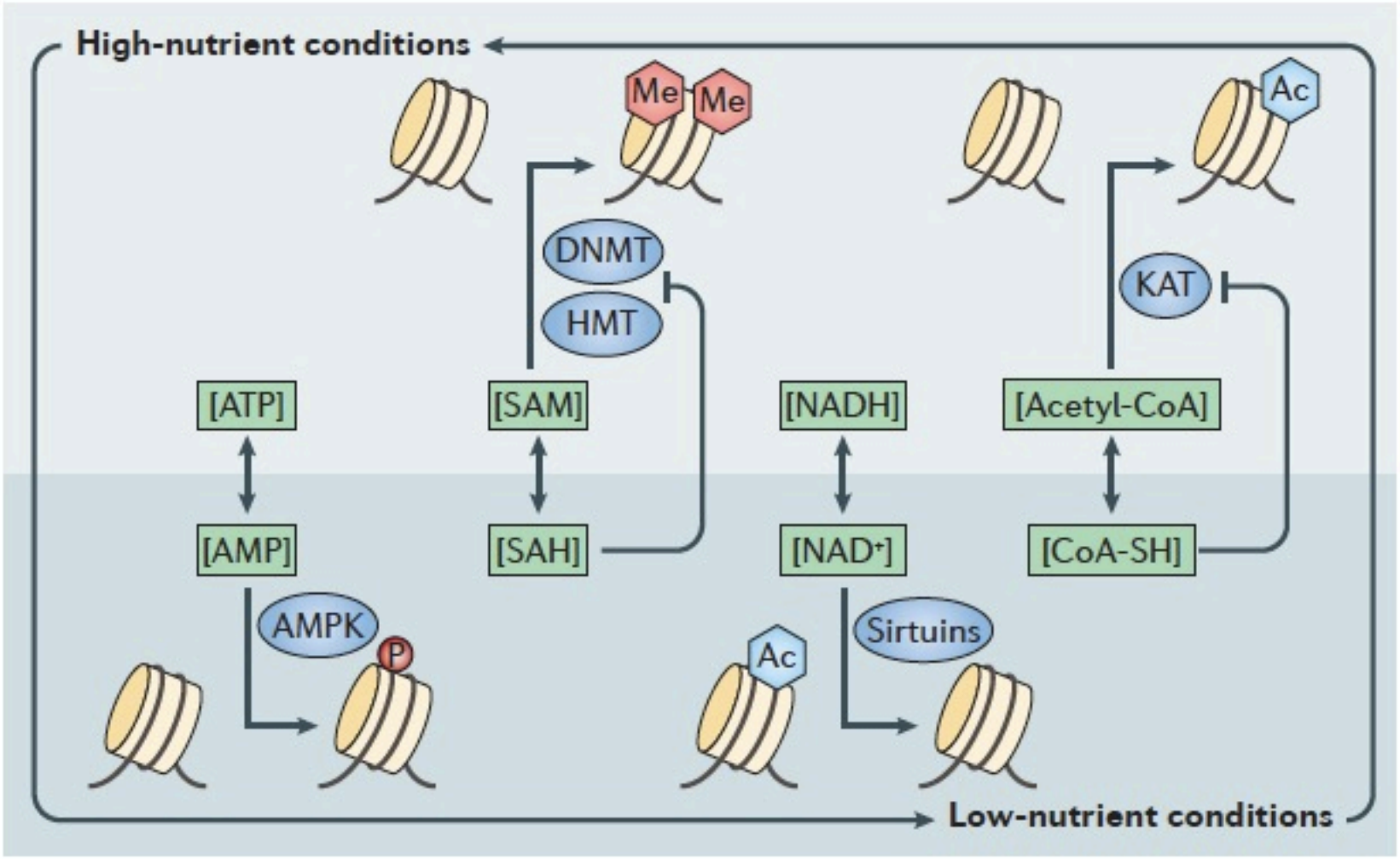
Corso di Biologia Cellulare del Cancro AA 2020-2021

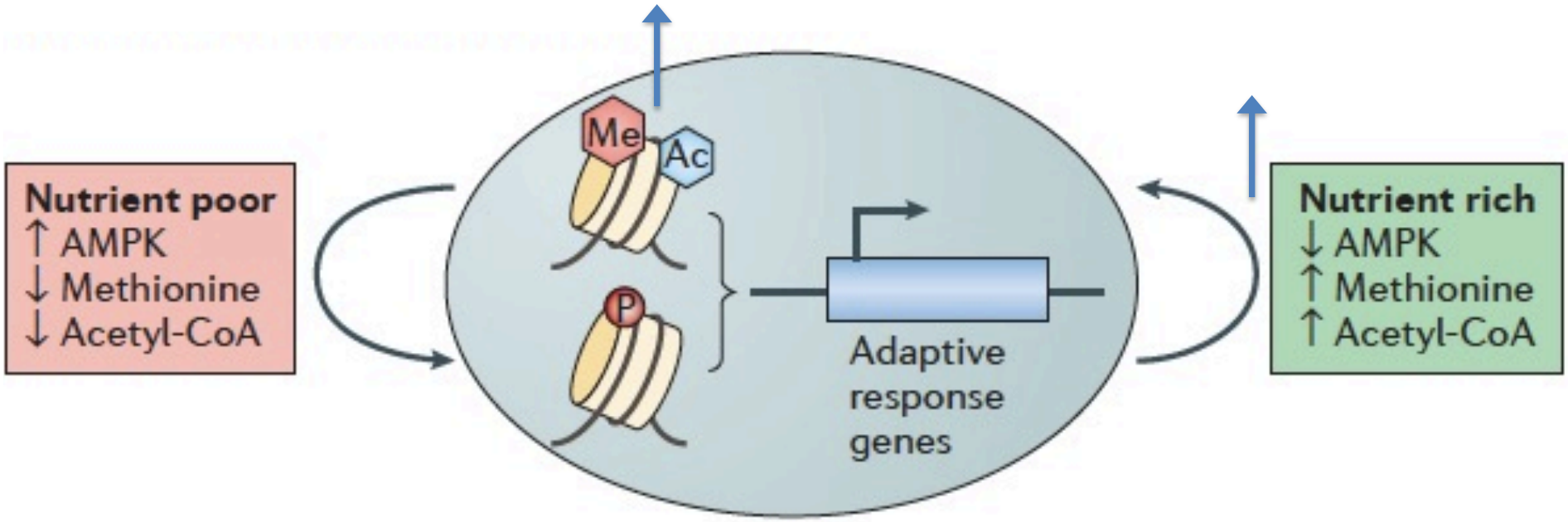
# LA RIPROGRAMMAZIONE DEL METABOLISMO NEL CANCRO – PARTE II

**Diversi metaboliti sono substrati o cofattori di enzimi responsabili di modificazioni epigenetiche**



# Regolazione della cromatina da nutrienti

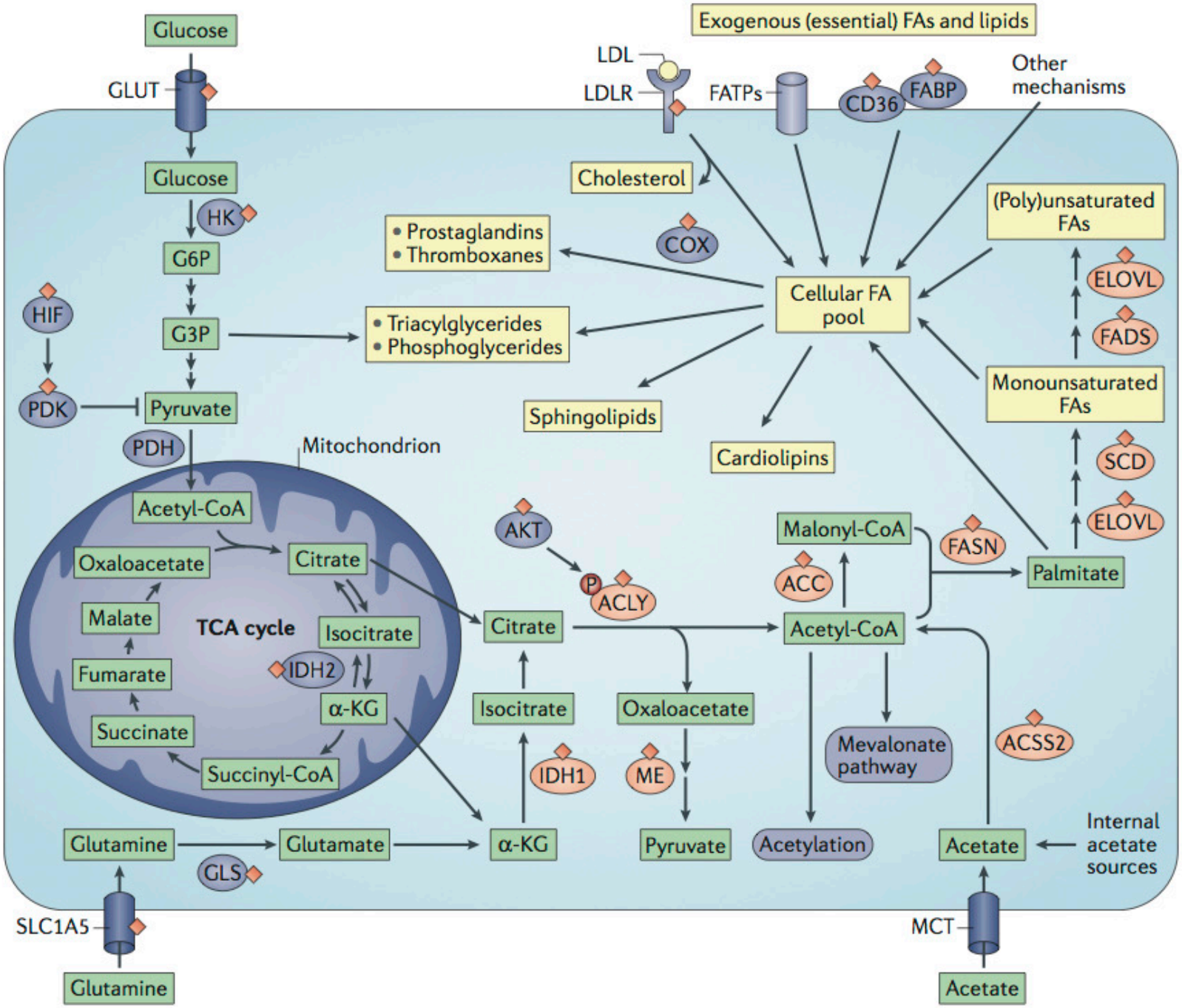
Induzione di oncogeni
Silenziamento di oncosoppressori

