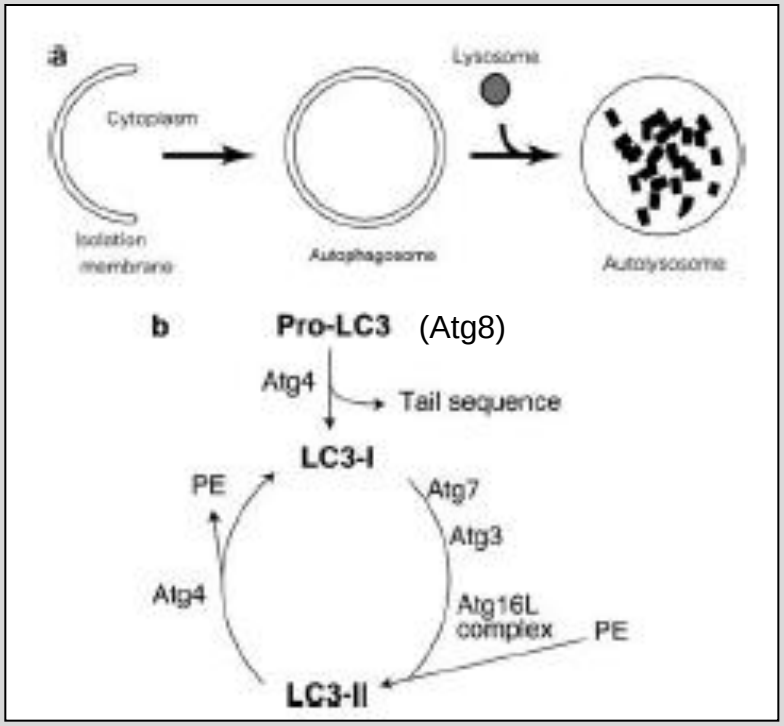
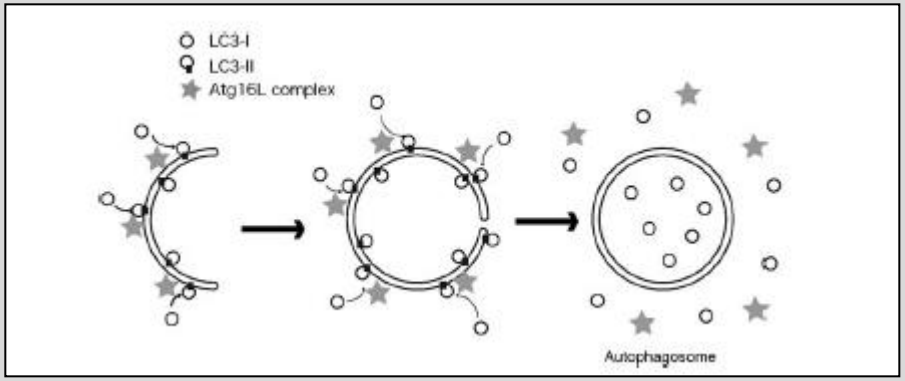
Autophagy (late phases)

LC3 interconversion (LC3I to LC3II) and autophagosome formation

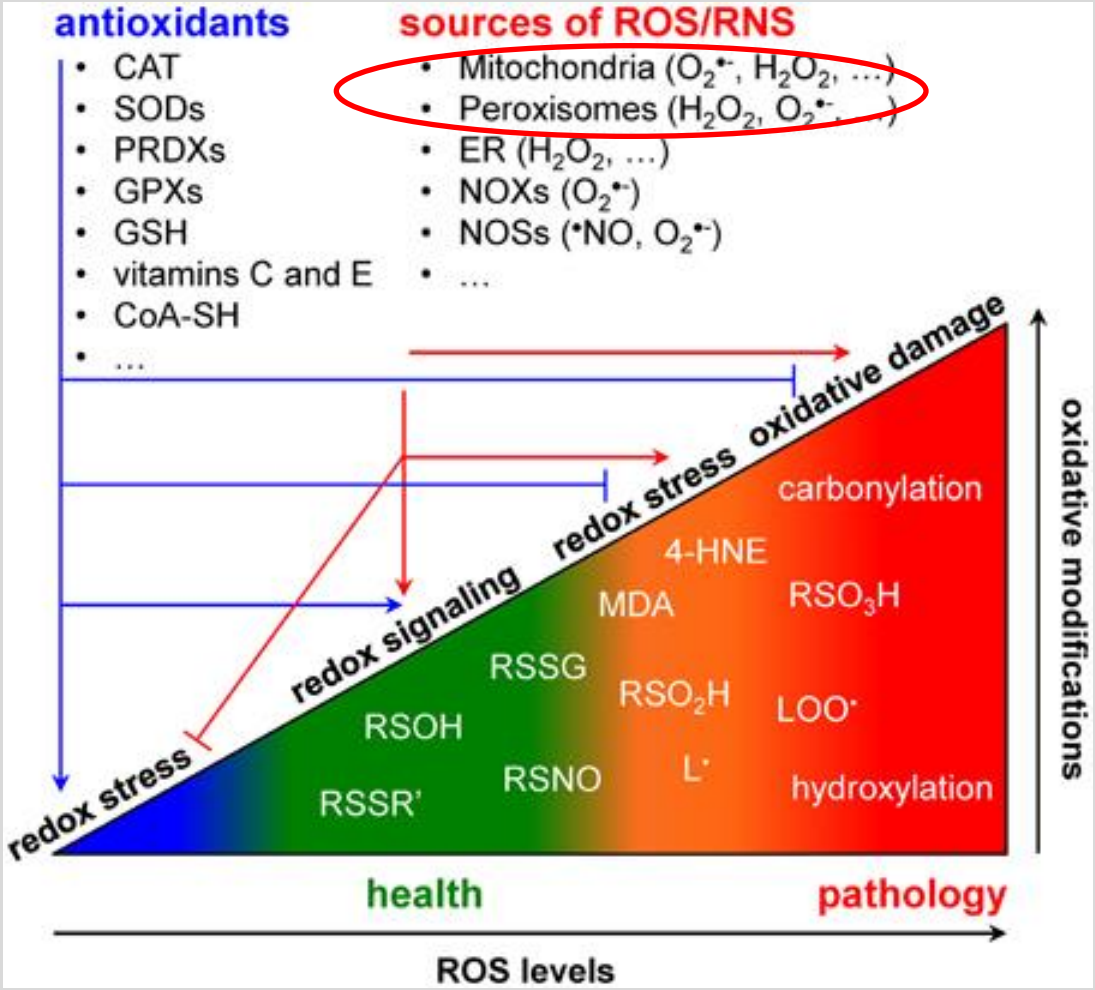




Noda T, Fujita N, Yashimari T. The late stages of autophagy: how does the end begin? Cell Death Differ 2009, 16: 984-990.

Gérard Lizard

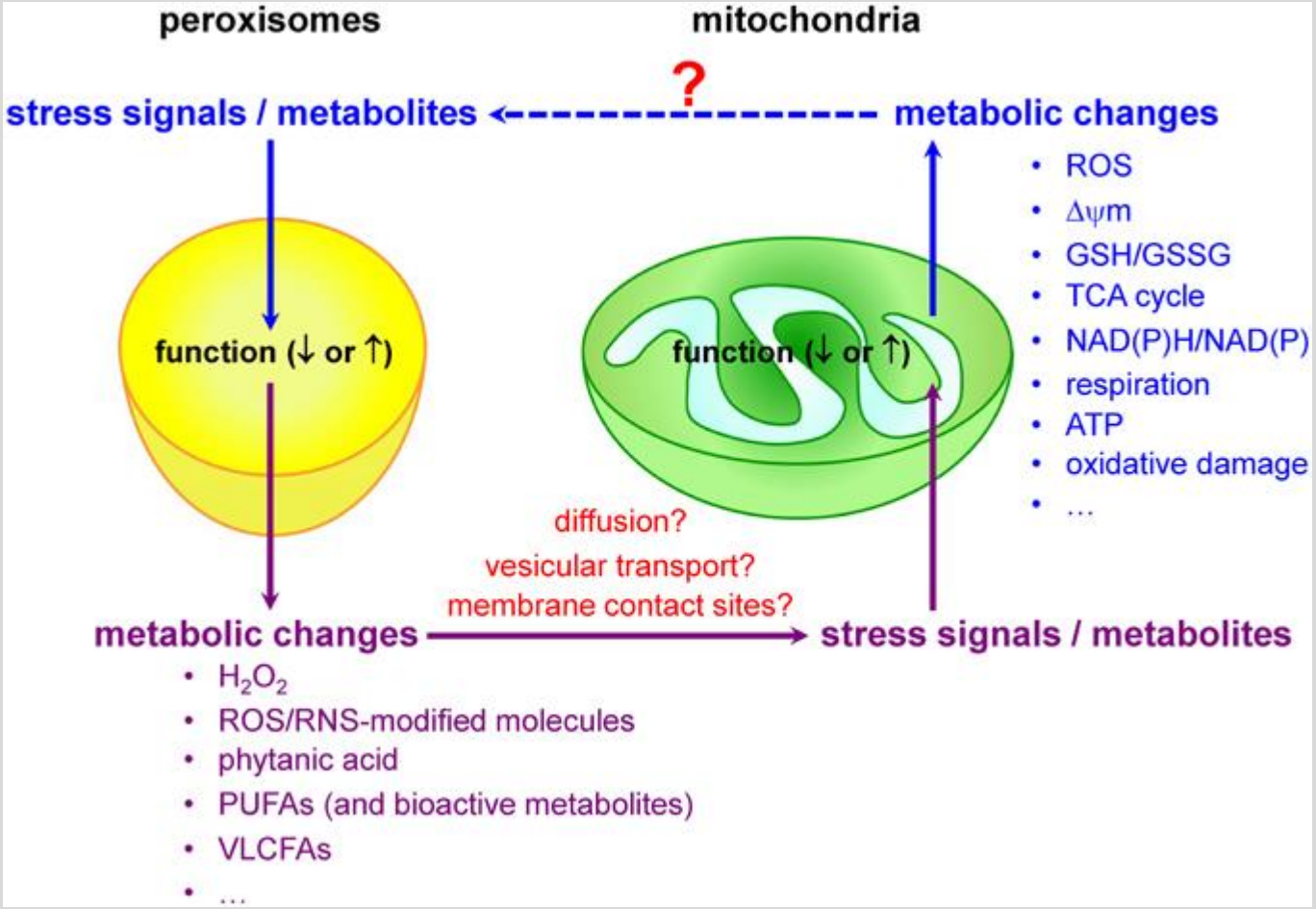
Rupture de l'équilibre RedOx et induction de mort cellulaire
Implication du peroxysome et de la mitochondrie



Lismont C, Nordgren M, Van Veldhoven PP, Fransen M. Front Cell Dev Biol. 2015, 27;3:35.

