



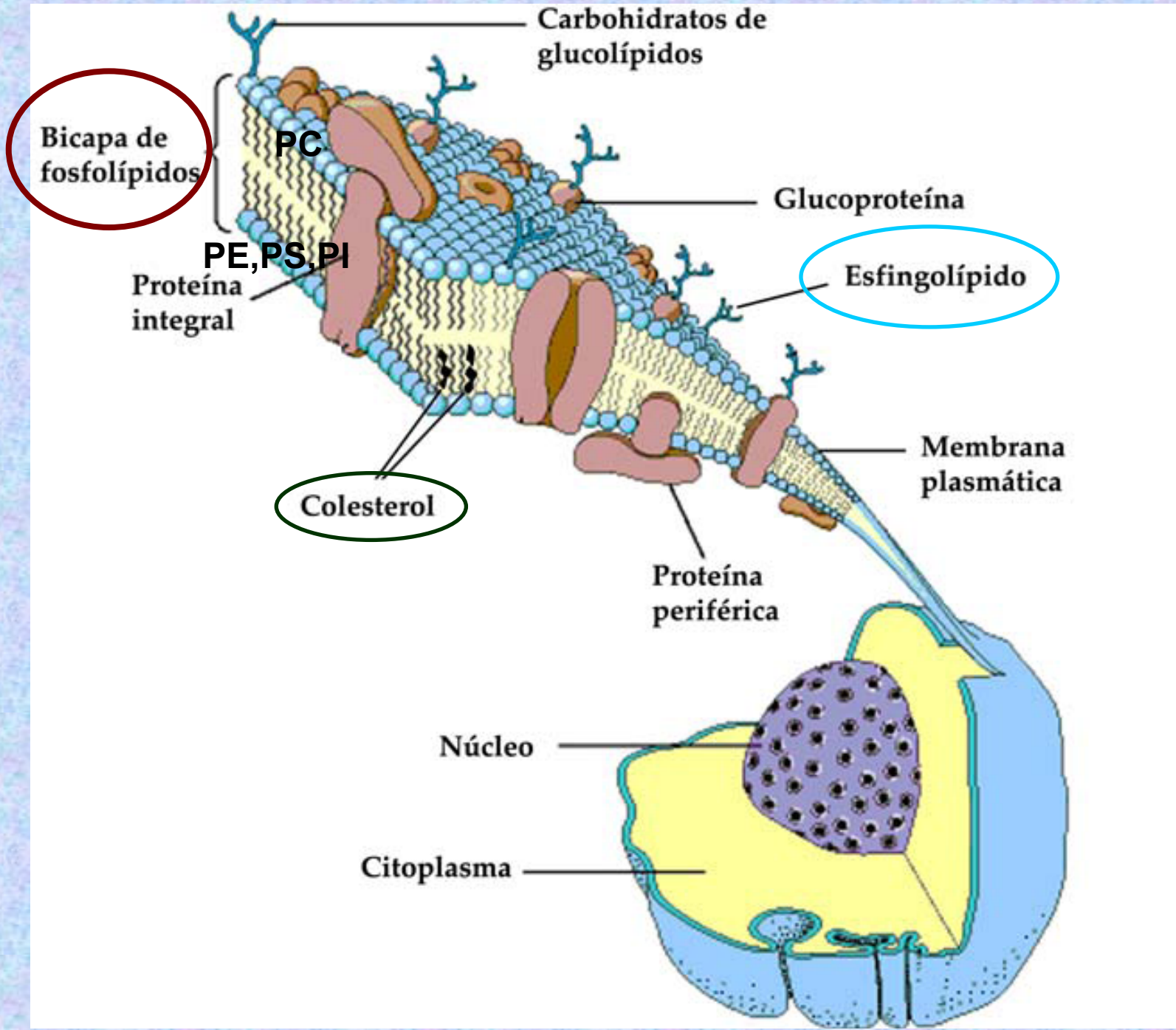
***"Fosfatidato fosfatasas nuevos jugadores en el metabolismo lipídico y en la señalización celular"***