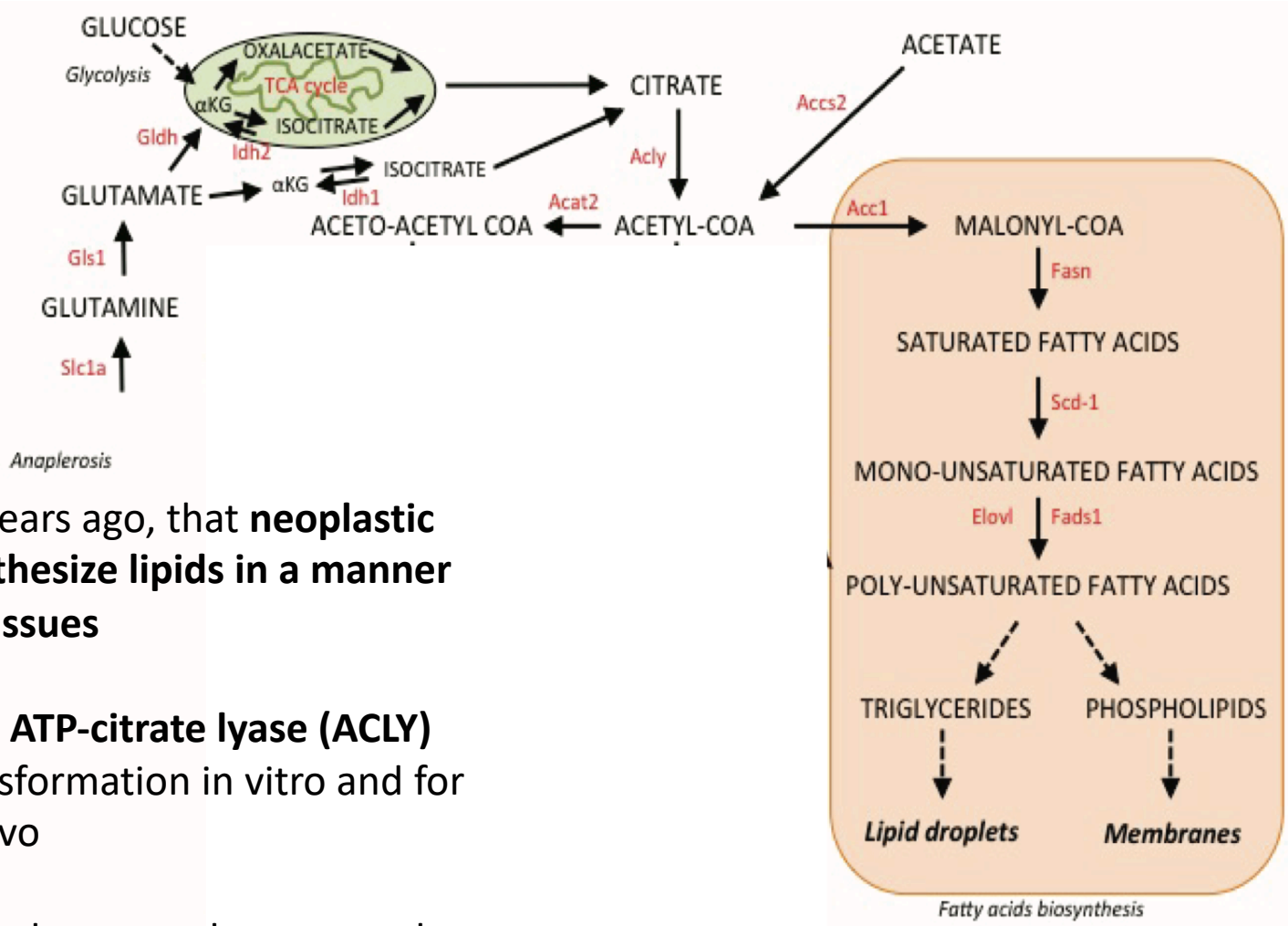


# Domande:

1. In cosa consiste la riprogrammazione del metabolismo LIPIDICO nel cancro?
2. Quali vantaggi selettivi conferisce alle cellule tumorali?
3. Come possono essere sfruttate queste conoscenze ai fini terapeutici?

- Sintesi de novo dei FA
- Attivazione della via biosintetica del mevalonato
- Beta-ossidazione degli acidi grassi
- Effetti sistemici


Glucose
GLUT
Glucose
HK
G6P
HIF
G3P
PDK
Pyruvate
PDH
Mitochondrion
Acetyl-CoA
Oxaloacetate
Citrate
Malate
TCA cycle
Isocitrate
Fumarate
IDH2
α-KG
Succinate
Succinyl-CoA
Glutamine
GLS
Glutamate
α-KG
SLC1A5
Glutamine
Exogenous (essential) FAs and lipids
LDL
LDLR
FATPs
CD36
FABP
Other mechanisms
Cholesterol
• Prostaglandins
• Thromboxanes
COX
• Triacylglycerides
• Phosphoglycerides
Sphingolipids
Cardiolipins
Cellular FA pool
(Poly)unsaturated FAs
ELOVL
FADS
Monounsaturated FAs
SCD
ELOVL
Palmitate
FASN
Malonyl-CoA
ACC
AKT
P
ACLY
Citrate
Acetyl-CoA
Isocitrate
IDH1
Oxaloacetate
ME
Pyruvate
Mevalonate pathway
Acetylation
ACSS2
Acetate
Internal acetate sources
MCT
Acetate




It was noted, over 50 years ago, that **neoplastic tissues are able to synthesize lipids in a manner similar to embryonic tissues**

it has been shown that **ATP-citrate lyase (ACLY)** is required for cell transformation in vitro and for tumour formation in vivo

Some cancers, including breast and prostate, show increased expression of **FASN**

The long-chain fatty-acid elongase **ELOVL7** was shown to be overexpressed in prostate cancer and required for prostate cancer-cell growth

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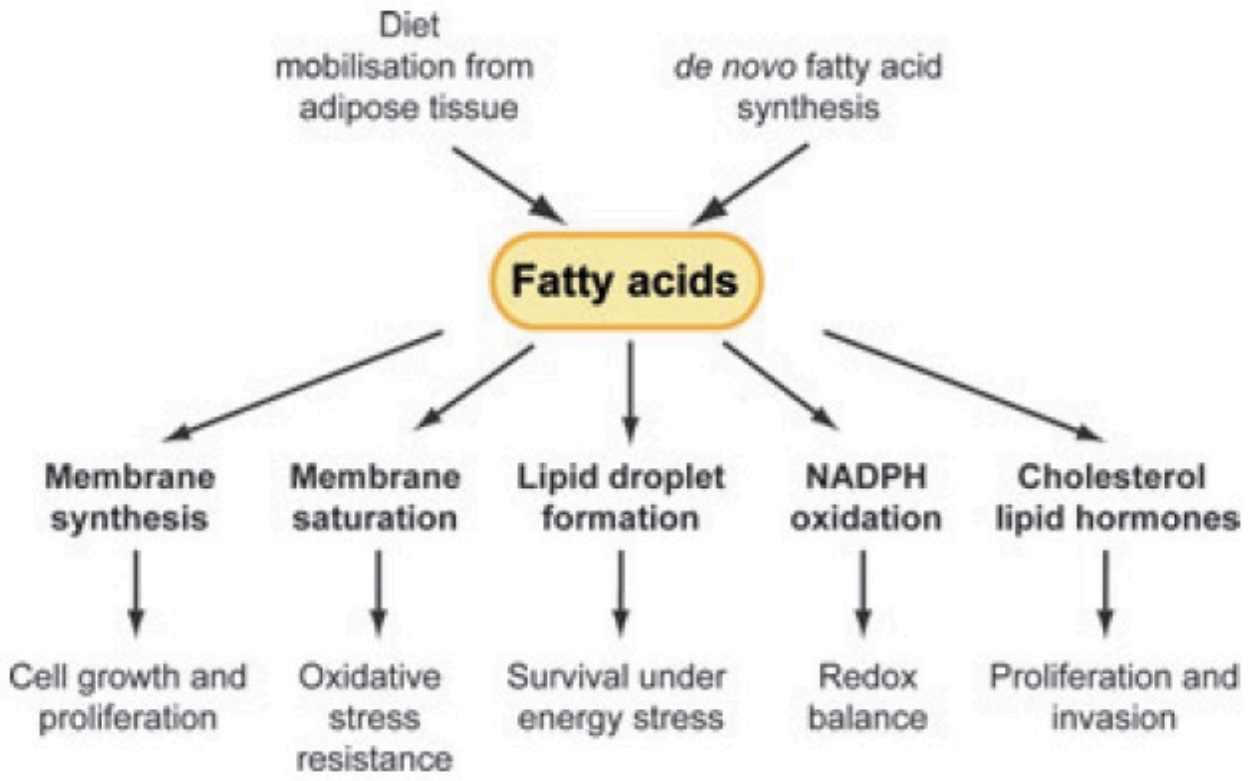


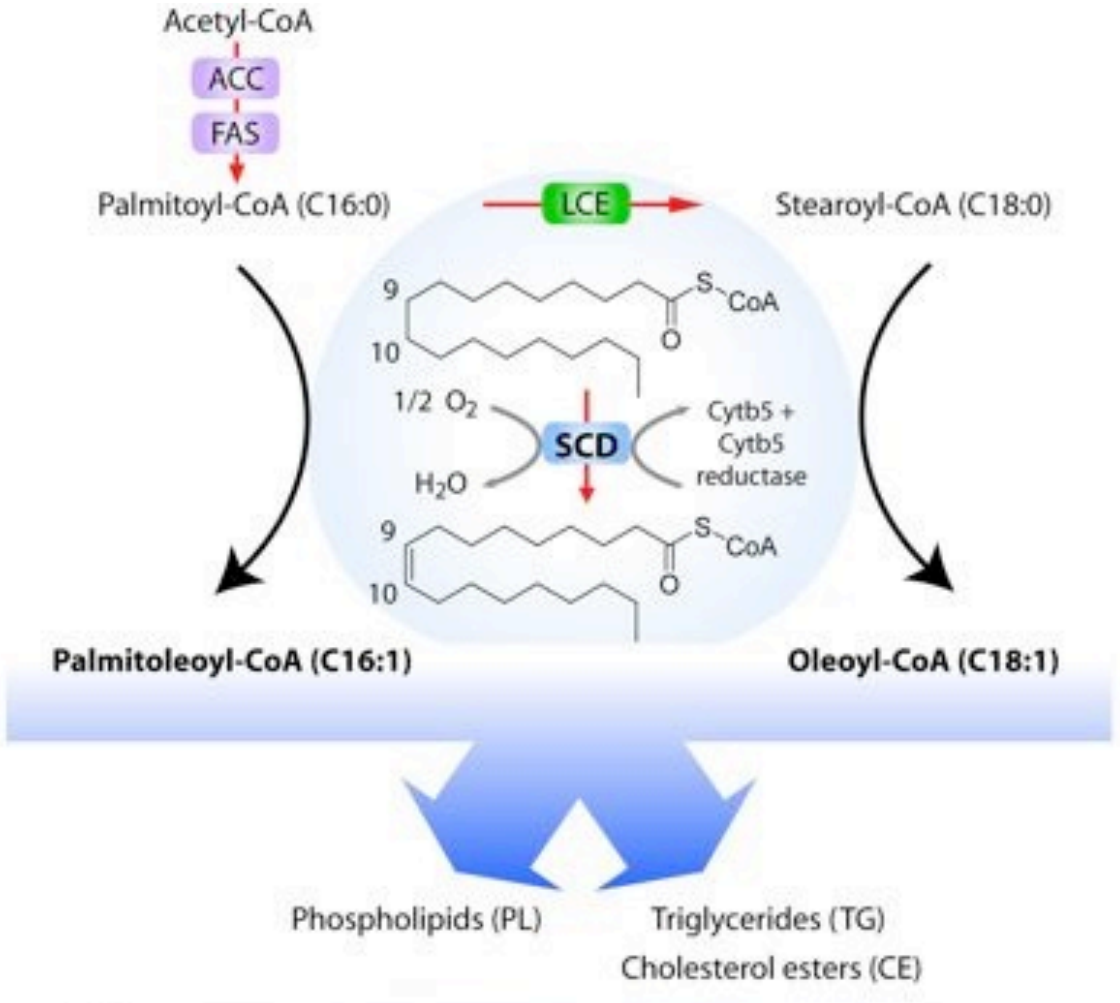

*Bioenergetics*

- Lipids provide substrates for energy production
- Lipids can be used for energy storage to fuel metabolism after reoxygenation

*Membrane synthesis*

- Fatty acids (FAs) are substrates for phosphoglyceride and sphingolipid synthesis during cell growth
- Membrane lipids support organelle function (for example, mitochondria)