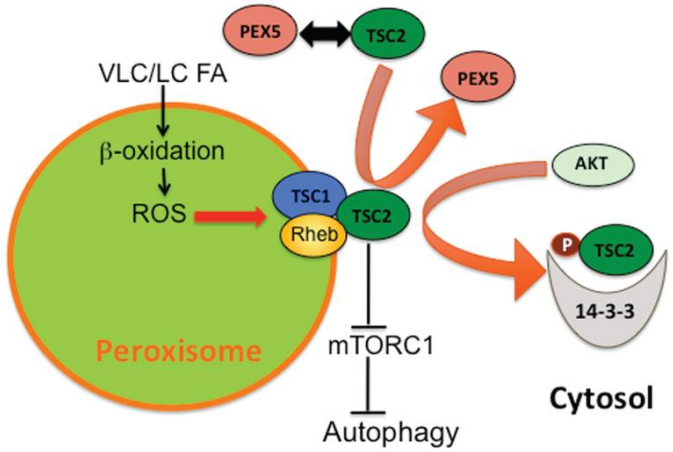
Relations peroxysome / mitochondrie

Implication dans le contrôle de l'équilibre RedOx et l'activation de la mort cellulaire



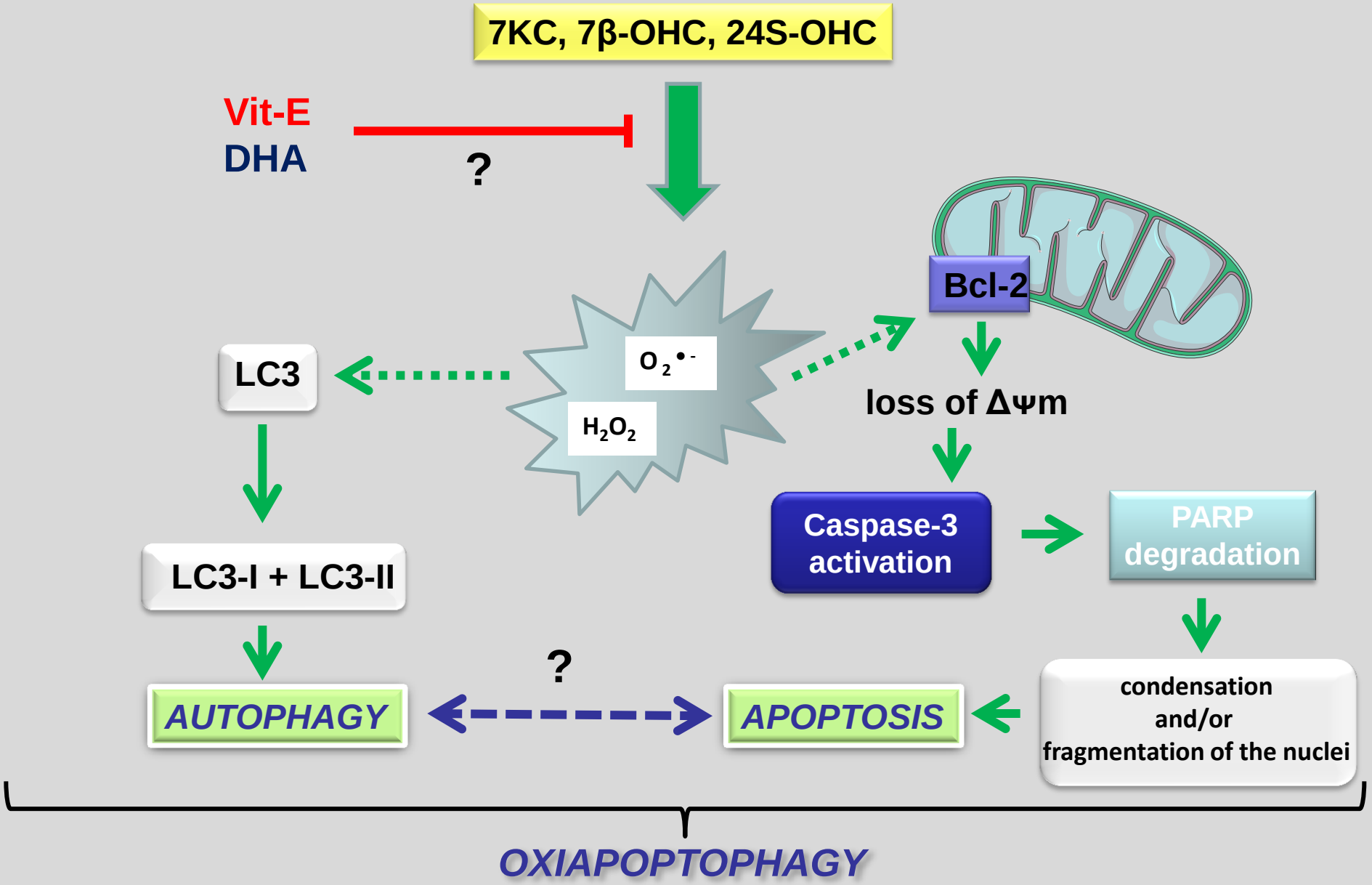
Lismont C, Nordgren M, Van Veldhoven PP, Fransen M. Front Cell Dev Biol. 2015, 27;3:35.

Contribution of peroxisomal proteins to autophagic process



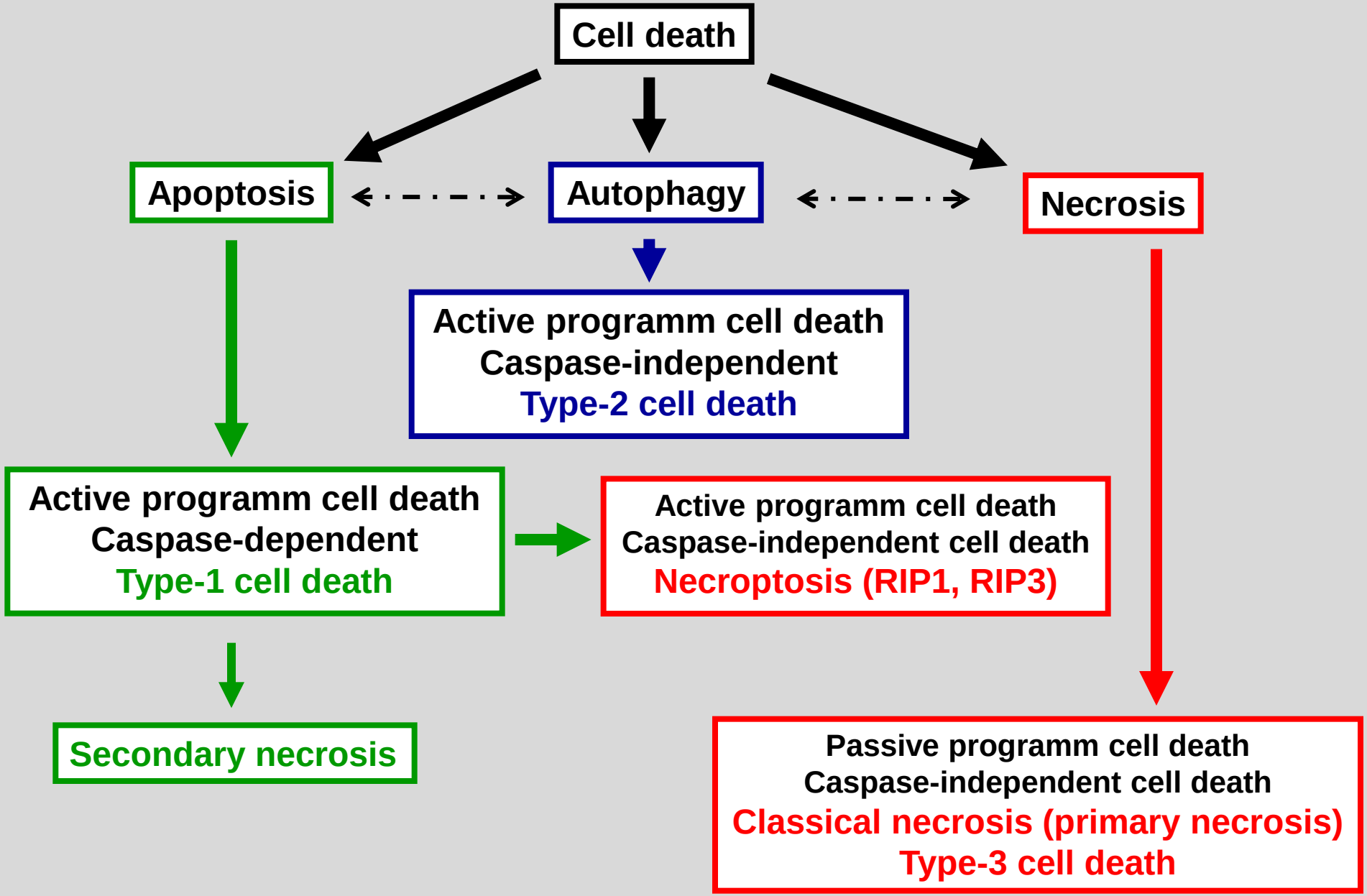
Model for TSC complex localization on peroxisomal membranes, and activation of the TSC1-TSC2-Rheb signaling node by peroxisomal ROS to repress mTORC1 and induce autophagy, or inactivation by AKT phosphorylation of TSC2, with subsequent binding of TSC2 by 14-3-3 and sequestration in cytosol.