**Curso: "Membranas biológicas: estudio de nivel estructural y funcional"**  
**Facultad de Ciencias Exactas, Físico-Químicas y Naturales**  
**Universidad Nacional de Río Cuarto**

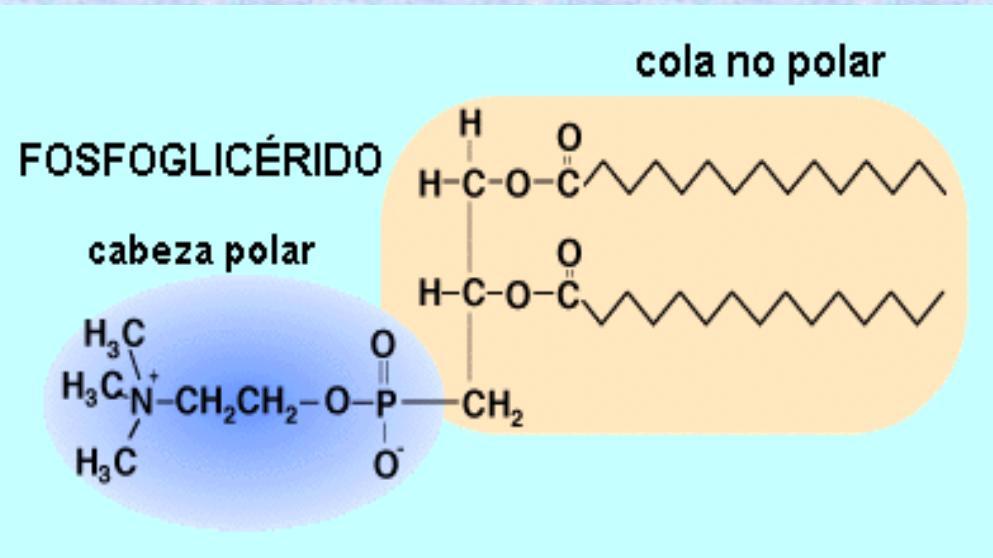
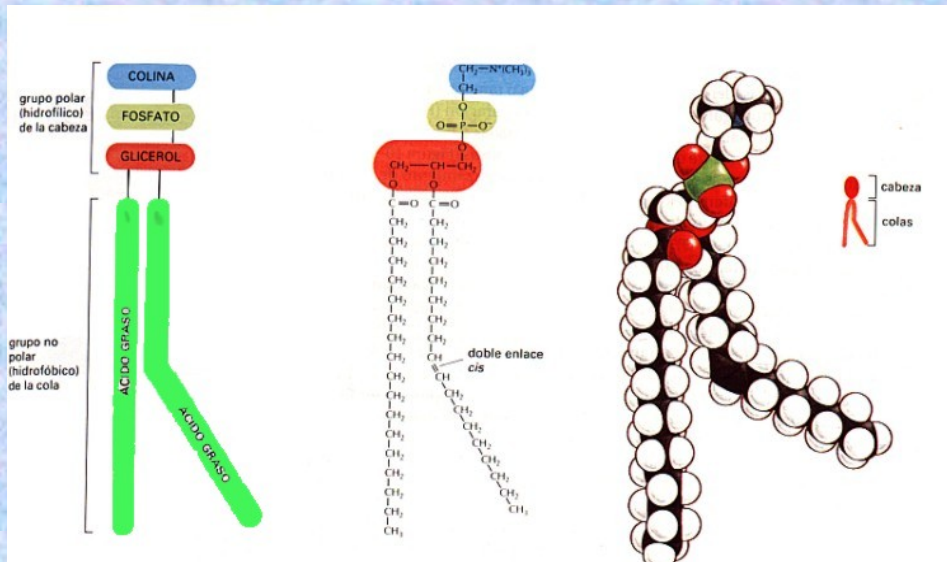
**SUSANA J. PASQUARÉ**  
**INIBIBB-UNS-CONICET**  
**BAHIA BLANCA-ARGENTINA**