# SCD1 è una desaturasi degli acidi grassi



# La desaturasi SCD1 genera acidi grassi monoinsaturi (MUFA)

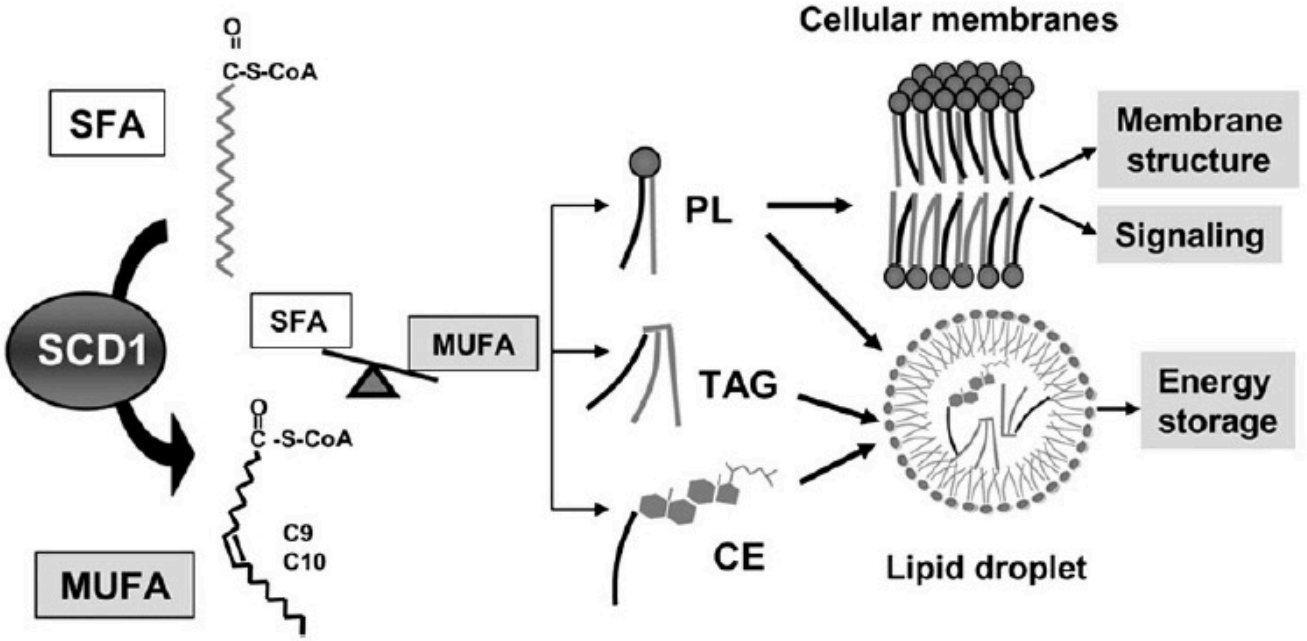


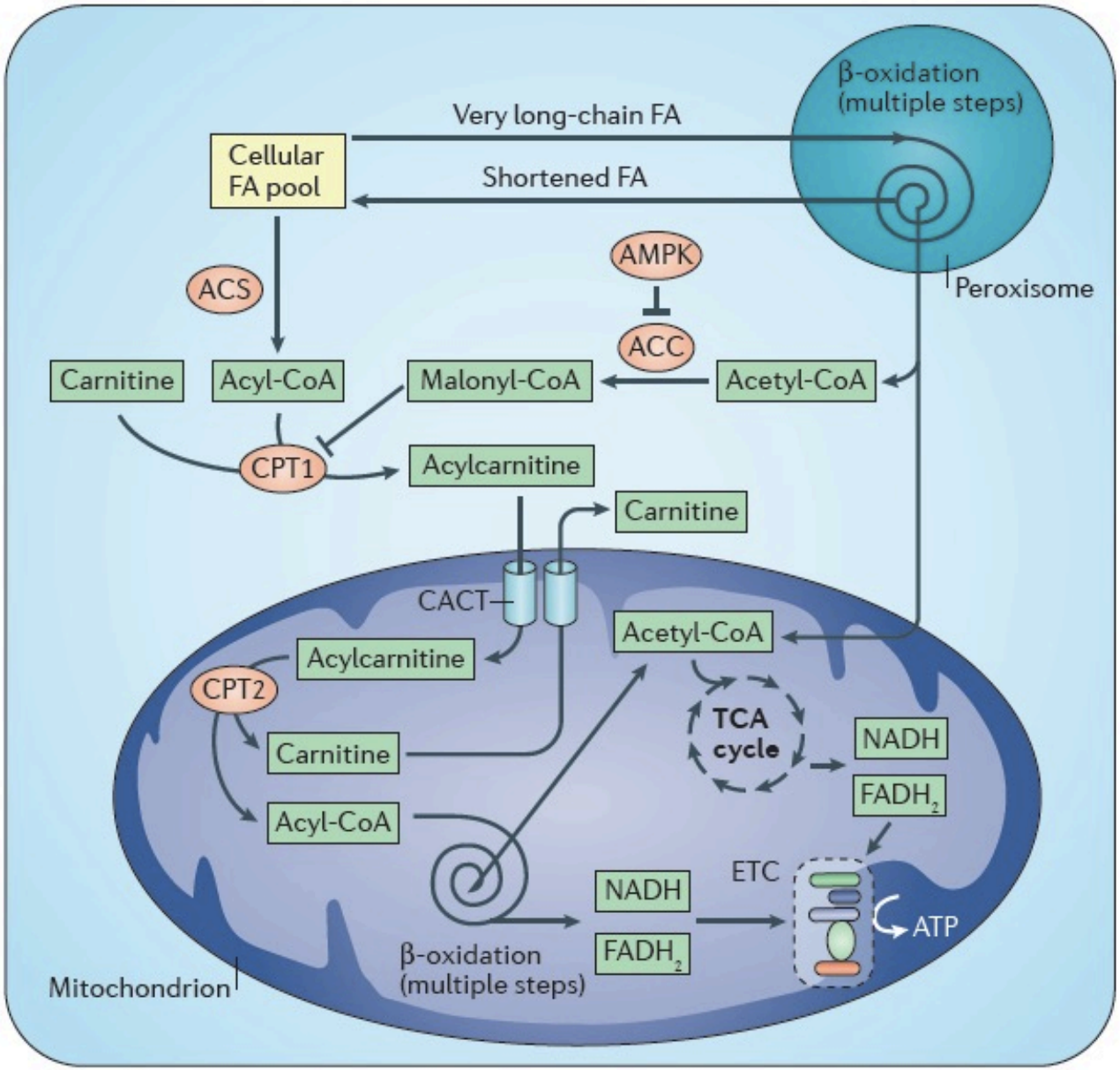

**Fig. 1.** Regulation of MUFA/SFA balance in mammalian cell lipids by SCD1. CE, cholesterol esters; PL, phospholipids; TAG, triacylglycerols.

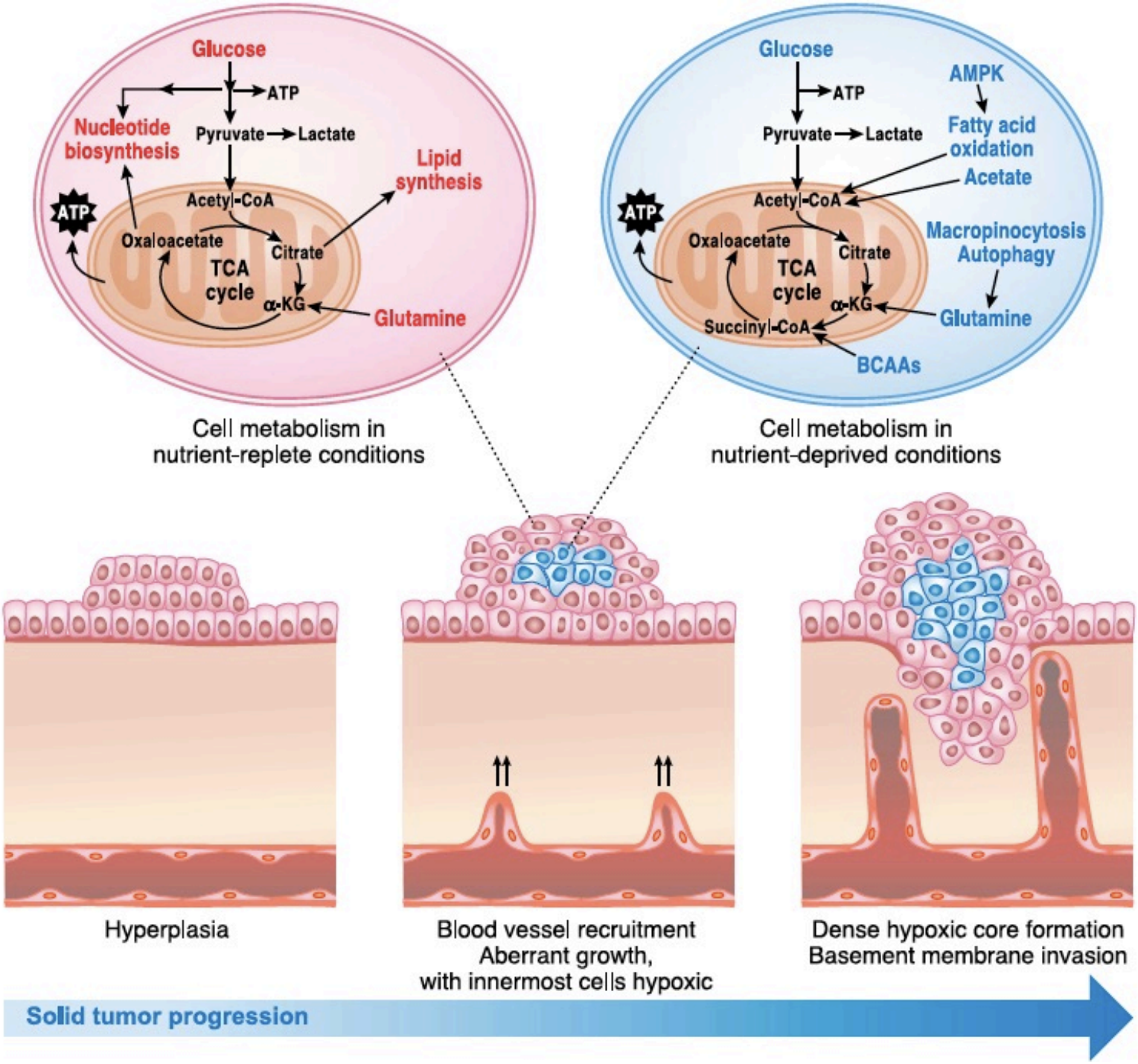
**Gli acidi grassi sono fondamentali per:**