Zhang et al. Nat Cell Biol 2013

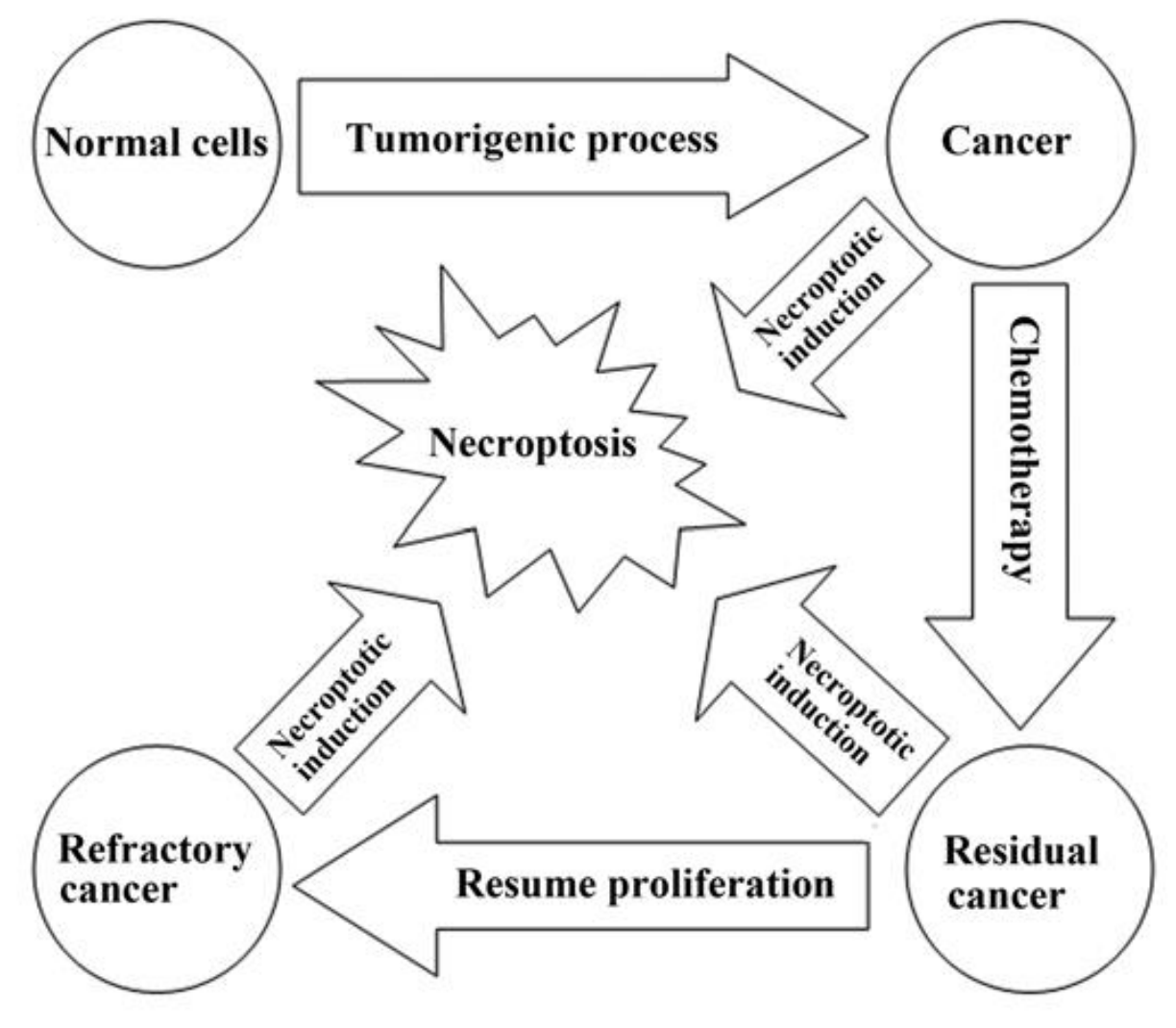


Hypothetic cascade of events leading to oxiapoptophagy (OXIdation, APOPTOsis, autoPHAGY) under treatment with 7-ketocholesterol (7KC), 7β-hydroxycholesterol (7β-OHC), and 24(S)-hydroxycholesterol (24S-OHC) on 158N murine oligodendrocytes. It is supposed that VitE and DHA, which are potent inhibitors of oxiapoptophagy, act at an early stage of this mode of cell death.

Nury *T et al*., graphical abstract



Gérard Lizard,



Targeting the weak point of cancer by induction of necroptosis.
Hu X, Han W, Li L. ***Autophagy. 2007; 3(5): 490-2.***

Gérard Lizard,

Interconnection Between Autophagy, Apoptosis, Mitoptosis and Necrosis

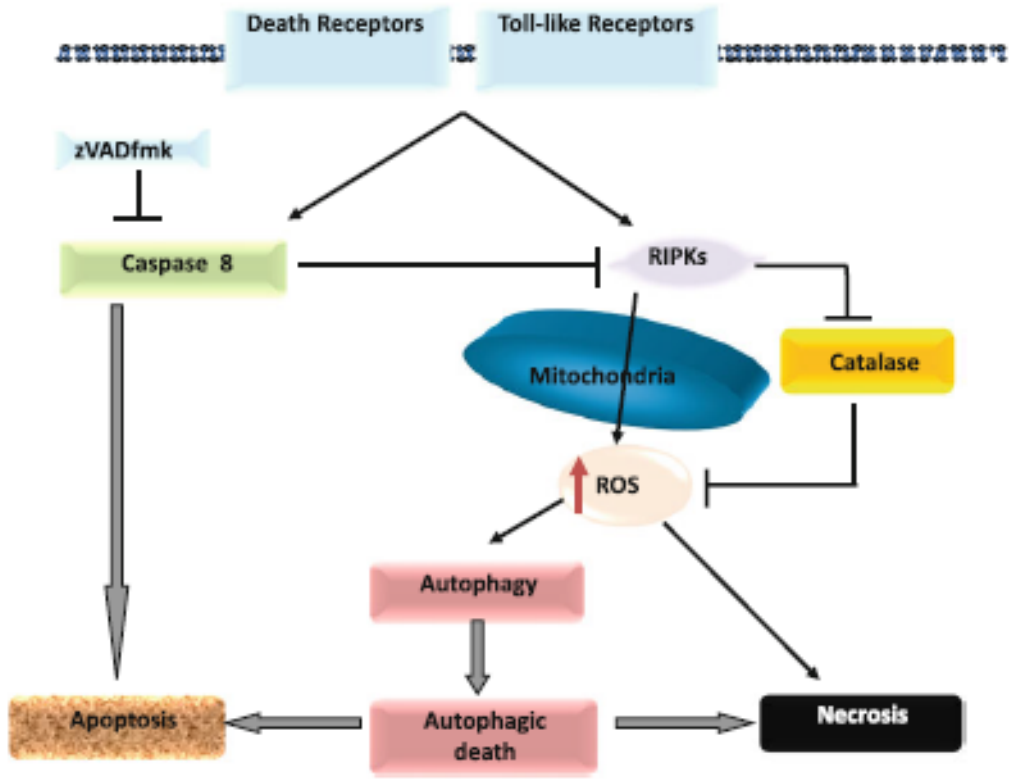


Fig. 4 Modulation of cell death mode by caspase activity, and consequences of caspase inhibition. The broad spectrum caspase inhibitor zVAD fmk modulates the three major types of cell death in different ways. zVAD fmk blocks apoptotic cell death while it sensitizes cells to necrotic cell death, and autophagy, presumably by shifting the balance from apoptosis towards necrosis/autophagy. Autophagy and necrotic cell death are interconnected and may partially consist of common underlying molecular pathways involving RIPKs and negative regulation by caspase 8. Furthermore, an activatory role for cyclophilin D and an inhibitory role for catalase in caspase independent cell death cascades have been demonstrated (see text for further details)

Autophagy, Apoptosis, Mitoptosis and Necrosis: Interdependence Between Those Pathways and Effects on Cancer
Wiem Chaabane • Sırma D. User • Mohamed El-Gazzah • Roman Jaksik • Elaheh Sajjadi • Joanna Rzeszowska-Wolny • Marek J. Łos;
Arch. Immunol. Ther. Exp. (2013) 61:43–58

Lipids and Cell Death

Gérard LIZARD : EA7270
Univ. Bourgogne Franche Comté / INSERM

Les lipides : structures et classification

Basé sur la structure chimique, on distingue

✓**Acides gras**

✓**Lipides simples**
- **glycérides**
- **stérols et stéroïdes**
- **cérides (esters d'alcools gras + acides gras)**