## **TEMARIO:**

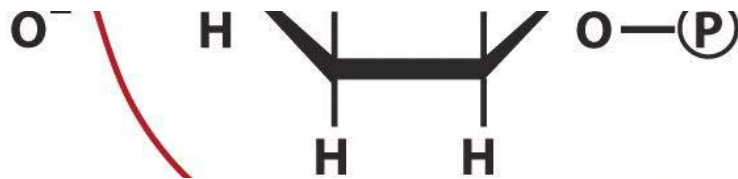
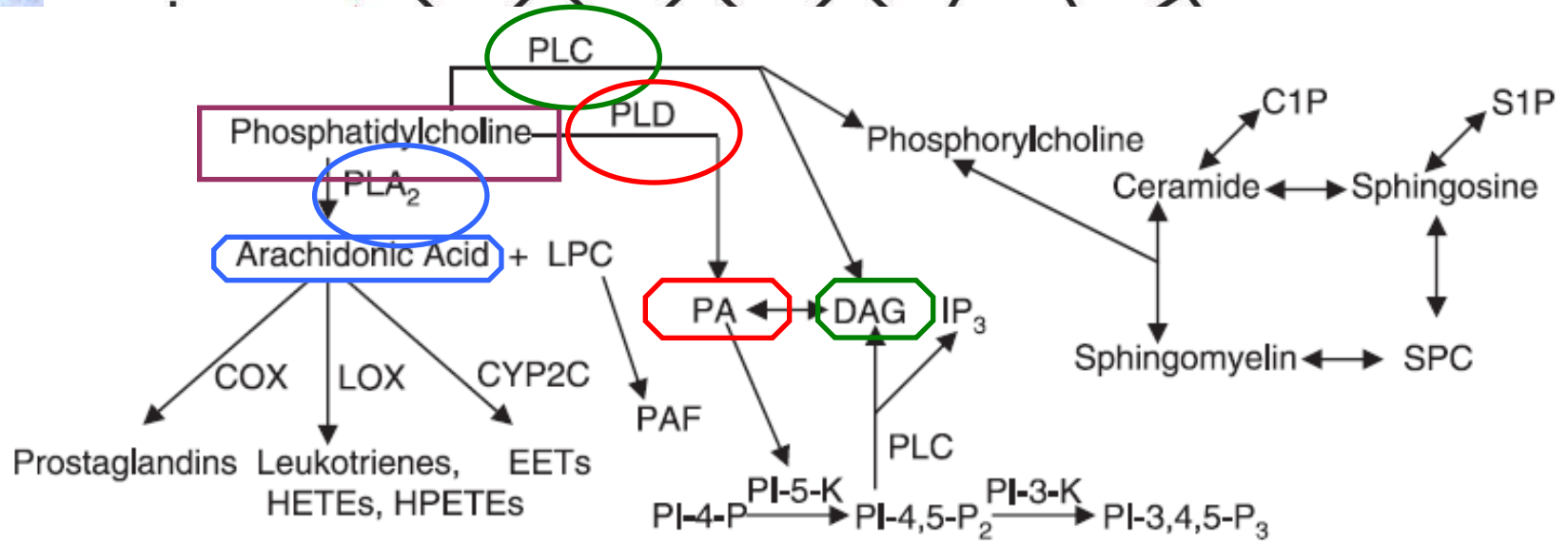
- 1. Degradación de ácido fosfatídico:**
  - 1a. Lípido fosfato fosfatasas (LPPs)**
  - 1b. Fosfatidato fosfatasas (Lipinas)**
- 2. Identificación, diferenciación por sus motivos catalíticos y medida de Lipinas y LPPs**
- 3. LPPs:**
  - 3a. Regulación de su actividad**
  - 3b. Funciones extra e intracelulares**
  - 3c. Roles en la señalización neuronal y en procesos neurodegenerativos**
  - 3d. Su relación en la regulación de otros lípidos fosforilados (LPA, S1P, C1P y DGPP)**
- 4. Lipinas:**
  - 4a. Una familia de proteínas**
  - 4b. Regulación de su actividad**
  - 4c. Funciones a nivel intracelular**
  - 4d. Su rol clásico en el metabolismo lipídico**
  - 4e. Su nuevo rol en la transcripción génica**
- 5. Conclusiones**