**proliferazione cellulare (sintesi delle membrane),**
**segnalazione cellulare (secondi messaggeri),**

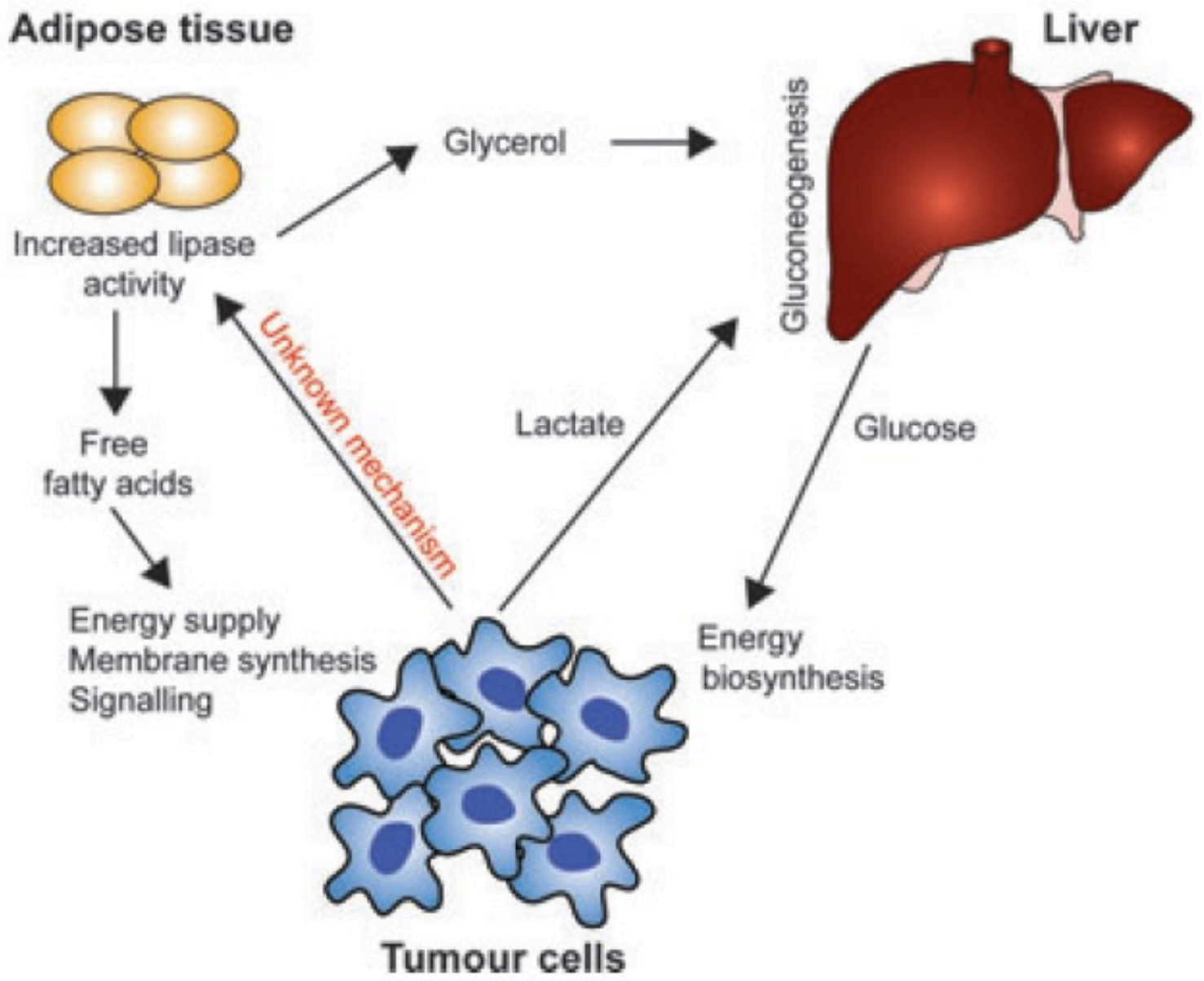
**riserva di energia (lipid droplets)**

# Lipid oxidation

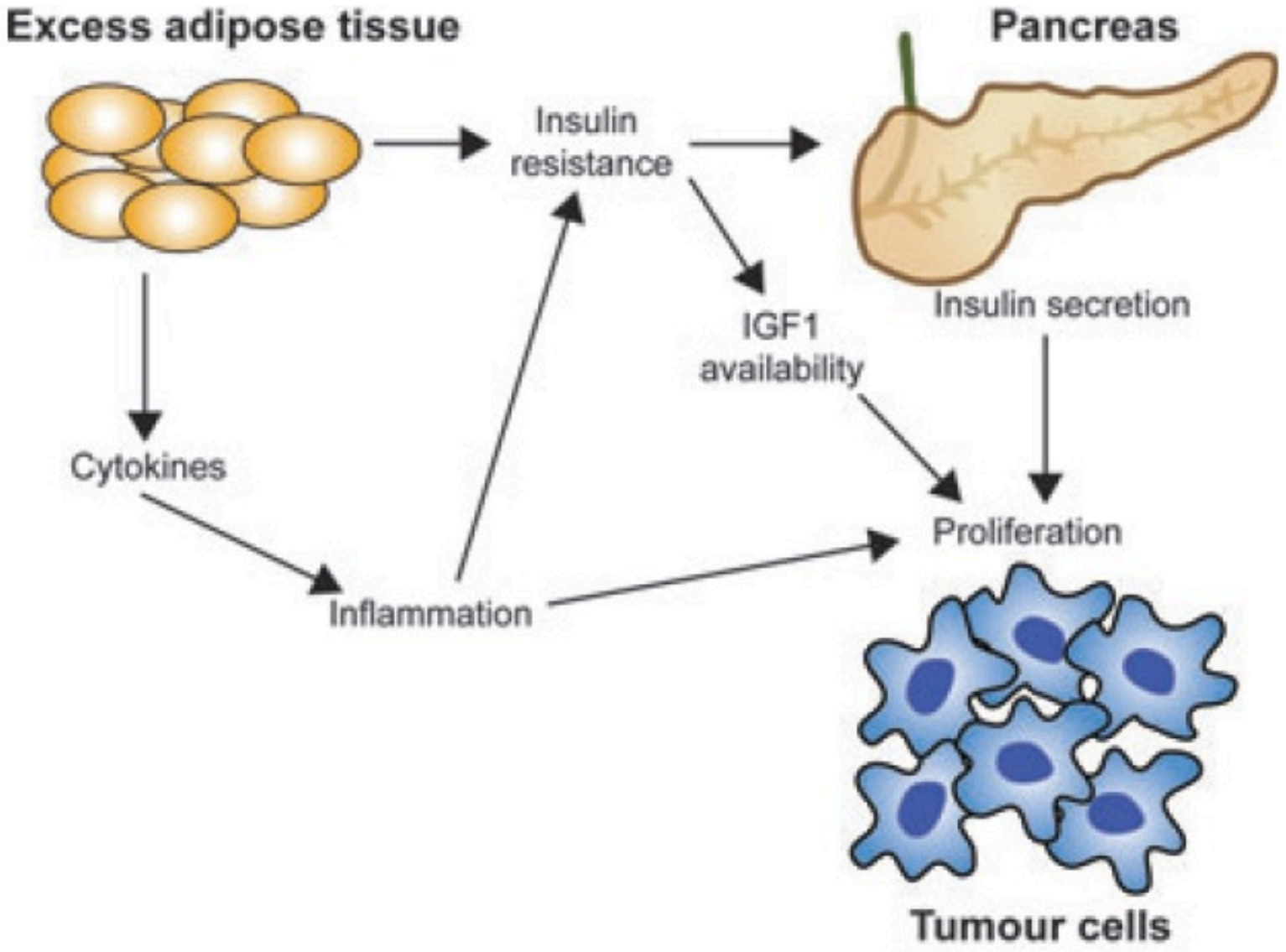



Glucose
ATP
Nucleotide biosynthesis
Pyruvate
Lactate
Lipid synthesis
ATP
Acetyl-CoA
Oxaloacetate
Citrate
TCA cycle
α-KG
Glutamine
Cell metabolism in nutrient-replete conditions
Glucose
ATP
AMPK
Pyruvate
Lactate
Fatty acid oxidation
Acetate
ATP
Acetyl-CoA
Macropinocytosis
Autophagy
Oxaloacetate
Citrate
TCA cycle
α-KG
Glutamine
Succinyl-CoA
BCAAs
Cell metabolism in nutrient-deprived conditions
Hyperplasia
Blood vessel recruitment
Aberrant growth,
with innermost cells hypoxic
Dense hypoxic core formation
Basement membrane invasion
Solid tumor progression

# Simbiosi metabolica e cachessia



# Ruoli del tessuto adiposo nella tumorigenesi

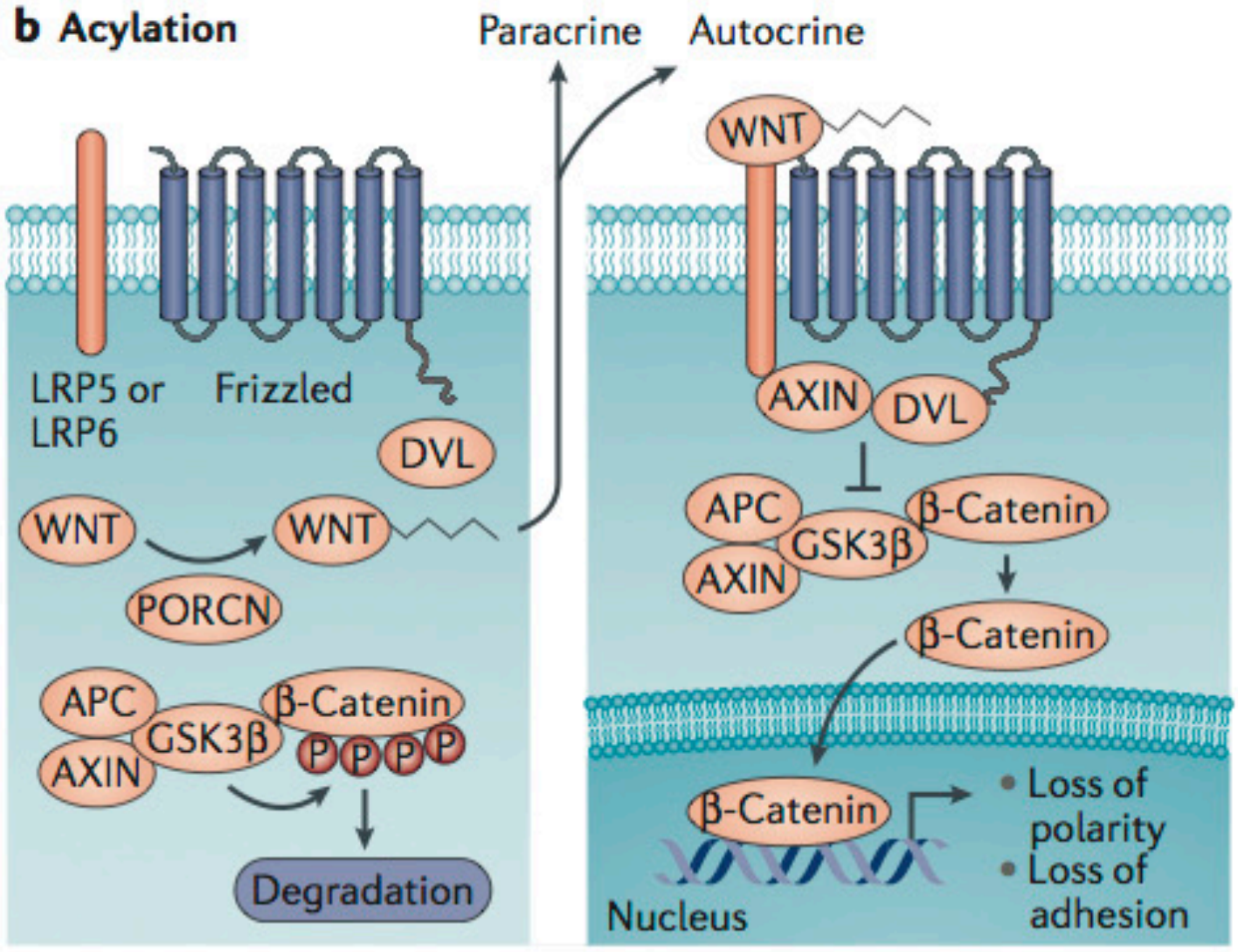


# Ruoli dei lipidi (FA) nella segnalazione cellulare

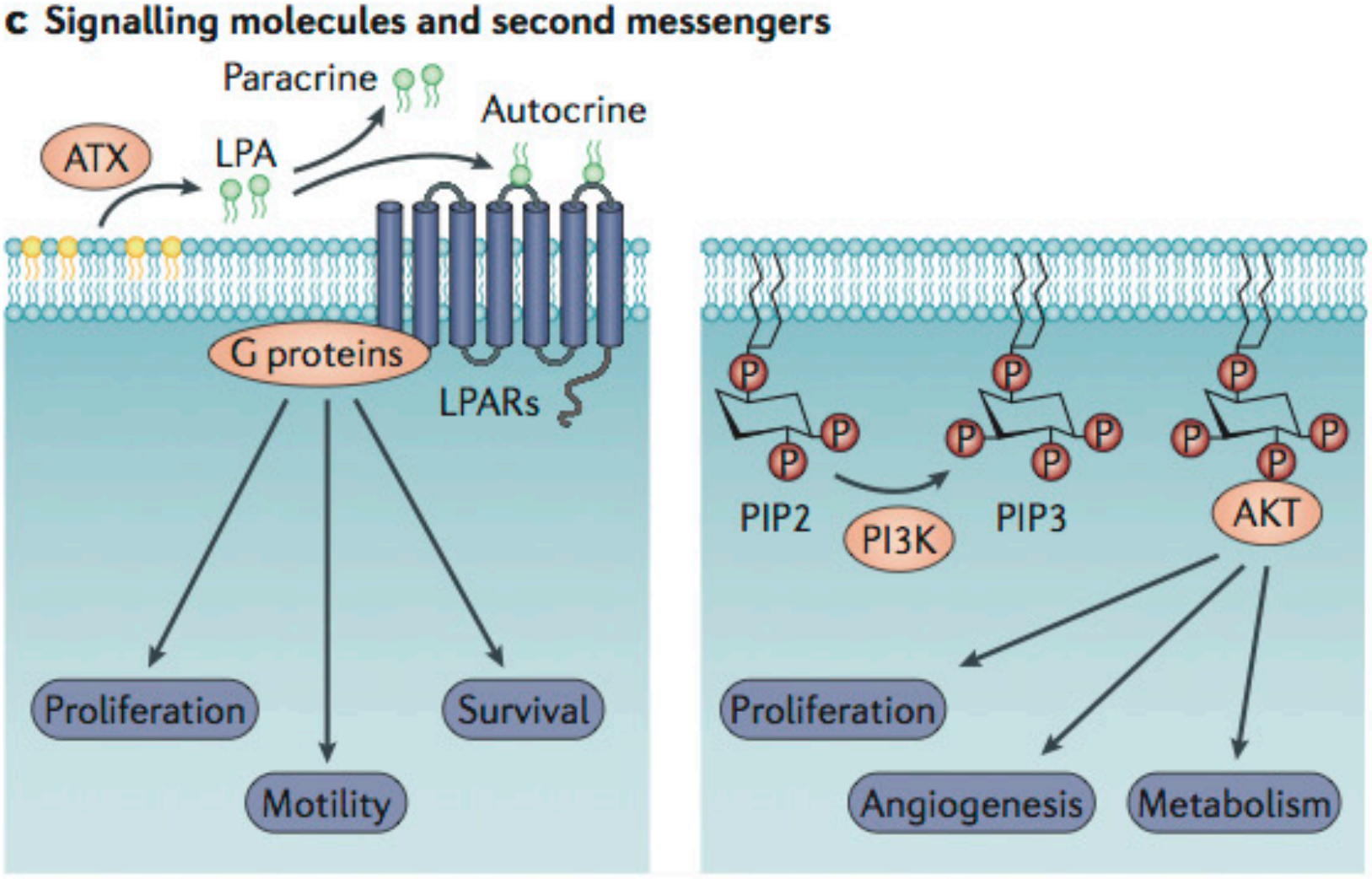
*Signalling*

- Lipid modification is required for activity of signalling molecules (for example, acylation of WNT and prenylation of RHO)
- Lipid mediators function as second messengers or ligands for autocrine receptor signalling (for example, phosphatidylinositol-3,4,5-trisphosphate (PIP3; also known as PtdIns(3,4,5)$P_3$) and lysophosphatidic acid (LPA))