✓**Lipides complexes**
- **phospholipides**
- **sphingolipides**
- **plasmalogènes**

✓**Lipides isopréniques**
- **carbures isopréniques (polymères d'isoprènes: terpènes)**
- **quinones et vitamines liposolubles**

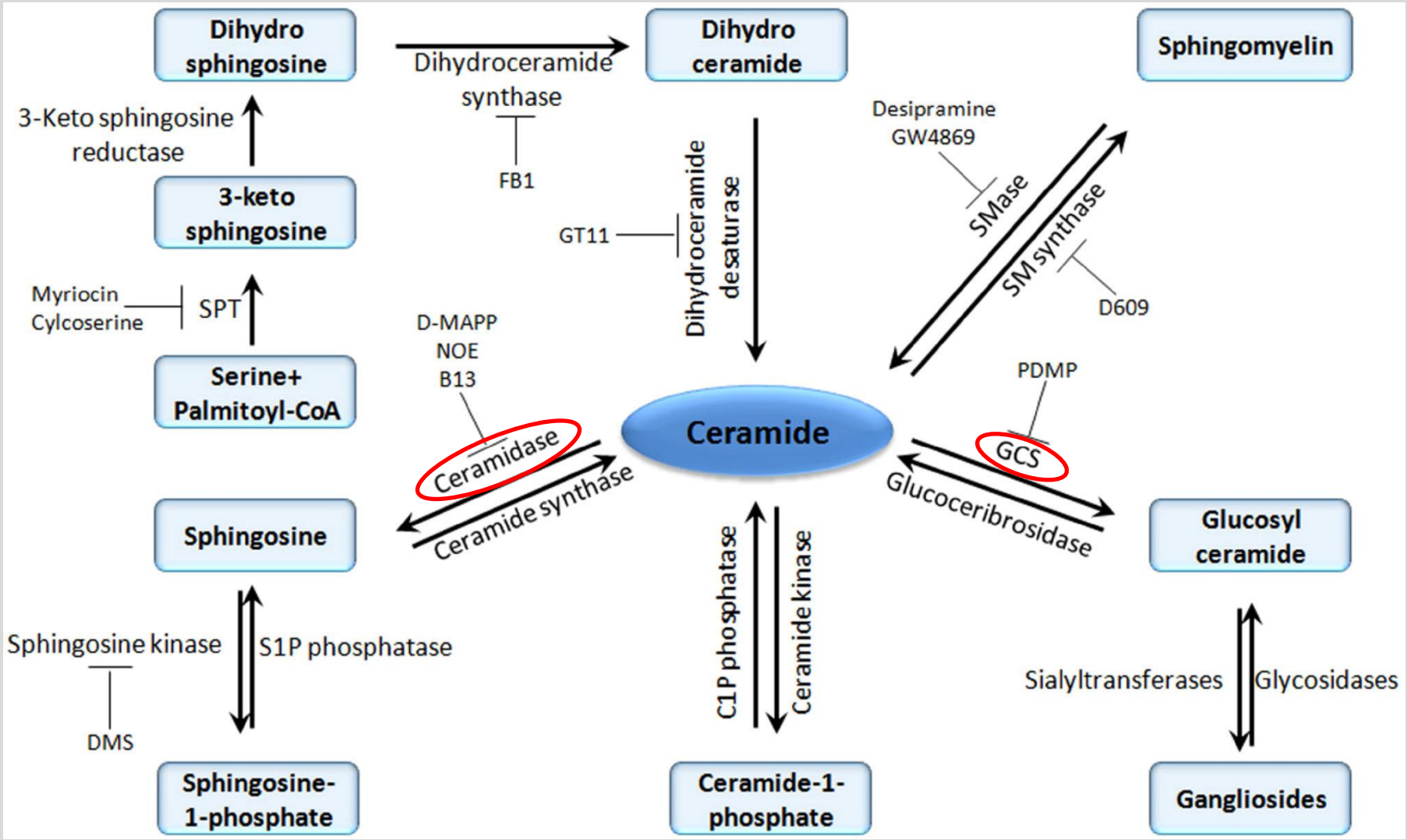
Insolubles dans l'eau, solubles dans les solvants organiques apolaires

(groupements chimiques communs: -CH=CH-; -CH2-; -CH3-)

http://slideplayer.fr/slide/1165755/

Gérard LIZARD : EA7270
Univ. Bourgogne Franche Comté / INSERM

Biosynthèse des céramides



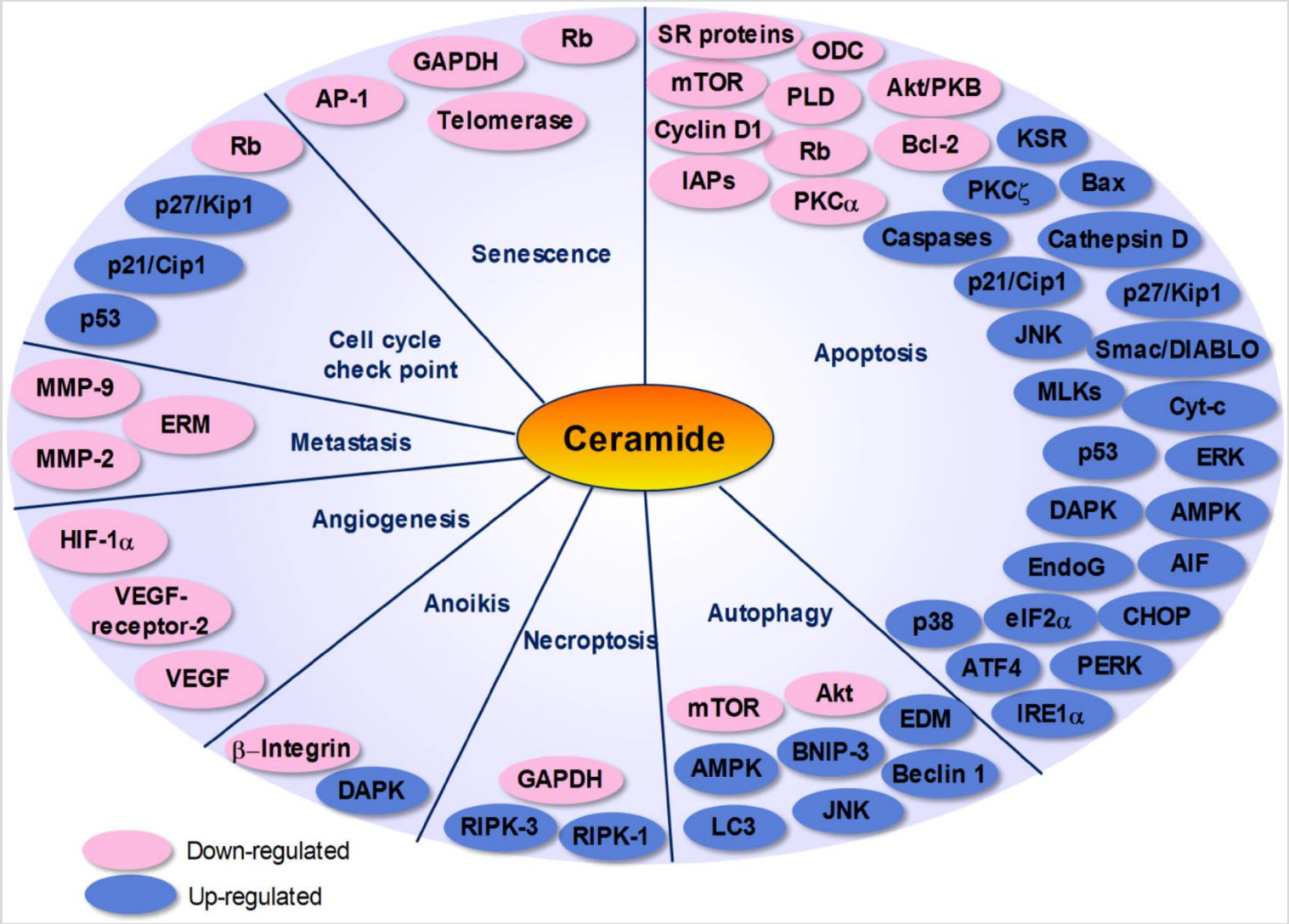
GCS: glucosylceramide synthase

Galadari S, Rahman A, Pallichankandy S, Thayyullathil F. Tumor suppressive functions of ceramide: evidence and mechanisms. Apoptosis. 2015;20(5):689-711.