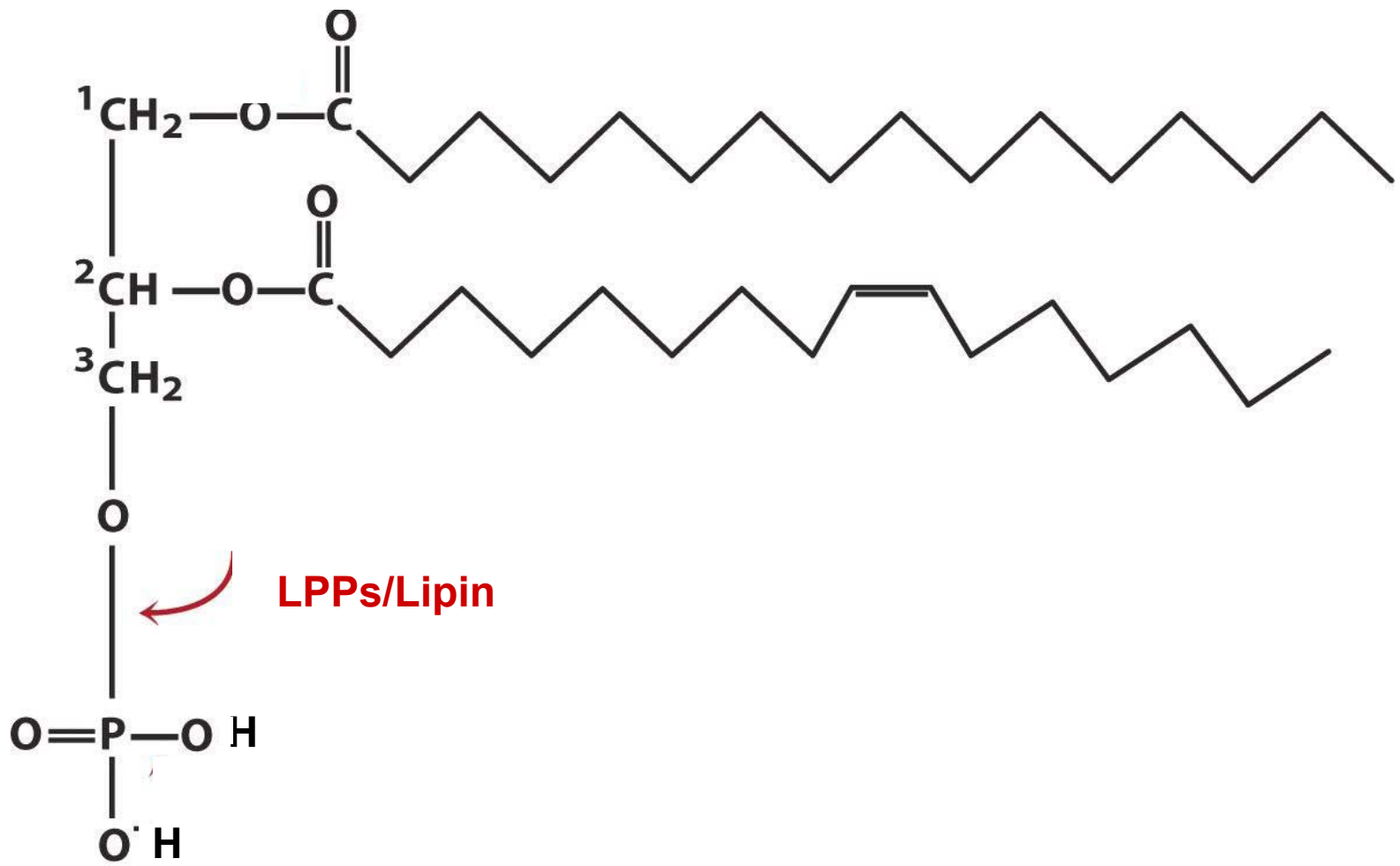


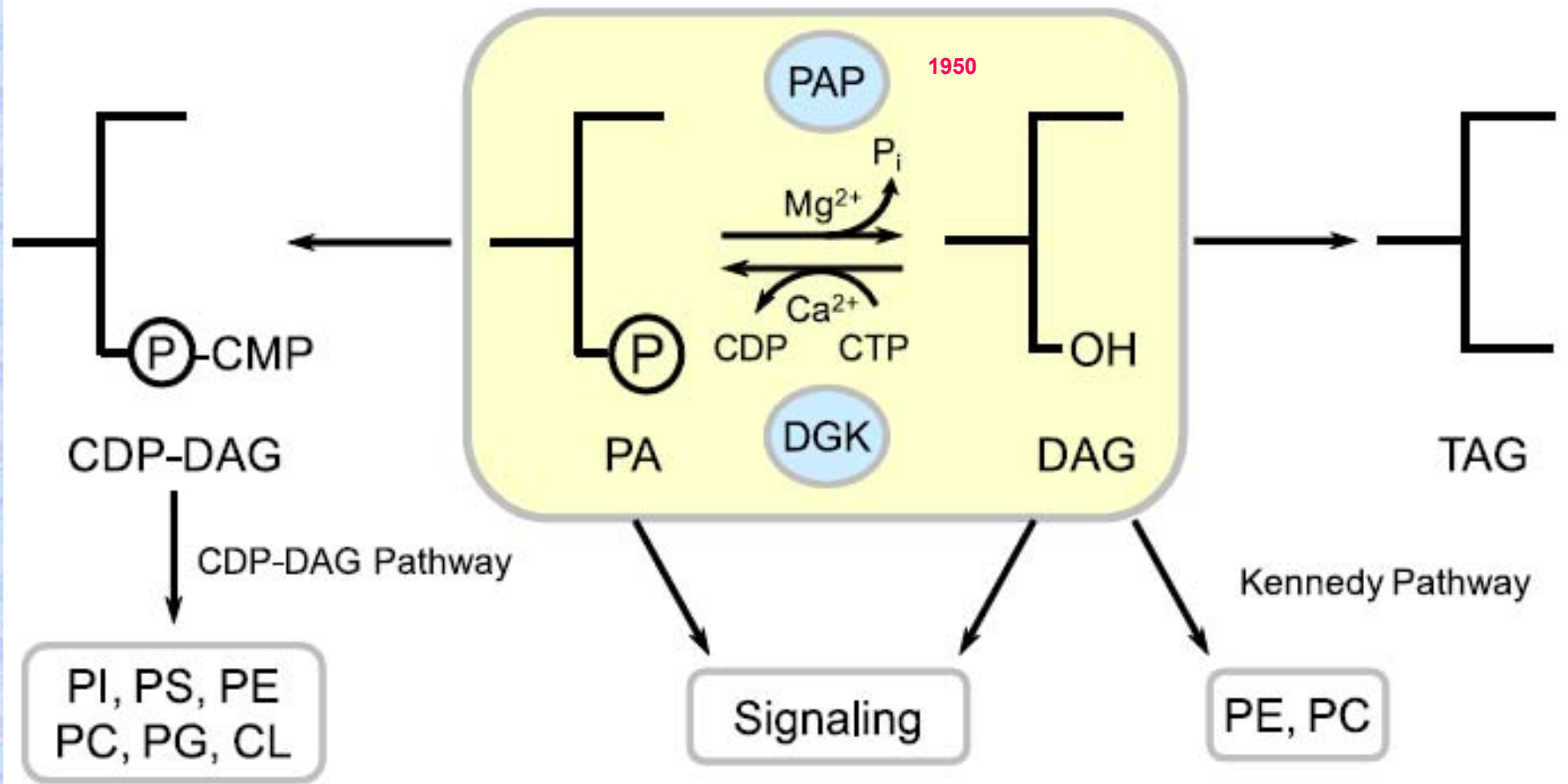


# Fosfolipasa A<sub>1</sub>



# Fosfolipasa D



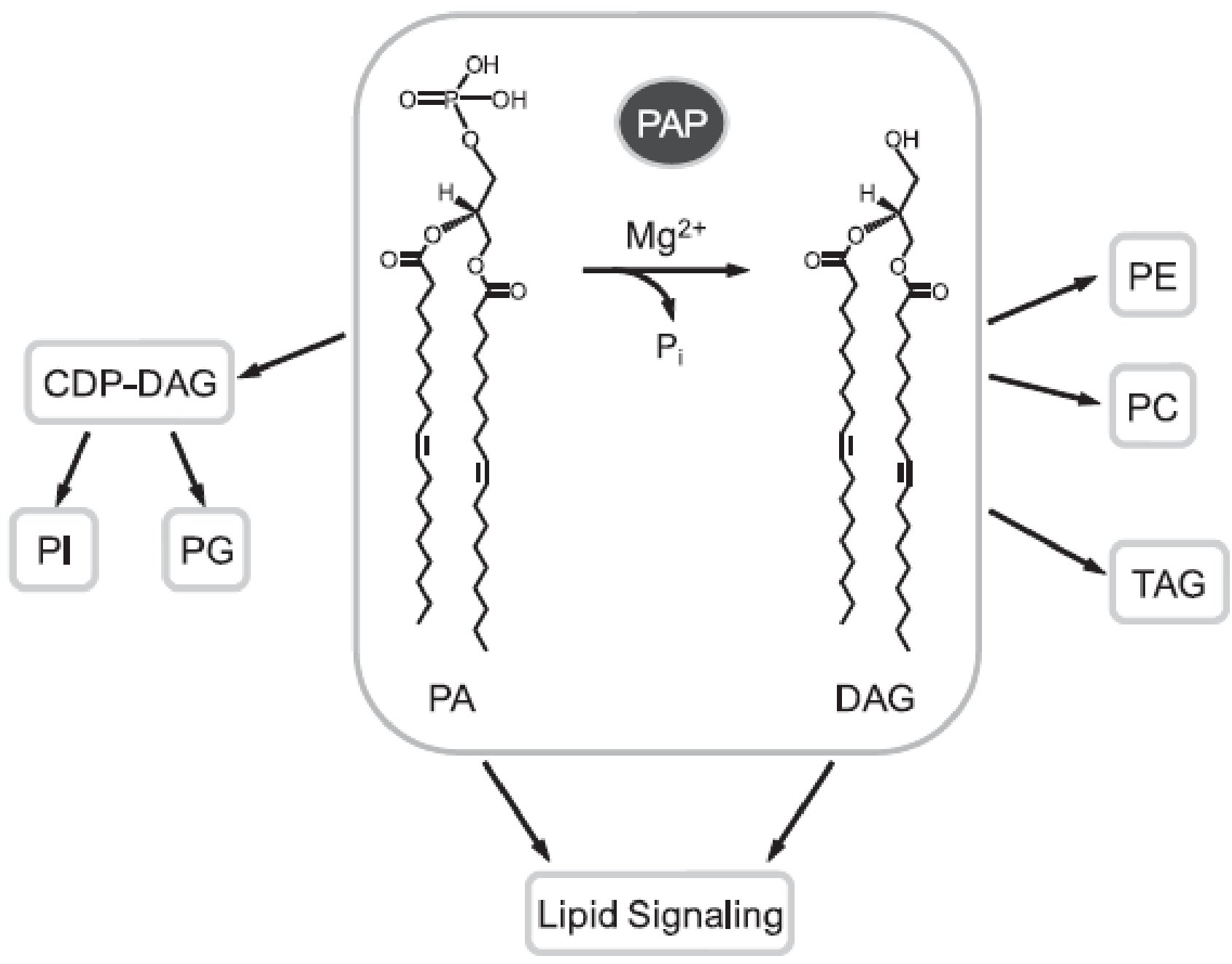


✓ **Retículo endoplásmico, algo contribuye mitocondrias**

✓ **Microsomas + AG + G3P  $\longrightarrow$  baja formación de TAG**

✓ **Microsomas + (soluble) + AG + G3P  $\longrightarrow$  alta formación de TAG**





*PAP1/Lipin*

[<sup>3</sup>H]PA/PC

+

Fracción membrana

→ 37°C, 20 min → [<sup>3</sup>H]-DAG, [<sup>3</sup>H]-MAG

[<sup>3</sup>H]PA/PC

+

Fracción membrana  
(NEM)