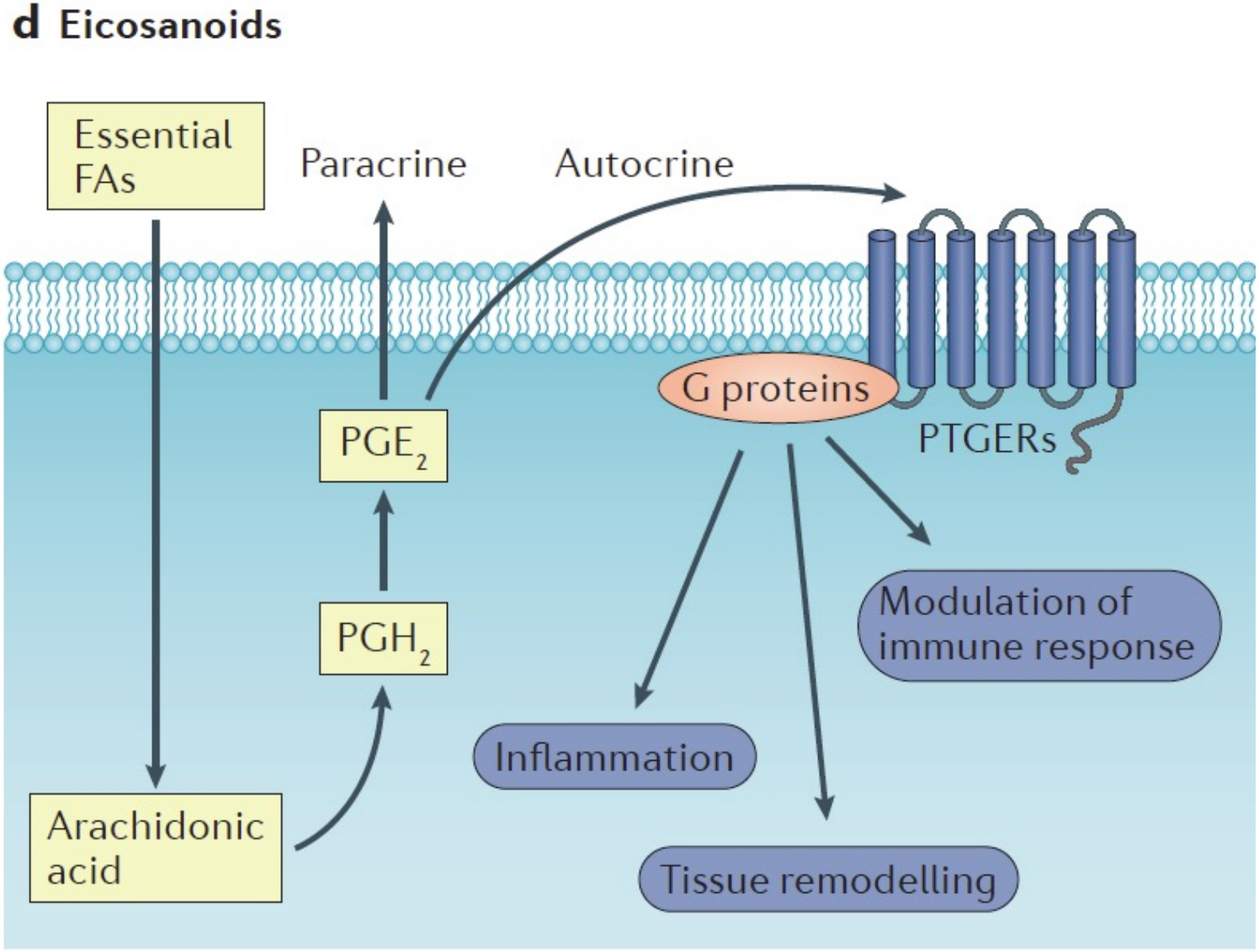
# I lipidi nella segnalazione cellulare



# I lipidi nella segnalazione cellulare



# I lipidi nella segnalazione cellulare



# Ruoli dei lipidi nella progressione tumorale

*Migration*

- Biophysical properties of structural lipids alter membrane fluidity
- Prostaglandin $E_2$ ($PGE_2$) production by transforming growth factor-β induces epithelial-to-mesenchymal transition
- Small GTPases are prenylated via the mevalonate pathway

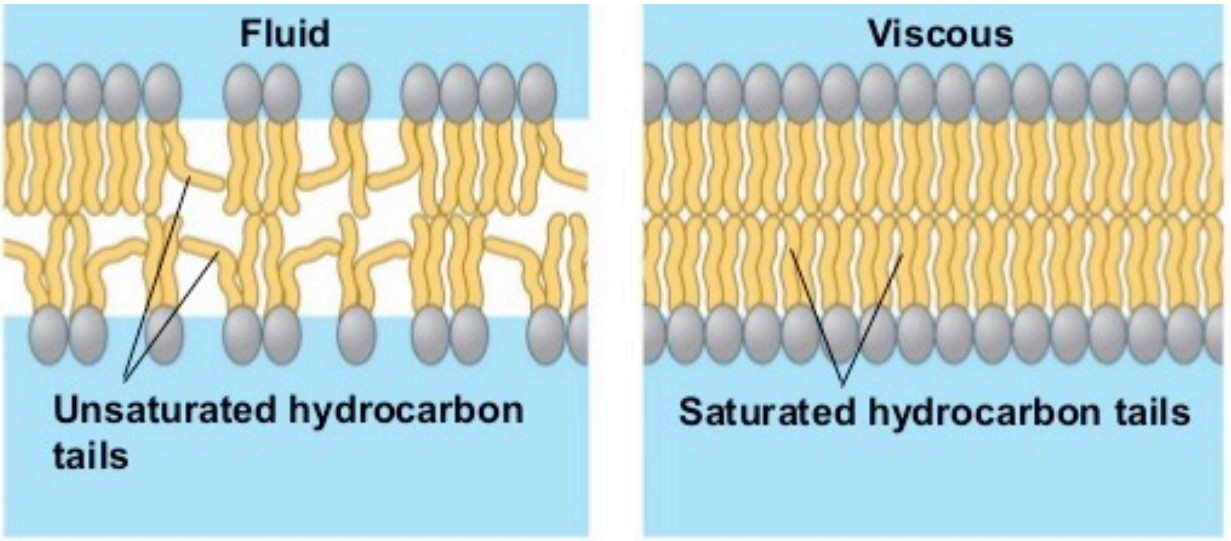
*Angiogenesis*

- $PGE_2$ secretion by cancer cells induces blood vessel outgrowth
- Free FAs induce vascular endothelial growth factor (VEGF) expression by binding to and activating peroxisome proliferator-activated receptor-γ (PPARγ)

*Immunosuppression*

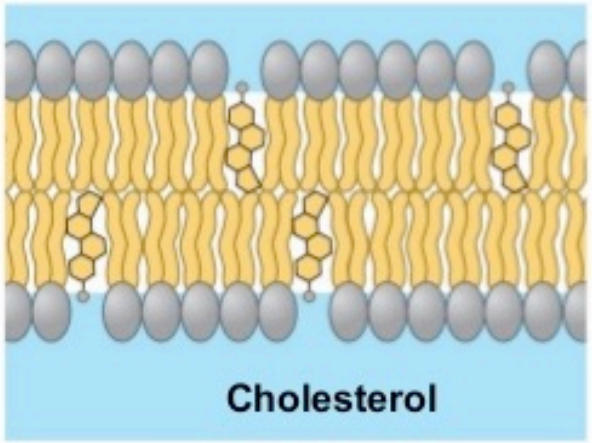
- $PGE_2$ induces reprogramming of macrophages to the M2 subtype
- Release of $PGE_2$ blocks the type 1 interferon-dependent innate immune response
- Secretion of linoleic acid causes loss of T helper cells
- Metabolic competition between cancer cells and immune cells restricts immune cell function