Céramides : cibles thérapeutiques

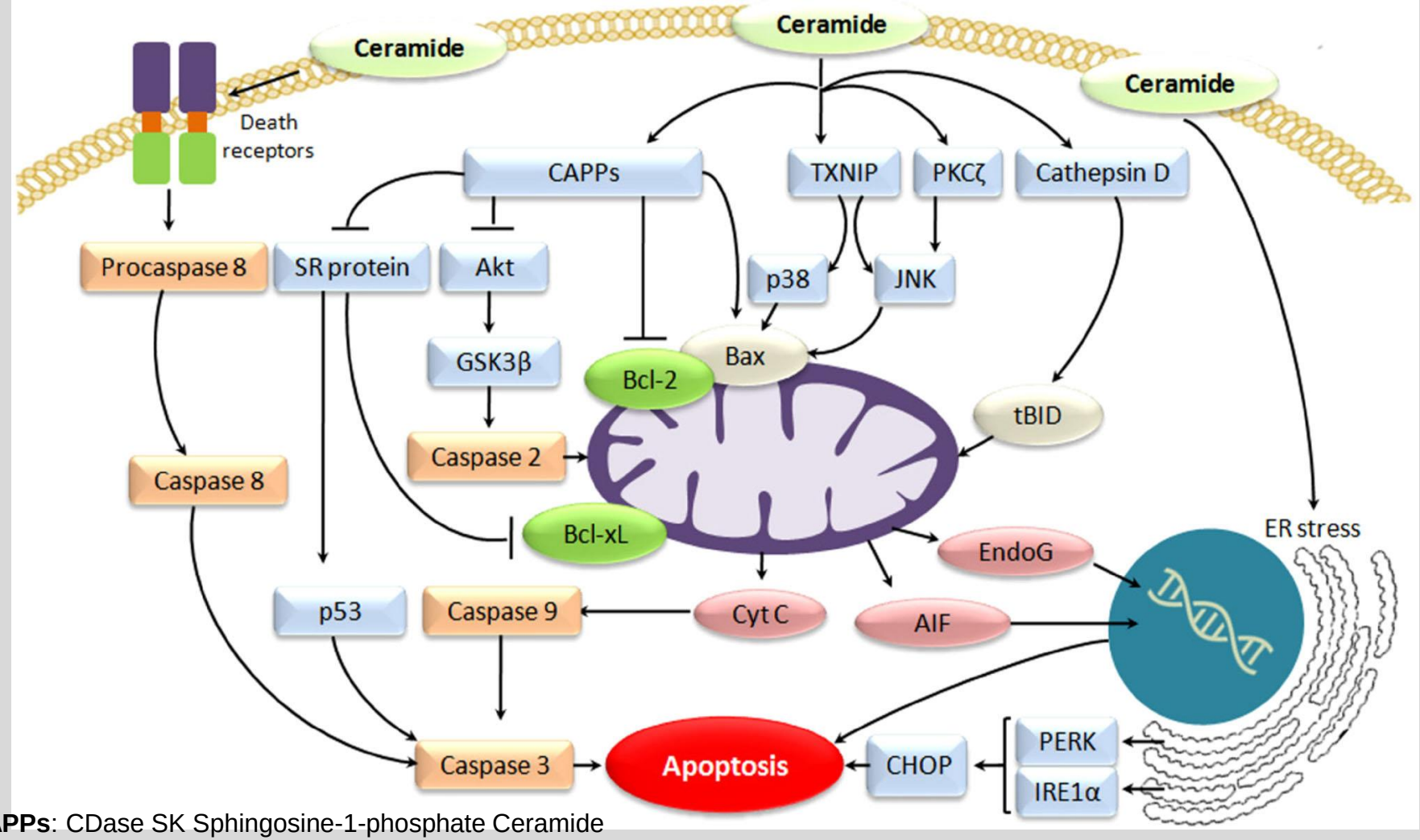
Enzymes	Cancer species (cell line)	Drug	Resistance
GCS ↑	Breast cancer (MCF-7)	Adriamycin	↑
	Colon cancer (SW620)	Adriamycin	↑
	Epidermoid carcinoma (KB-3-1)	Adriamycin Vinblastine	↑
	Leukemia (HL-60)	Vincristine	↑
	Melanoma (MeWo)	Etoposide	↑
	Leukemia (HL-60)	Doxorubicin	↑
GCS ↓	Adriamycin-resistant MCF-7	Adriamycin	↓
	Adriamycin-resistant MCF-7	Vinblastine Paclitaxel	↓
	Adriamycin-resistant MCF-7 and murine breast cancer (EMT6)	Doxorubicin	↓
	Adriamycin-resistant SW620	Doxorubicin	↓
	Doxorubicin-resistant ovarian carcinoma (A2780)	Doxorubicin	↓
	Doxorubicin-resistant cervical cancer (KB-A1)	Doxorubicin	↓
	Hepatoma (HepG2)	Doxorubicin	↓
	Multidrug-resistant leukemia (K562/A02)	Adriamycin	↓
Acid Ceramidase ↑	Prostate cancer (DU145)	Doxorubicin Cisplatin Etoposide Gemcitabine	↑
Acid Ceramidase ↓	Hepatoma (HepG2, Hep-3B, SK-Hep and Hepa1c1c7)	Daunorubicin	↓

Céramides : effecteurs et cibles moléculaires



Galadari S, Rahman A, Pallichankandy S, Thayyullathil F. Tumor suppressive functions of ceramide: evidence and mechanisms. Apoptosis. 2015;20(5):689-711.

Céramides : inducteurs d'apoptose / activité anti-tumorale



CAPPs: CDase SK Sphingosine-1-phosphate Ceramide
TXNIP: Thioredoxin-interacting protein

Galadari S, Rahman A, Pallichankandy S, Thayyullathil F. Tumor suppressive functions of ceramide: evidence and mechanisms. Apoptosis. 2015;20(5):689-711.

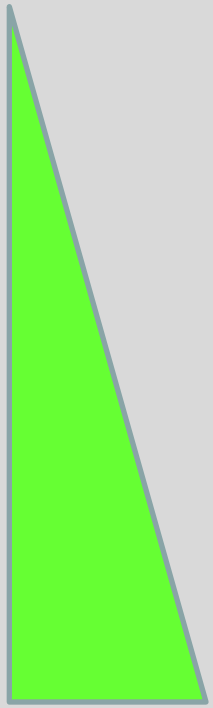
Stimuli apoptotique : génération de céramides (détection par immunofluorescence)

