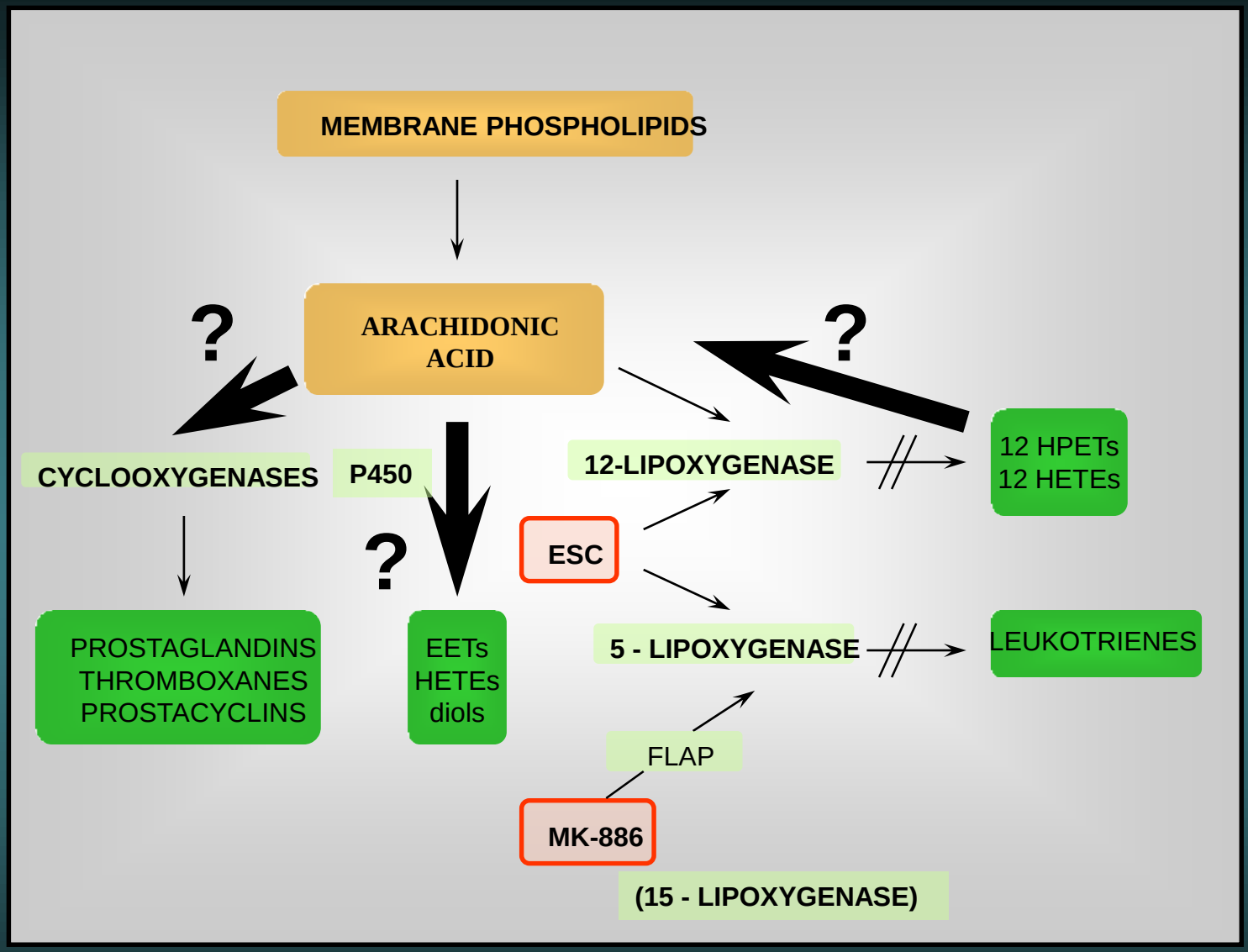


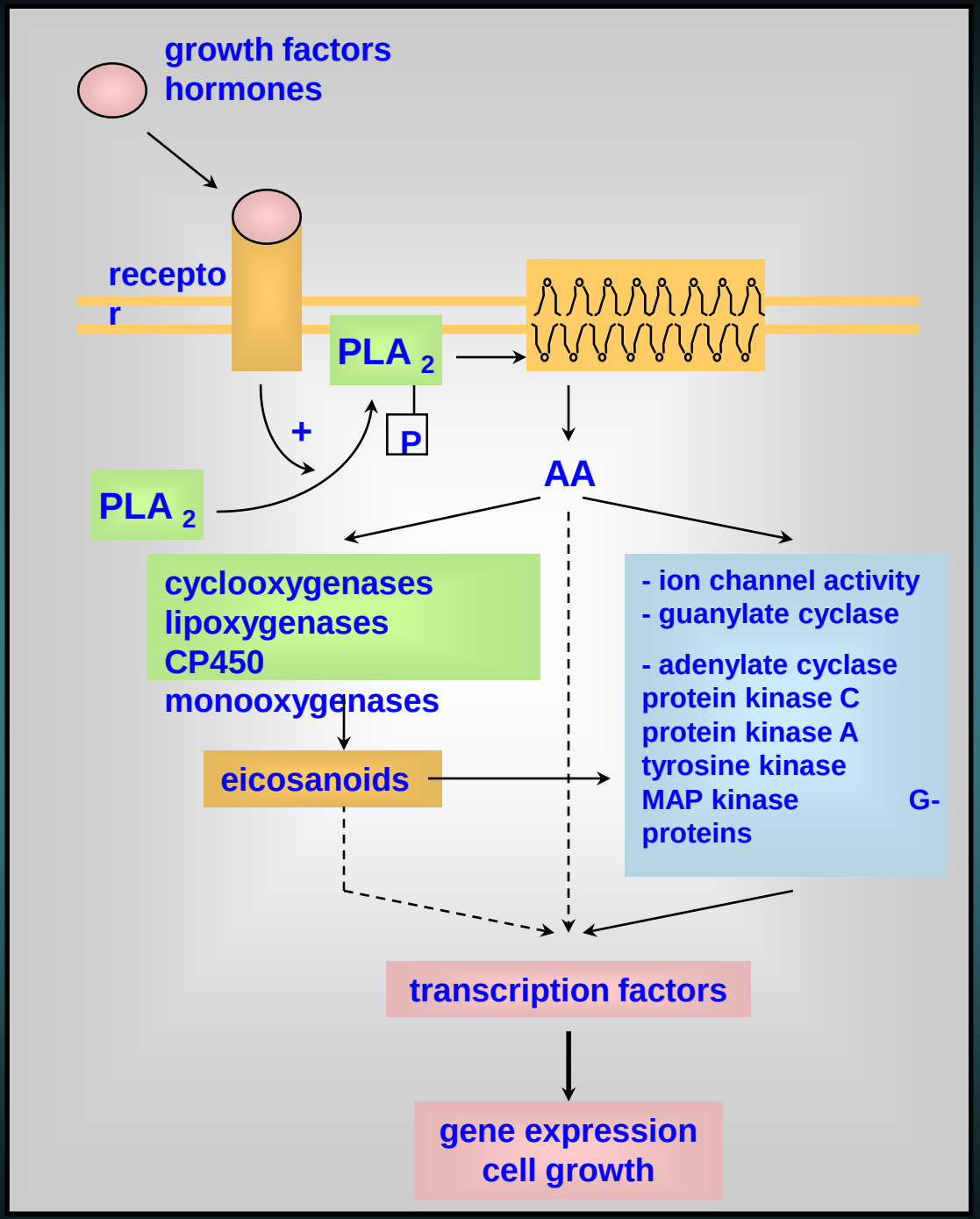
Ibuprofen



NDGA




MEMBRANE PHOSPHOLIPIDS
ARACHIDONIC ACID
?
?
?
CYCLOOXYGENASES
P450
12-LIPOXYGENASE
12 HPETs
12 HETEs
ESC
PROSTAGLANDINS
THROMBOXANES
PROSTACYCLINS
EETs
HETEs
diols
5 - LIPOXYGENASE
LEUKOTRIENES
FLAP
MK-886
(15 - LIPOXYGENASE)



According to: A. Sellmayer et al.:

Prostaglandins, Leukotrienes and Essential Fatty Acids ;

57: 353 - 357, 1997.

Laboratoř Cytokinetiky

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