# L'insaturazione degli acidi grassi aumenta la fluidità della membrana

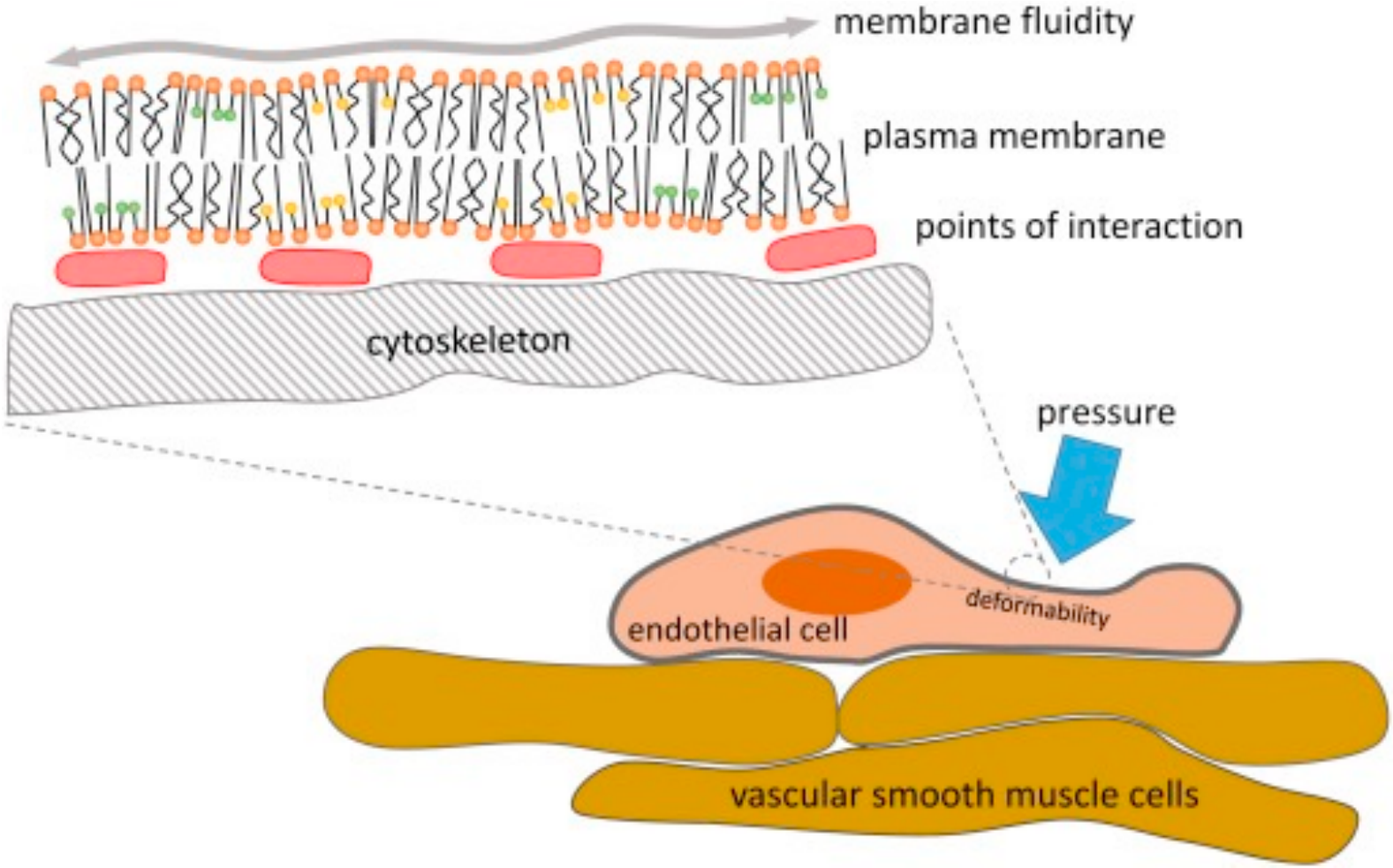



(a) Unsaturated versus saturated hydrocarbon tails

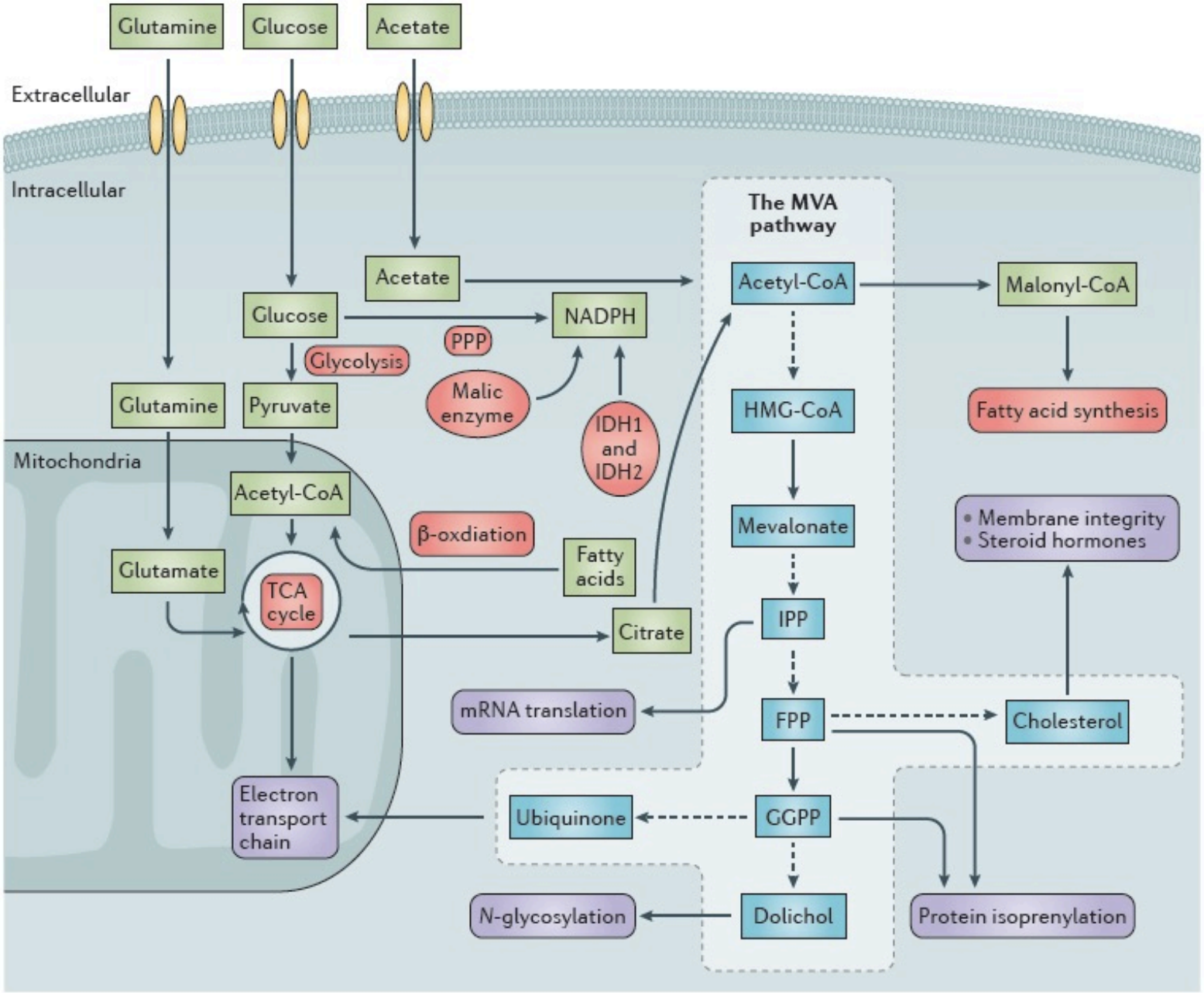
(b) Cholesterol within the animal cell membrane



# La fluidità della membrana facilita la migrazione cellulare e l'invasione



# La via biosintetica del mevalonato



# La via biosintetica del mevalonato

**Colesterolo**

componente dI:

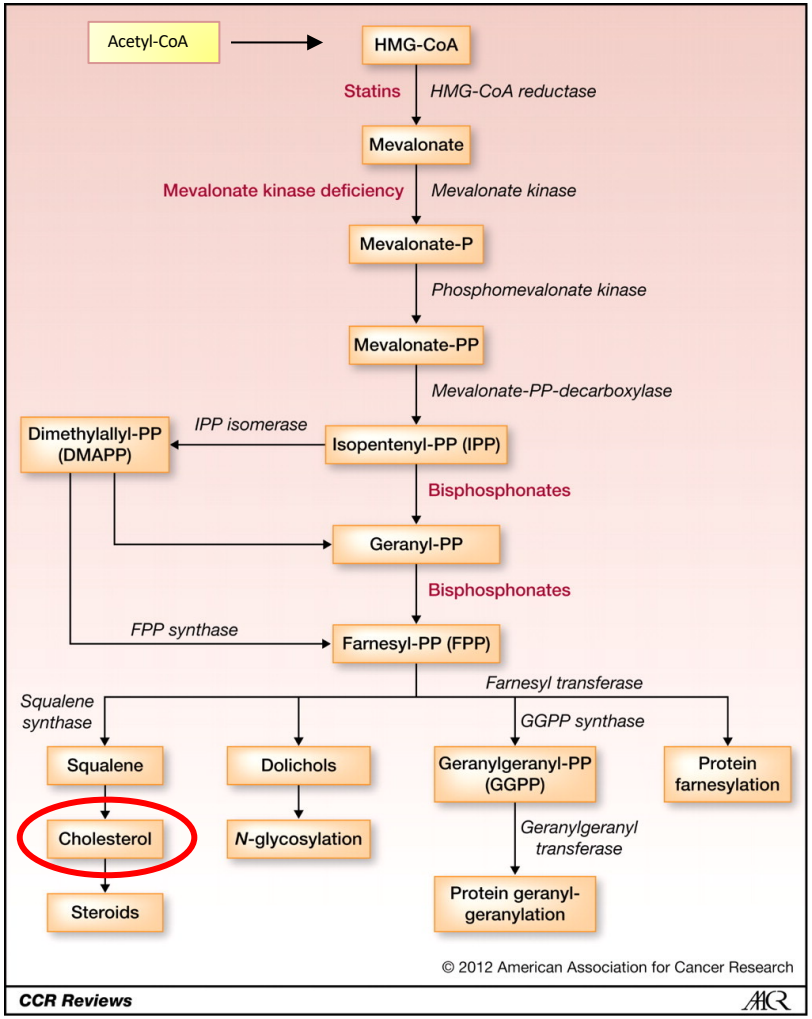
membrana plasmatica

Lipid rafts coordinano l'attivazione di signal transduction pathways

Membrane intracellulari (via secretoria)

Steroidi

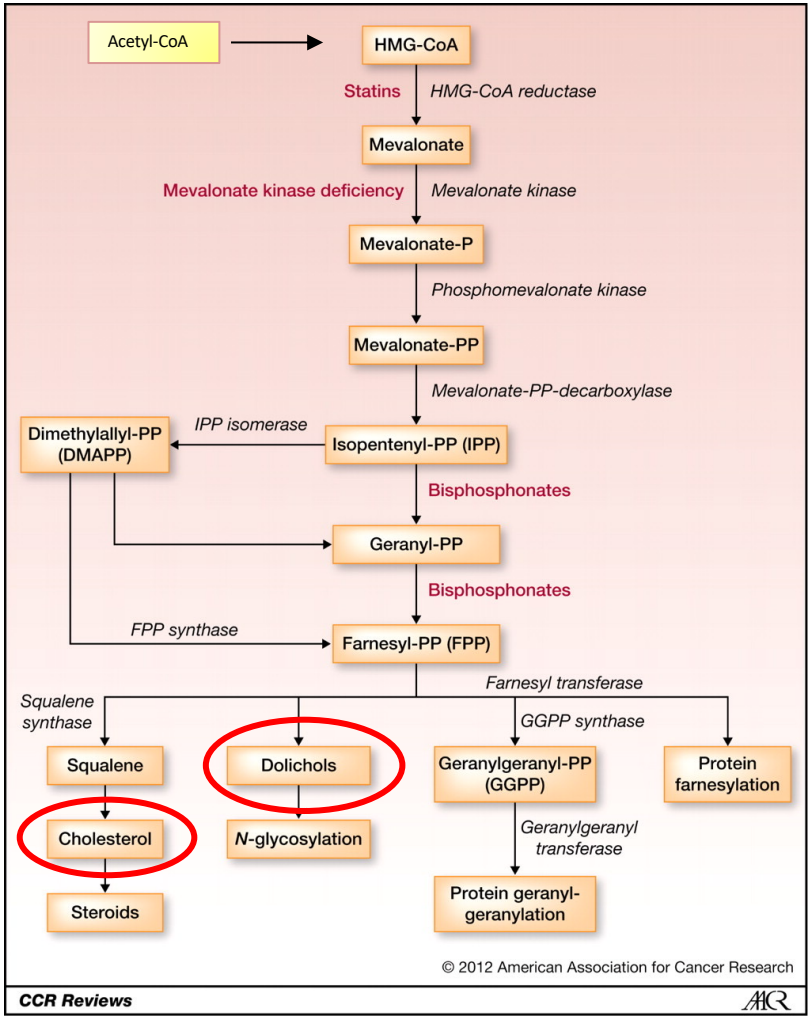
Molecole di segnalazione (e.g. Hedgehog)