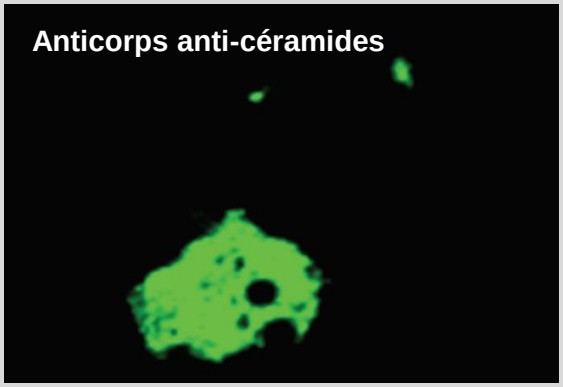
Cellule normale

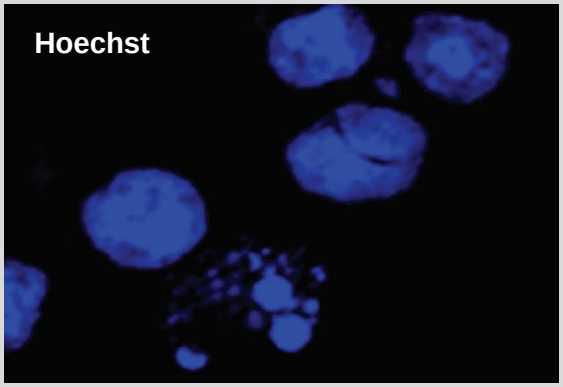
Cellule pré-apoptotique

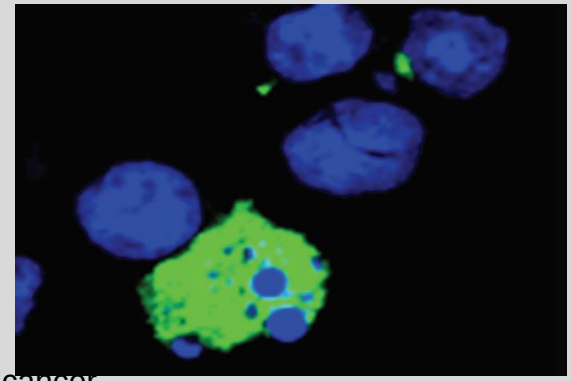
Cellule apoptotique

Expression de céramides



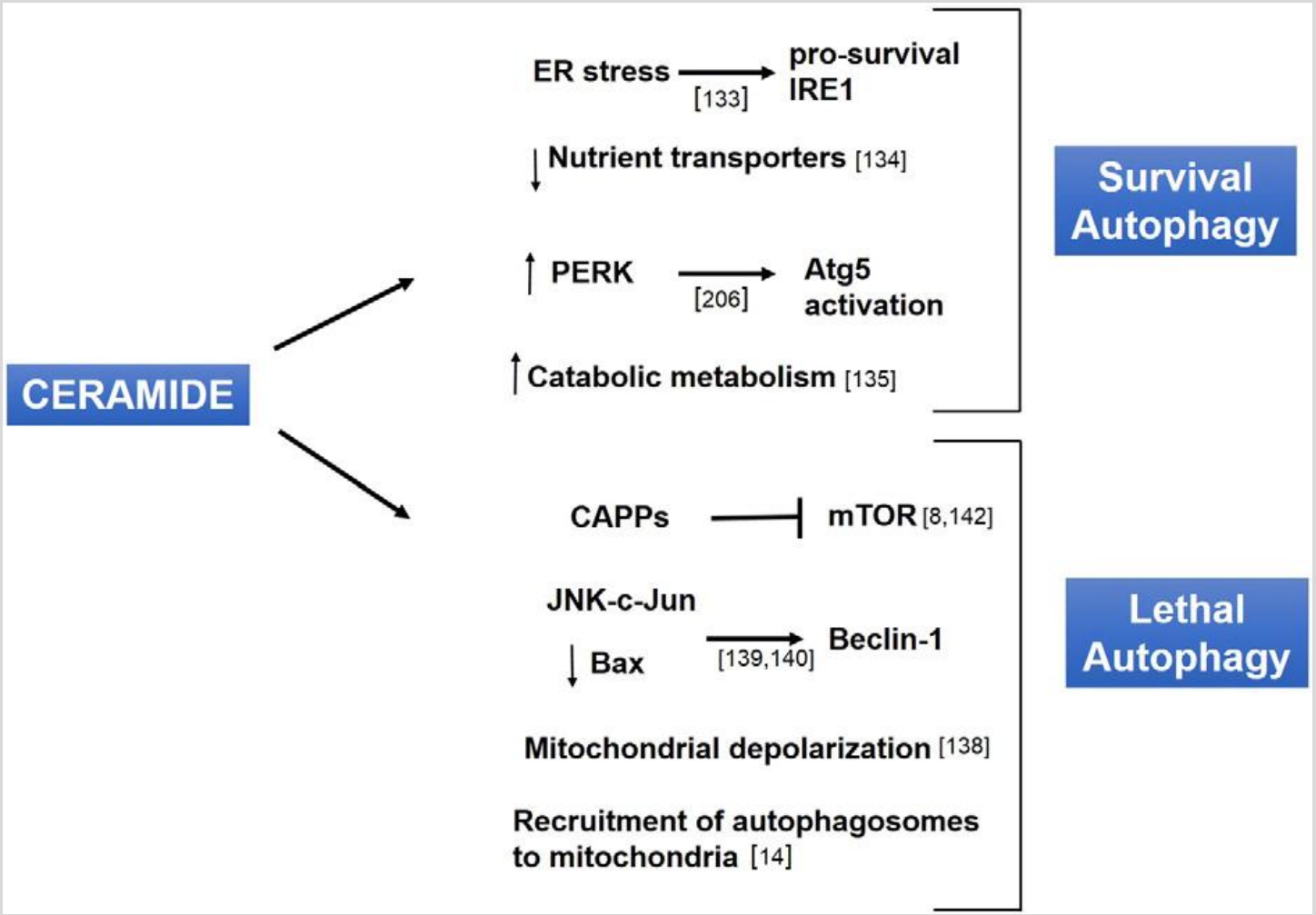






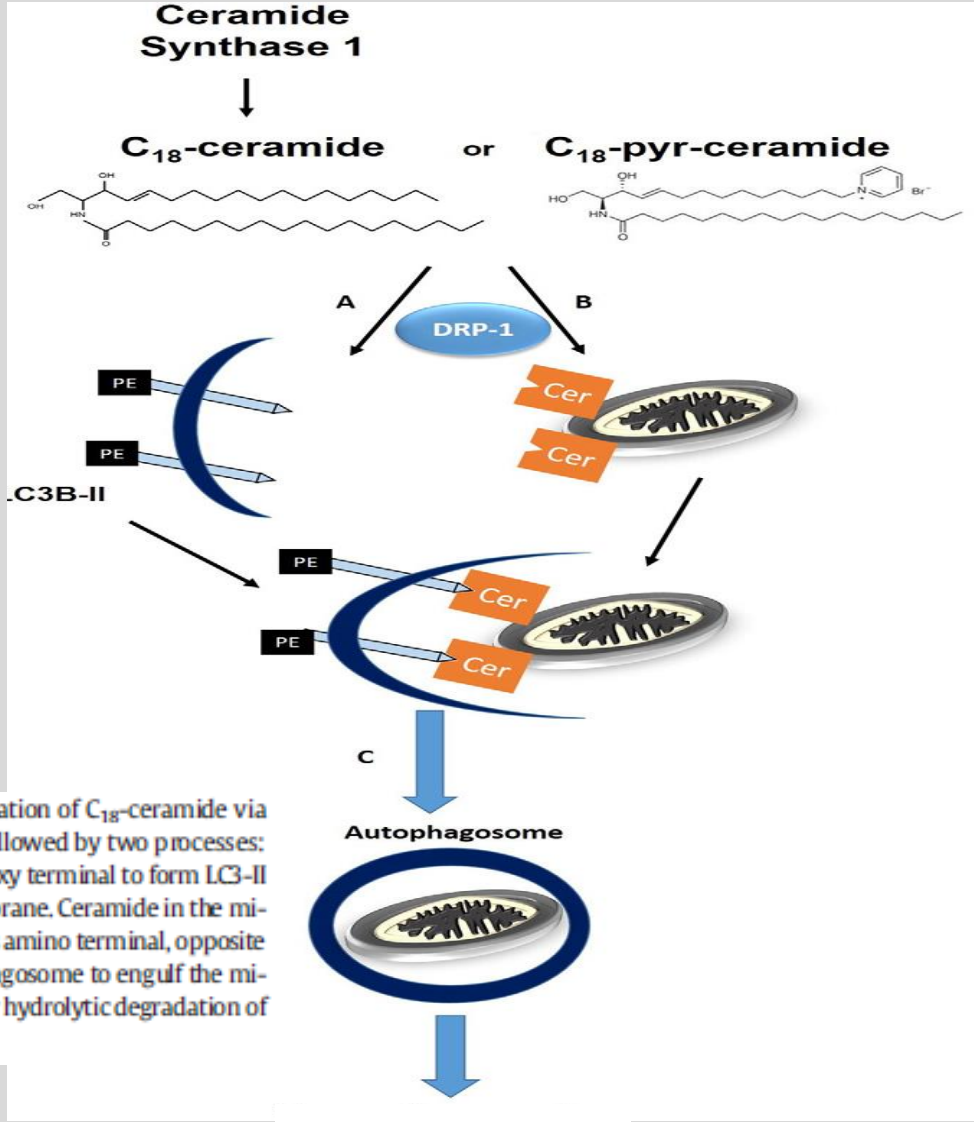
Huang WC, Chen CL, Lin YS, Lin CF. Apoptotic sphingolipid ceramide in cancer therapy.

Céramides : autophagie cytoprotectrice et léthale



Dany M, Ogretmen B. Ceramide induced mitophagy and tumor suppression. Biochim Biophys Acta. 2015;1853(10 Pt B):2834-45.

Céramides : régulation de la mitophagie

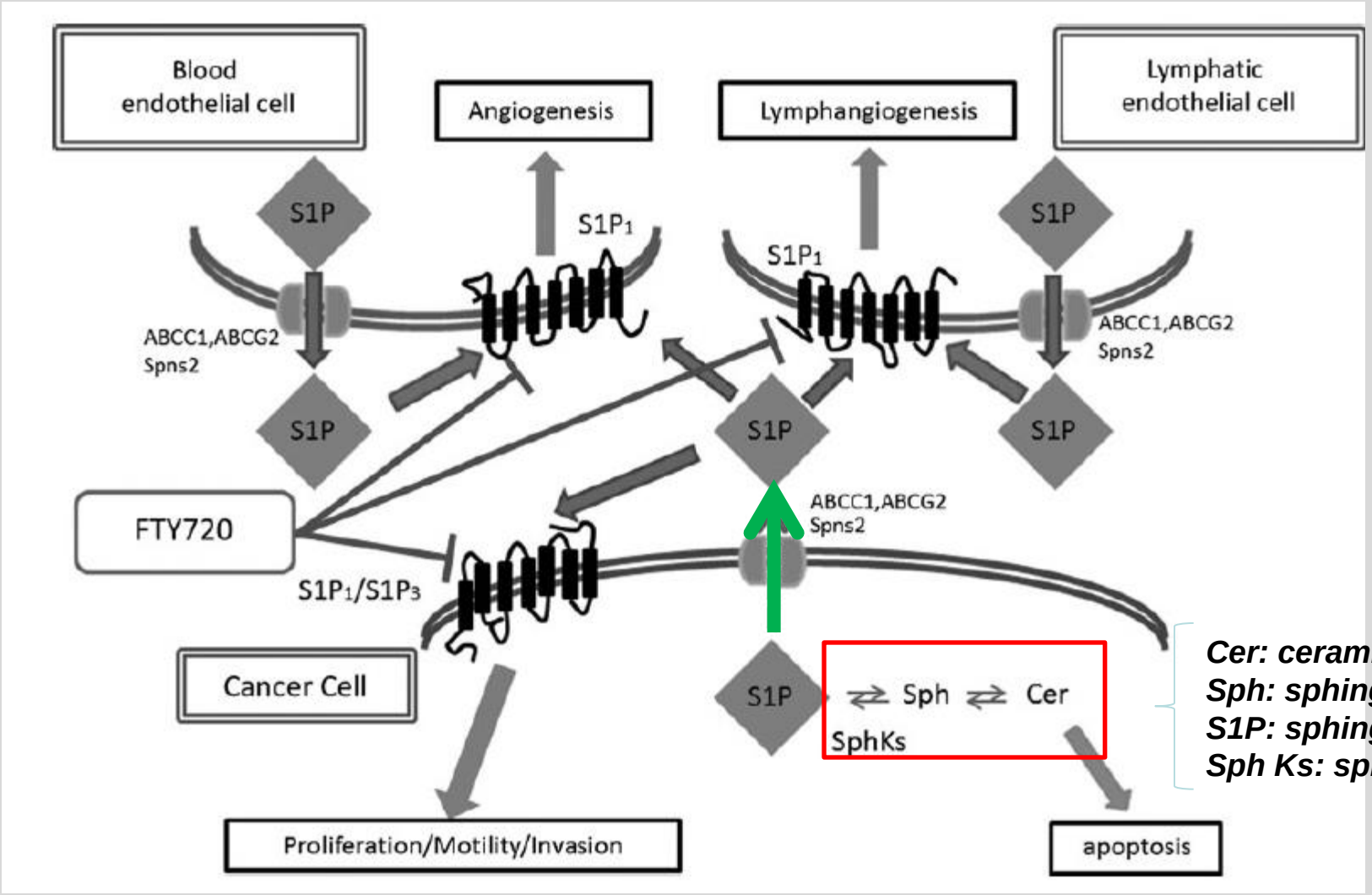


Regulation of mitophagy by ceramide. Endogenous generation of C_{18}-ceramide via CerS1 or exogenous treatment by C_{18}-pyridinium-ceramide is followed by two processes: A. conjugation of LC3-I to phosphatidylethanolamine on the carboxy terminal to form LC3-II and B. accumulation of ceramide in the mitochondrial outer membrane. Ceramide in the mitochondrial membrane acts as a receptor to LC3-II by binding to its amino terminal, opposite to where PE is conjugated. This results in C. recruiting the autophagosome to engulf the mitochondria. Lysosomes then fuse with the autophagosomes (D) for hydrolytic degradation of the contents.