*Adattato da Thurnher et al., 2012*

# La via biosintetica del mevalonato

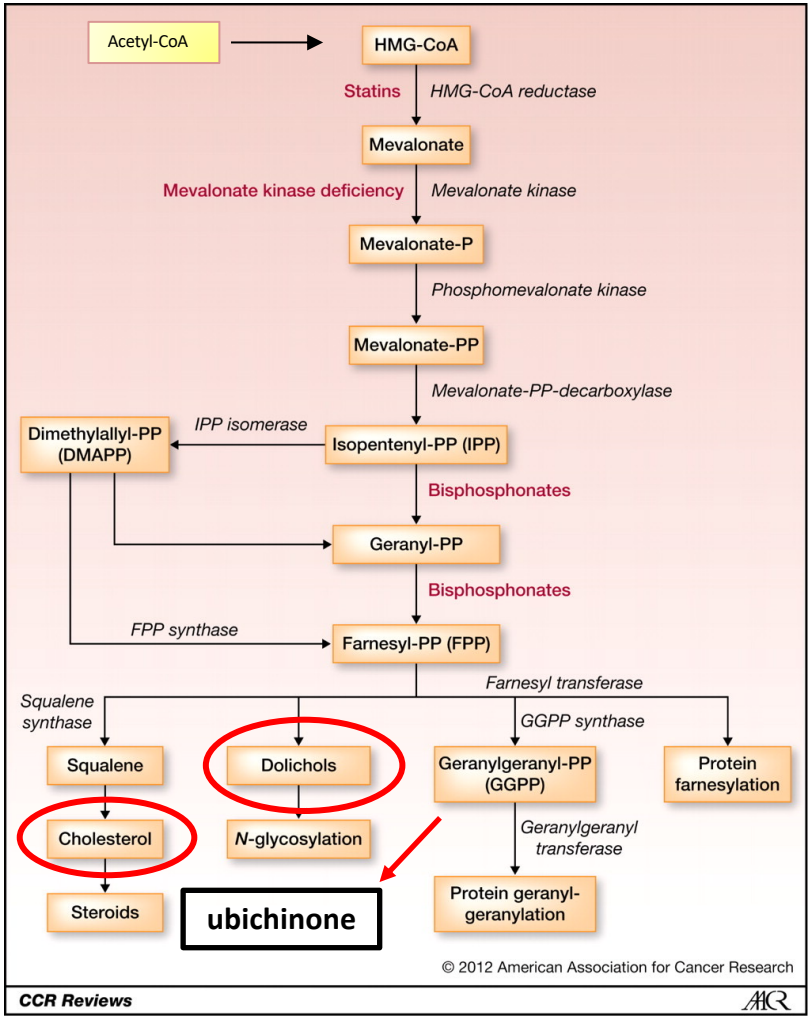
**Dolicolo**
*N*-glicosilazione




*Adattato da Thurnher et al., 2012*

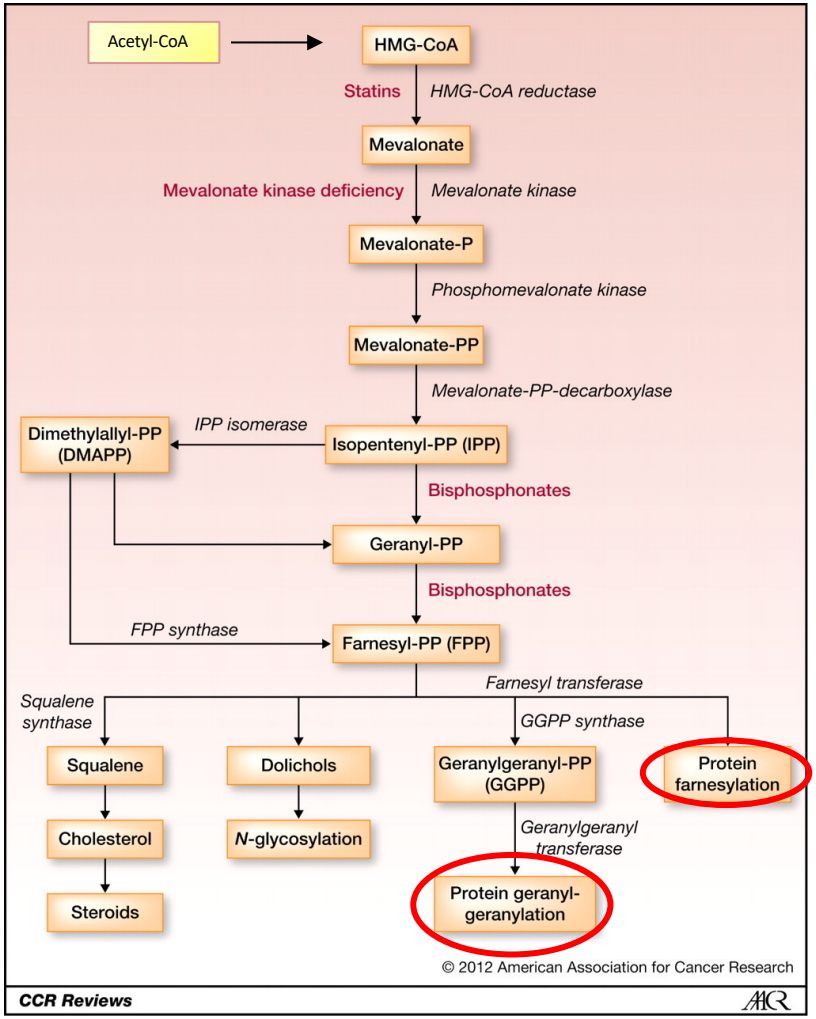
# La via biosintetica del mevalonato

**Ubichinone**
Catena di trasporto degli elettroni




*Adattato da Thurnher et al., 2012*

# La via biosintetica del mevalonato

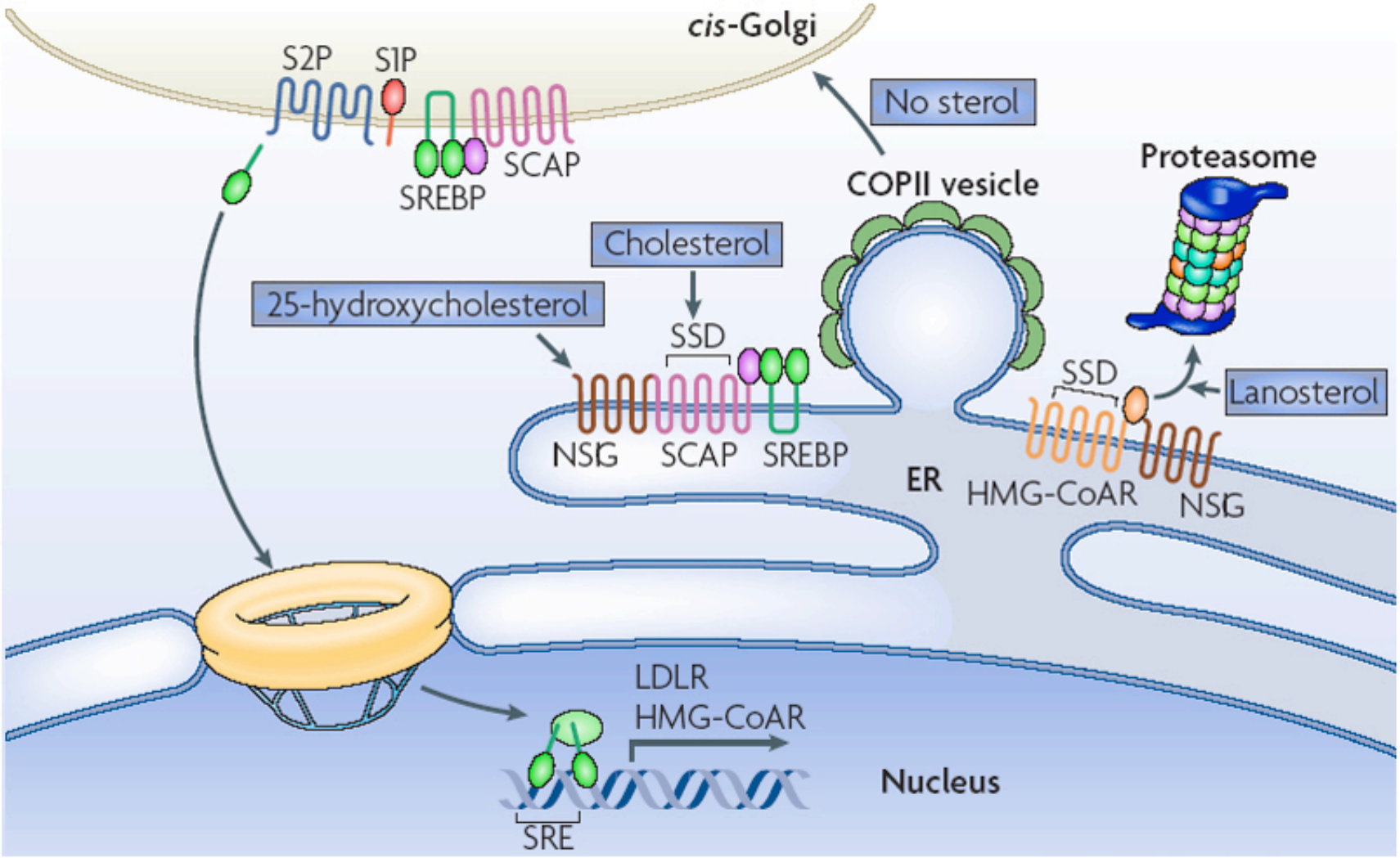



**Geranilgeranil pirofosfato**
Geranilgeranilazione delle proteine (es. Rho, Rab)

**Farnesil pirofosfato**
Farnesilazione delle proteine (es. Ras)

*Adattato da Thurnher et al., 2012*

# SREBPs: regolatori del metabolismo lipidico



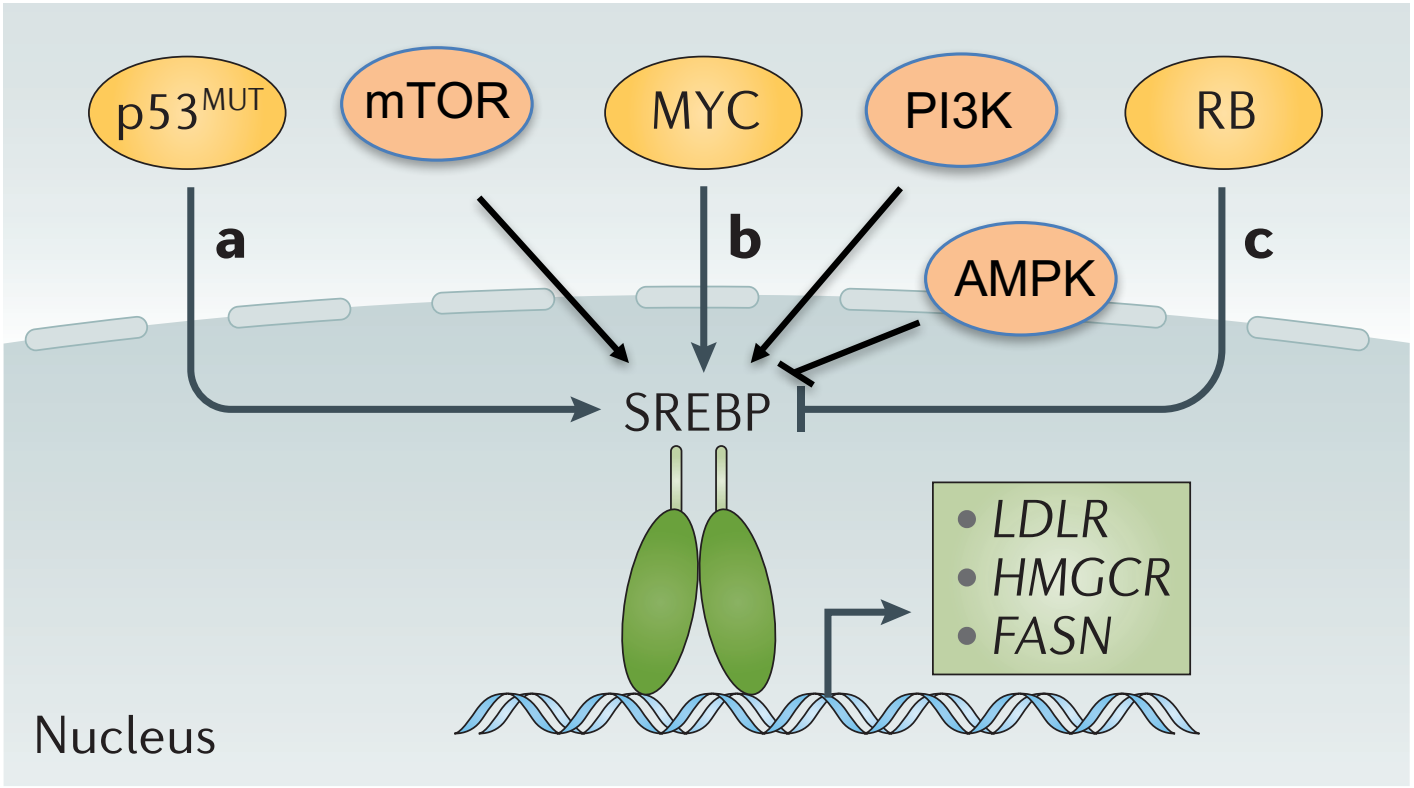

*Elina Ikonen,* **Nature Reviews Molecular Cell Biology, 2008**

# Sterol Regulatory Element-Binding Proteins (SREBPs)

The mevalonate pathway enzymes are under transcriptional control of a family of endoplasmic reticulum membrane-bound transcription factors designed as Sterol Regulatory Element-Binding Proteins (SREBPs). SREBPs directly activate the expression of more than 30 genes dedicated to the synthesis of cholesterol, isoprenoids, fatty acids, triglycerides and phospholipids. These transcription factors belong to the basic helix-loop-leucine zipper (bHLH-Zip) family and are synthesized as inactive precursor bound to the endoplasmic reticulum (ER). Each precursor is composed by three domains: a) an NH2-terminal domain of about 480 amino acids that contains the region for DNA binding; b) two hydrophobic transmemebrane-spanning segments interrupted by a short loop of about 30 amino acids that projects into the lumen of the ER; and c) a regulatory COOH-terminal domain of about 590 amino acids. To localize into the nucleus and act as transcription factor, the NH2-terminal domain must be released from the membrane proteolytically. Essential for his maturation process are three proteins. One is an escort protein designed SREBP cleavege-activating protein (SCAP). The other two are proteases, designed Site-1 protease (S1P) and Site-2 protease (S2P). SCAP is a sensor of sterols: when cells become depleted in cholesterol, SCAP escorts the SREBP from the ER to the Golgi apparatus, where the two proteases reside. S1P cleaves SREBP and the NH2-terminal domain is then released from the membrane via a second cleavage mediated by S2P.

The NH2-terminal domain (nSREBP) translocates to the nucleus, where it binds sterol response elements (SREs) in the promoters of multiple genes of the mevalonate pathway. In mammals there are three SREBP isoforms: SREBP-1a, SREBP-1c and SREBP-2. SREBP-1a is a potent activator of all the genes involved in the synthesis of cholesterol, fatty acids and tryglicerides. SREBP-1c preferentially enhances transcription of genes required for fatty acid synthesis, while SREBP-2 preferentially activates genes essential for cholesterol synthesis.

# Oncogeni e oncosoppressori controllano i fattori SREBP




*Mullen et al., Nature Rev. Cancer*

# Terapie metaboliche

Per il design di terapie metaboliche si deve tenere in considerazione

Finestra terapeutica:
- Inibire pathways che abbiano un ruolo essenziale nelle cellule tumorali ma non nei tessuti normali:

Plasticità metabolica delle cellule tumorali:
- Inibire contemporareamente diverse vie biochimiche per evitare il fenomeno della compensazione
- Combinare inibitori metabolici con inibitori di pathways oncogeniche

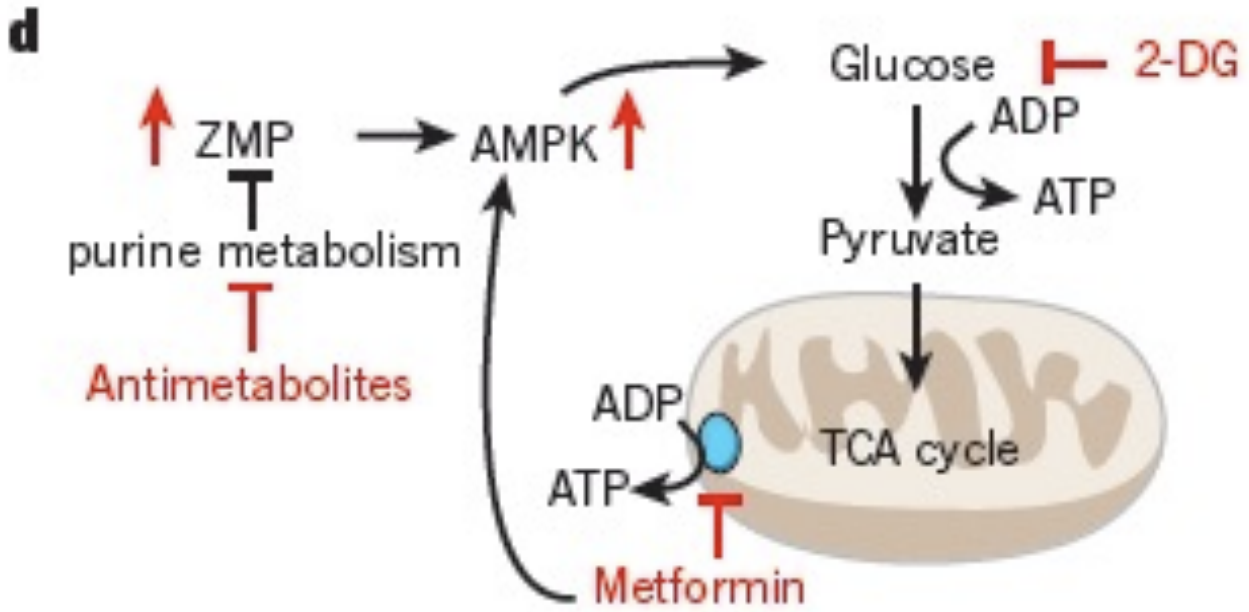
# Esempi di target

GLICOLISI: HK2, Lattato deidrogenasi (LDH)

GLUTAMINASI

METABOLISMO MITOCONDRIALE:
METFORMINA = INIBITORE mitochondrial complex I

# Terapie metaboliche: metformina




the antidiabetic drug Metformin leads to **reduction of circulating glucose and insulin levels** by causing mitochondrial energy stress in the liver.
Given its widely reported inhibitory effects on cancer cell growth, repurposing of Metformin for both treatment (www.ClinicalTrials.gov) and primary prevention of breast cancer is being investigated in large clinical trials.

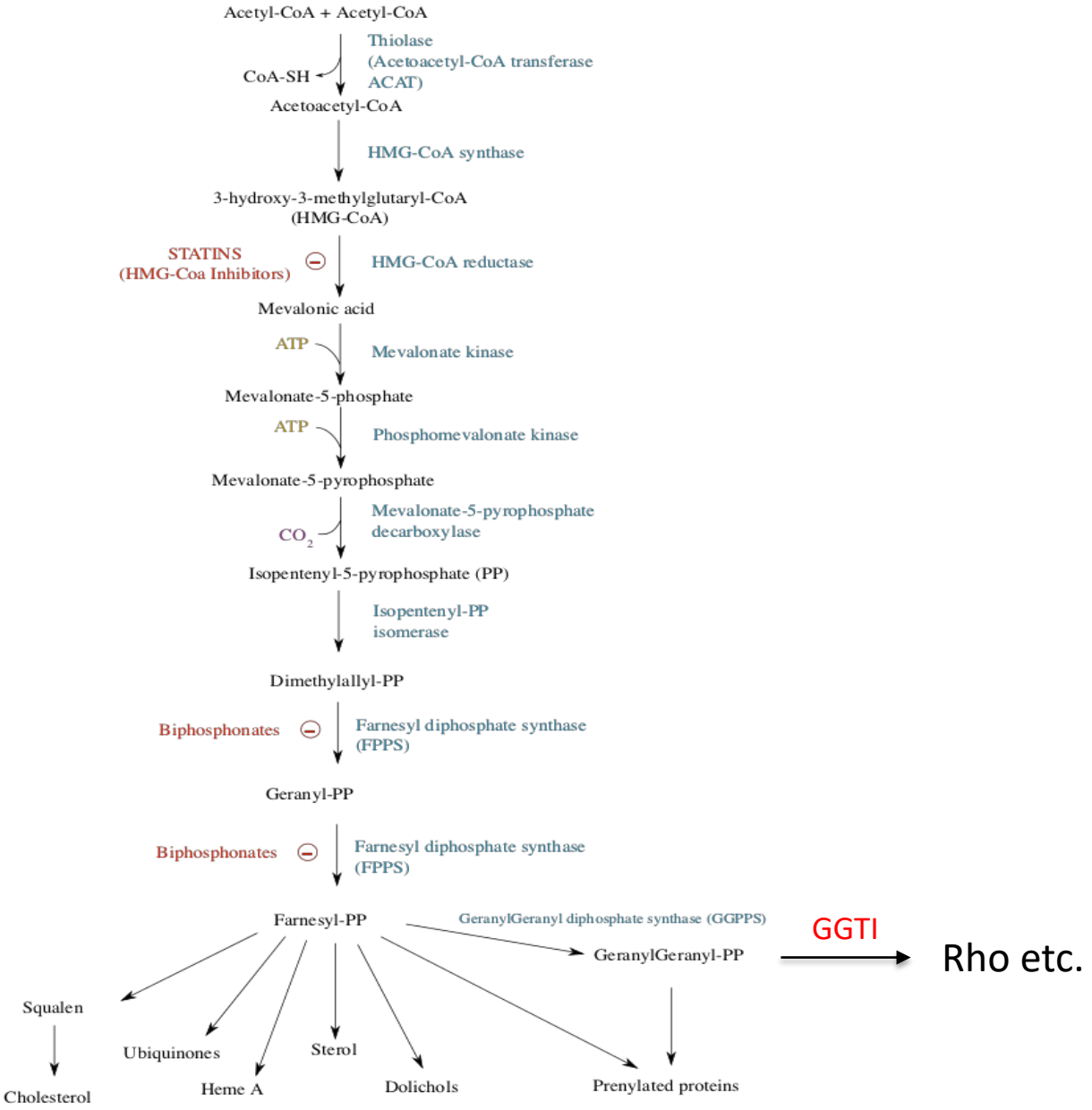
# Metabolismo lipidico:

# Bersagli terapeutici

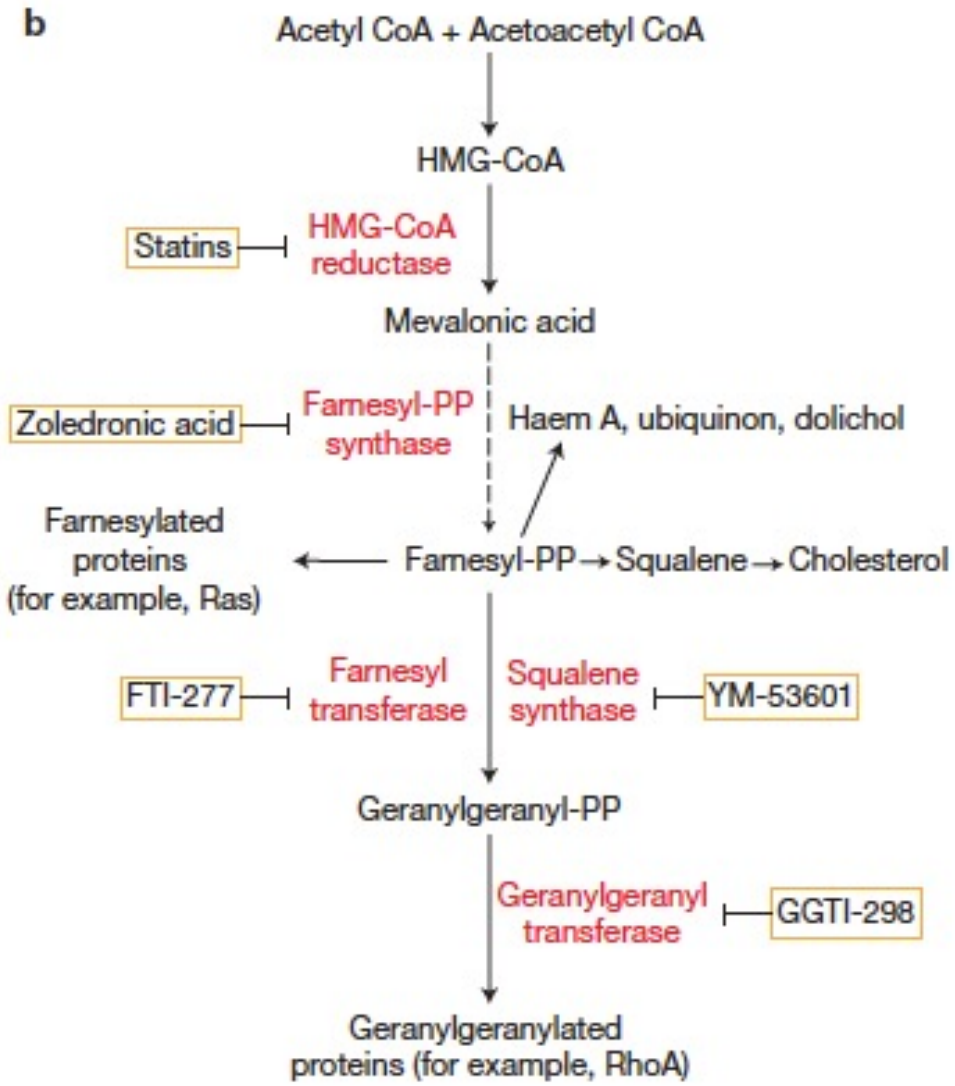
ACLY
FASN
ELOVL
SCD

SREBP-SCAP (fatostatin, betulina)

# PATHWAY DEL MEVALONATO



# PATHWAY DEL MEVALONATO



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Statin Use and Reduced Cancer-Related Mortality

Sune F. Nielsen, Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc.
and Stig E. Bojesen, M.D., Ph.D., D.M.Sc.

New England Journal of Medicine, 2012

Table 1 | **Agents that target the MVA pathway and/or its SREBP-regulated feedback mechanism**

| Drugs | Target | Stage of clinical development | Refs |
|---|---|---|---|
| *MVA pathway inhibitors* | | | |
| Statins | HMGCR | Approved as cholesterol-lowering agents and currently in phase I, II and III clinical trials for the treatment of various cancer types | 171–175 |
| Bisphosphonates | FDPS | Approved for the treatment of osteoporosis, multiple myeloma and solid tumour bone metastases, in combination with standard therapy | 194–196 |
| *Isoprenylation inhibitors* | | | |
| FTIs and GGTIs | Farnesyltransferases and geranylgeranyl-transferases | In phase I, II and III clinical trials for the treatment of various cancer types, as single agents or in combination with standard therapy | 65,197,198 |
| *SREBP inhibitors* | | | |
| Fatostatin | SCAP | In preclinical development | 190–192 |
| Betulin | SCAP | In preclinical development | 199 |
| Tocotrienols | Unknown | In preclinical development | 188,189 |
| Nelfinavir | S2P | Approved for the treatment of HIV infection and in phase I and II clinical trials for the treatment of various cancer types | 200–202 |
| Dipyridamole | Unknown | Approved for the prevention of cerebral ischaemia and in preclinical development as an inhibitor of SREBP | 51 |

FDPS, farnesyl diphosphate synthase; FTI, farnesyltransferase inhibitor; GGTI, geranylgeranyltransferase inhibitor; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; MVA, mevalonate; S2P, site-2 protease; SCAP, SREBP cleavage-activating protein; SREBP, sterol regulatory element-binding protein.