Dany M, Ogretmen B. Ceramide Biochim Biophys Acta. 2015;1853(10 Pt B):2834-45.

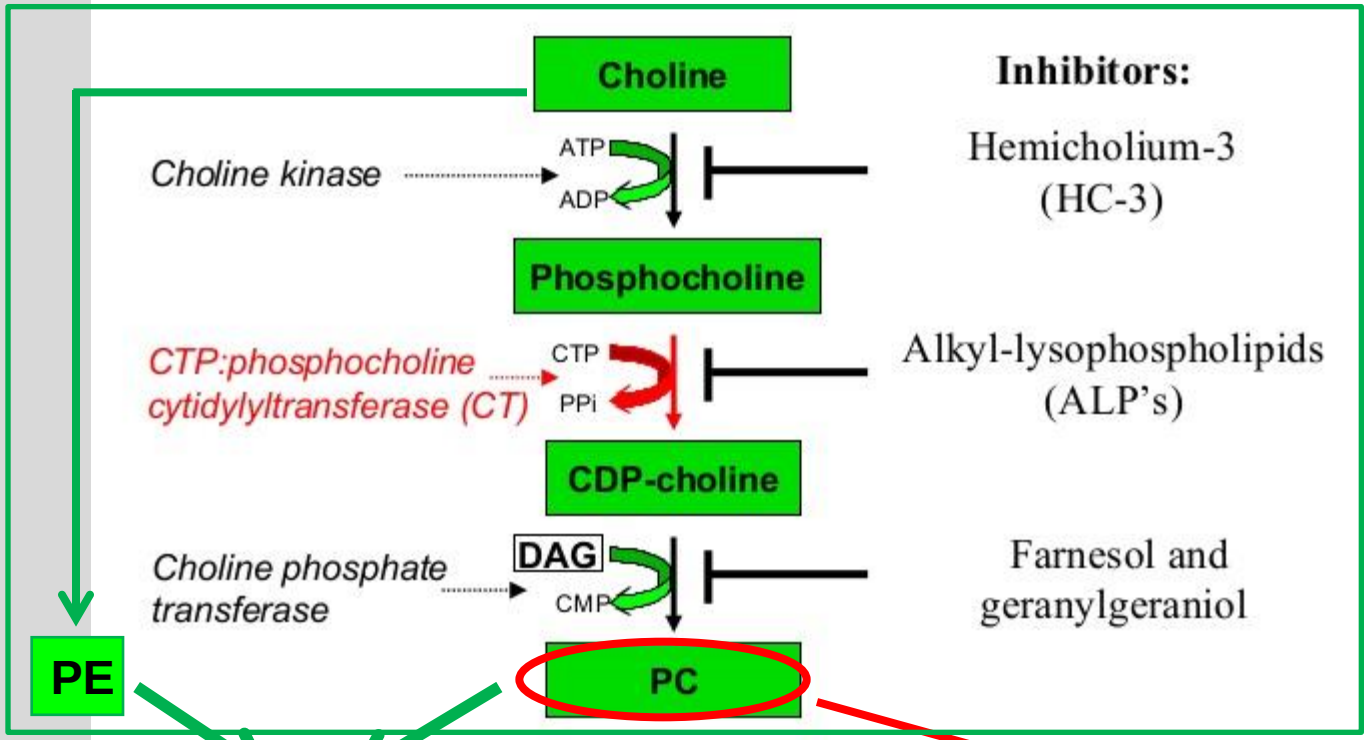
Gérard LIZARD : EA7270
Univ. Bourgogne Franche Comté / INSERM

Sphingosine 1 kinase / Sphingosine 1 phosphate (S1P) : facteur de risque associé à plusieurs cancers



Aoyagi T, Nagahashi M, Yamada A, Takabe K. The role of sphingosine-1-phosphate in breast cancer tumor-induced lymphangiogenesis. Lymphat Res Biol. 2012;10(3):97-106.

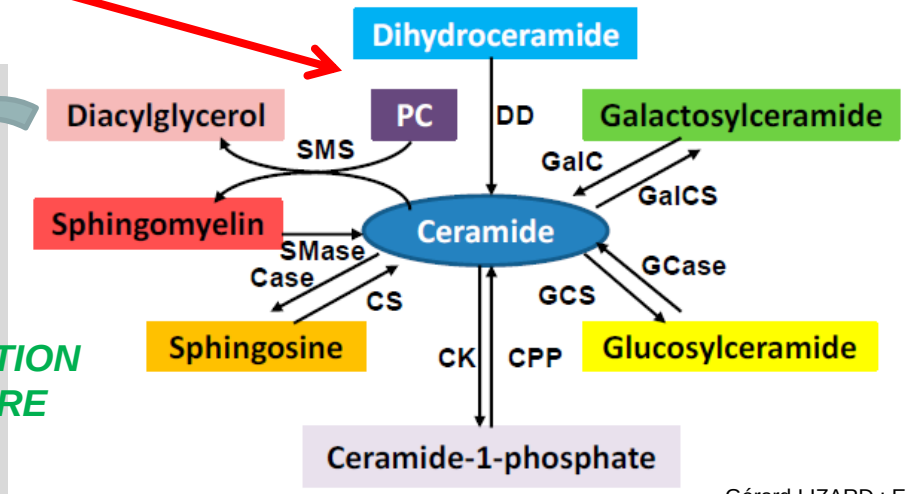
Synthèse de novo de phosphatidylcholine : voie de Kennedy



Voie de Kennedy

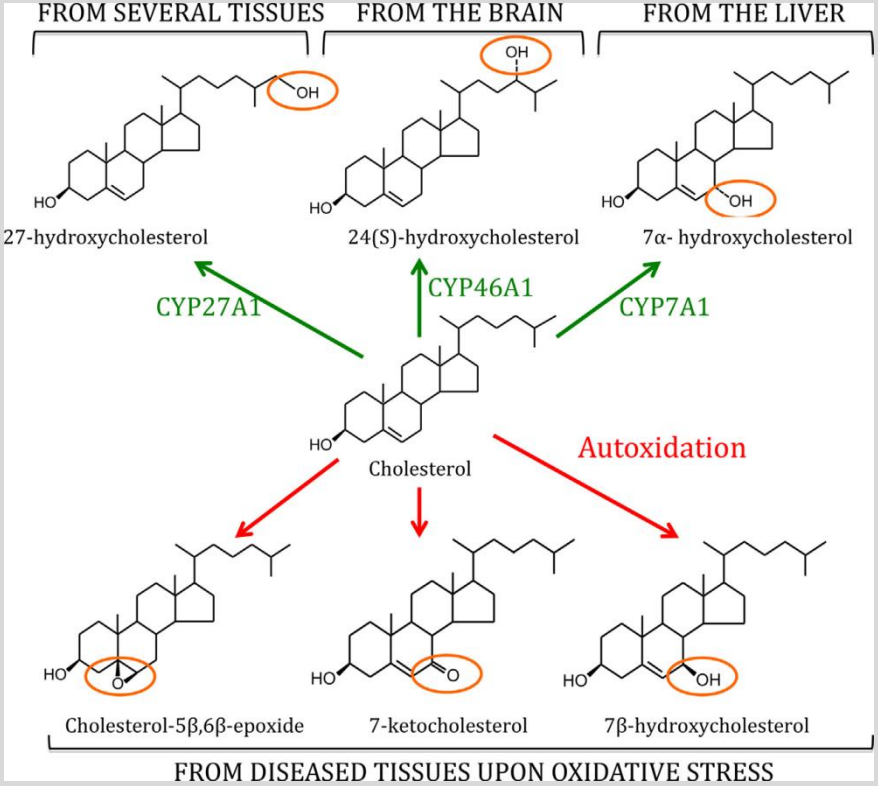
MORT CELLULAIRE

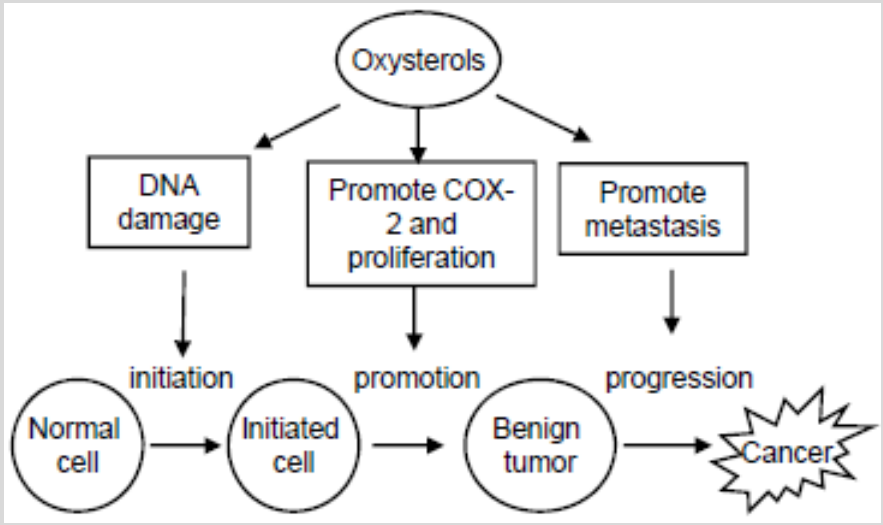
PROLIFERATION CELLULAIRE



http://fr.slideshare.net/michielvds/heidelberg-17113935
Gibellini F & Smith TK Life 2010, 62(6): 414-428.
Huang C & Freter C Int. J. Mol. Sci. 2015, 16, 924-949

Oxystérols et cancer



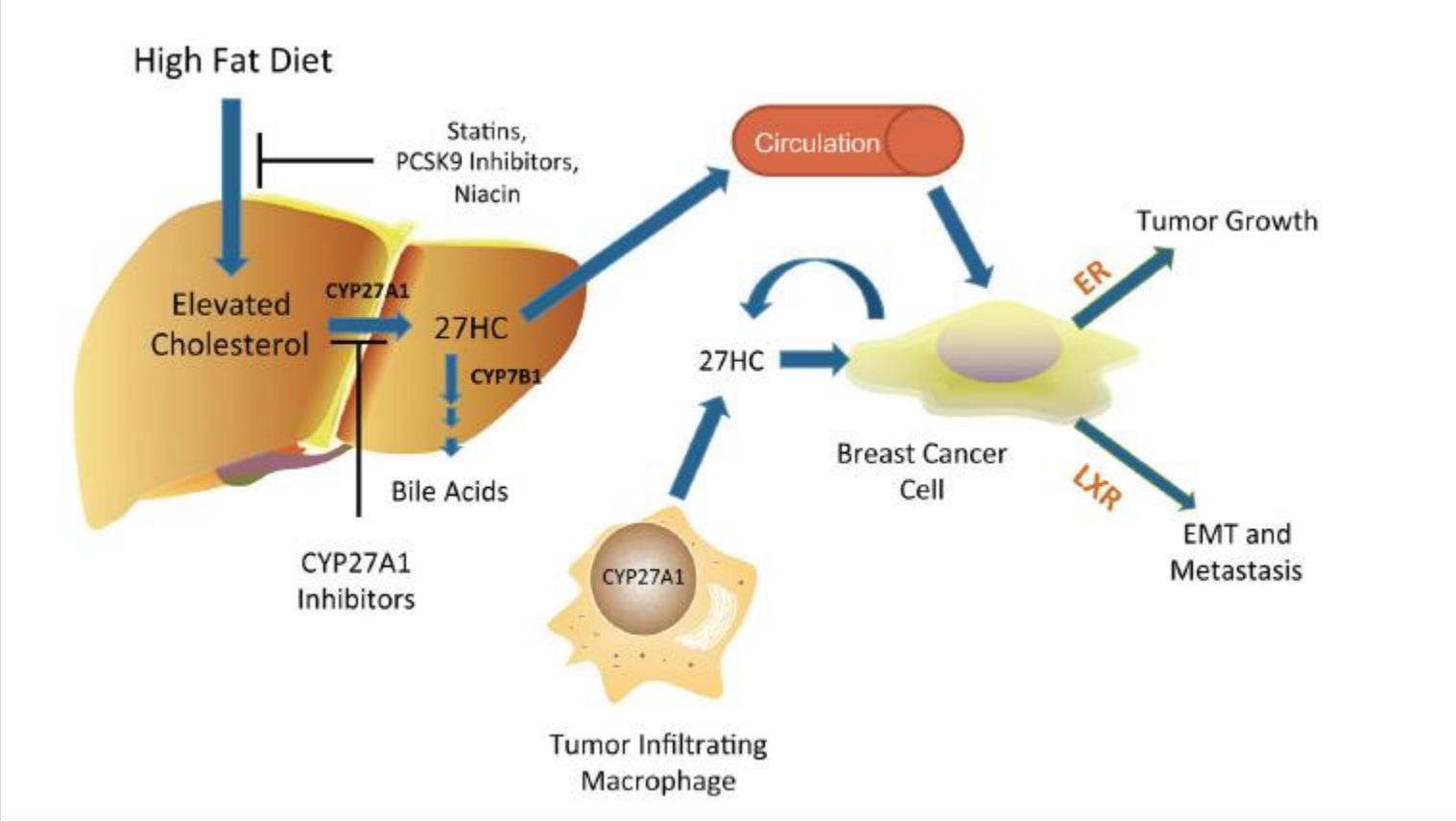


Activités pro-tumorales des oxystérols ??????

Olkkonen VM et al. J Steroid Biochem Mol Biol. 2015 Dec 28. doi: 10.1016/j.jsbmb.2015.12.026.

Gérard LIZARD : EA7270
Univ. Bourgogne Franche Comté / INSERM

Cancer du sein :
implication du cholestérol et du 27-hydroxycholestérol



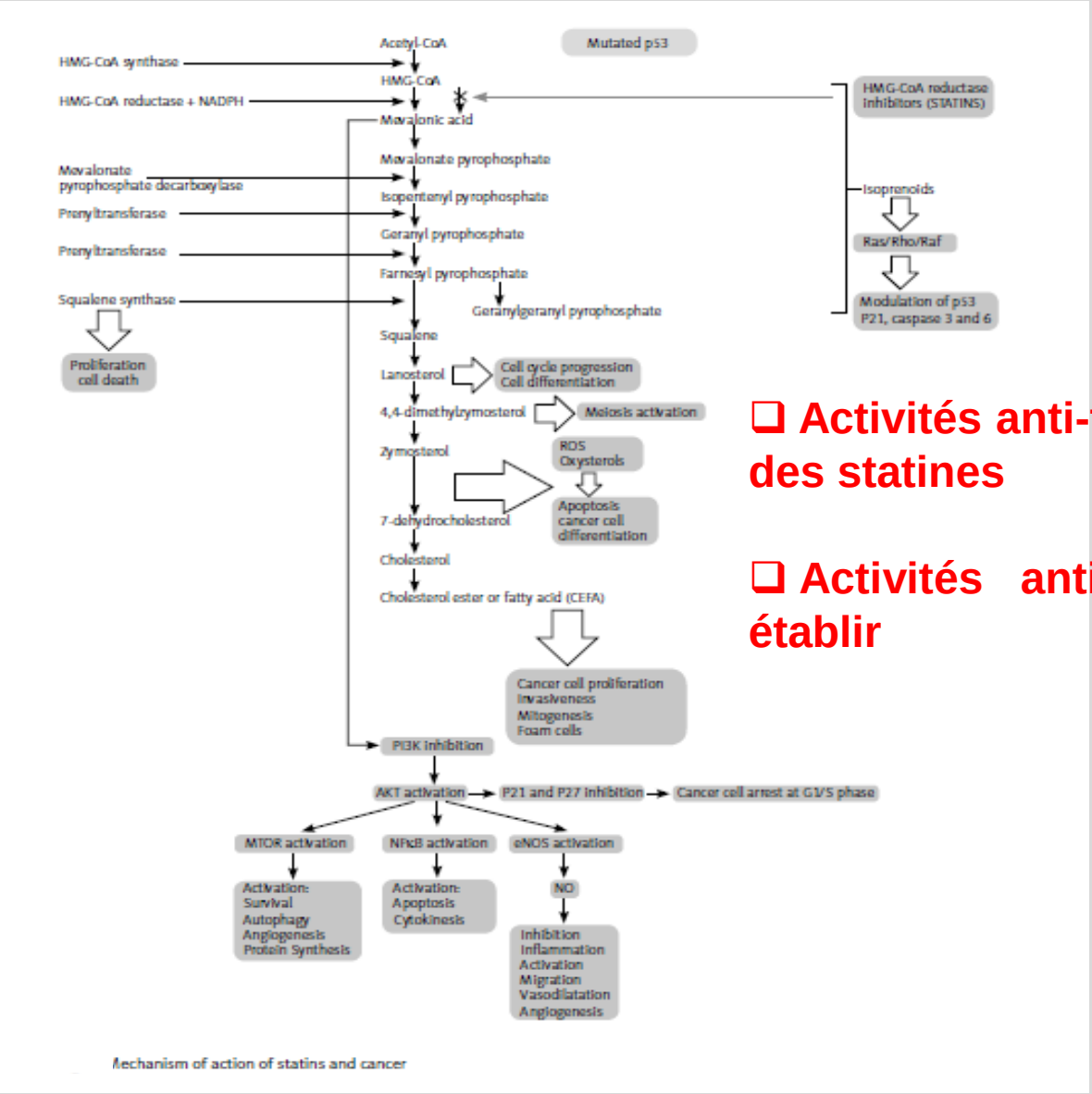
CYP27A1
Obésité → cholestérol → 27-hydroxycholestérol (27HC) → Récepteurs aux oestrogènes (ER)

Prolifération tumorale / métastases
(activité pro-tumorale)

Nelson ER, Chang CY, McDonnell DP. Cholesterol and breast cancer pathophysiology. Trends Endocrinol Metab. 2014;25(12):649-55.

Gérard LIZARD : EA7270
Univ. Bourgogne Franche Comté / INSERM

Statines et cancer



Mechanism of action of statins and cancer

- **Activités anti-tumorales théoriques des statines**
- **Activités anti-tumorales réelles à établir**

Stryjkowska-Góra A, Karczmarek-Borowska B, Góra T, Krawczak K. Statins and cancers. Contemp Oncol (Pozn). 2015;19(3):167-75.