→ 37°C, 20 min → [<sup>3</sup>H]-DAG, [<sup>3</sup>H]-MAG

*PAP2/LPPs*

[<sup>3</sup>H]PA

+

Fracción membrana  
(NEM)

→ 37°C, 20 min → [<sup>3</sup>H]-DAG, [<sup>3</sup>H]-MAG

# **LIPIDO FOSFATO FOSFATASAS (LPPs)**

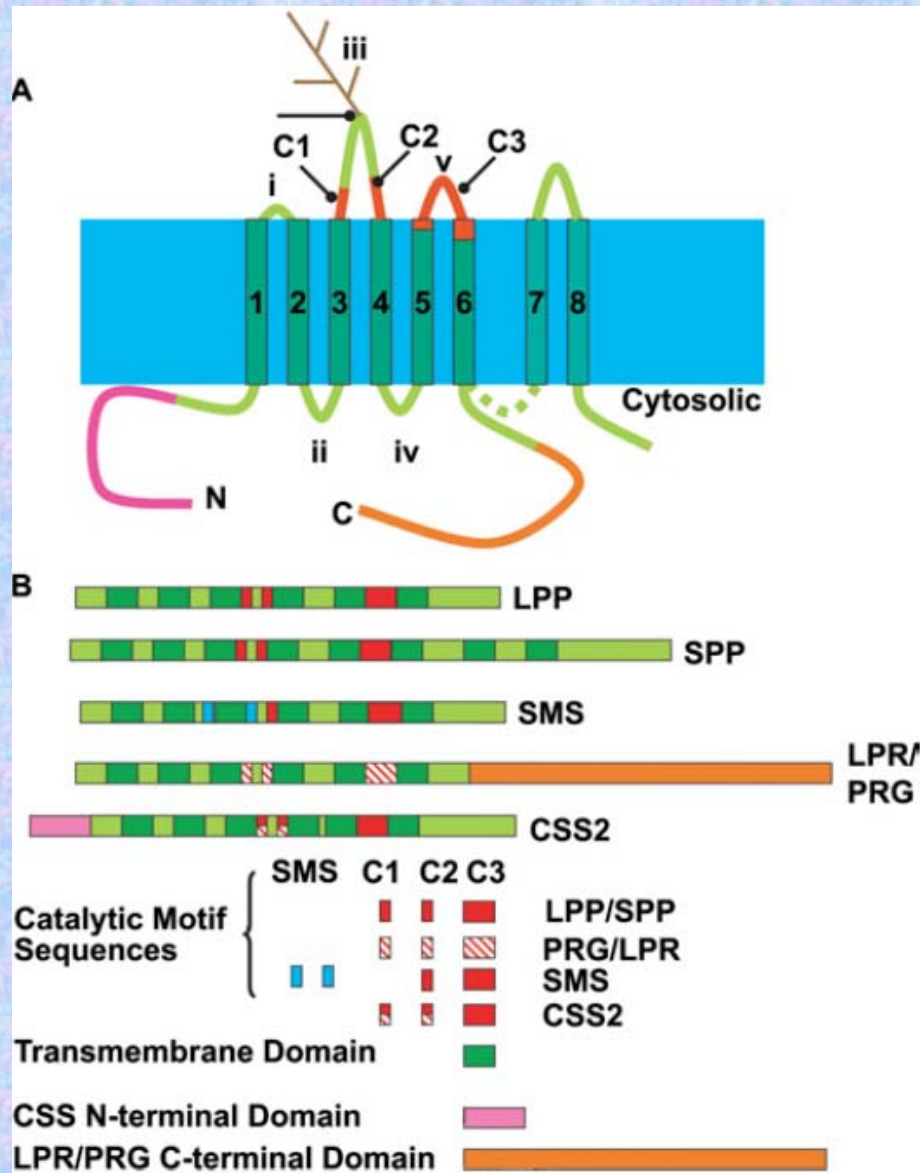


Figure 2 Structural organization of LPT family members

**Fosfatasas/fosfotransferasas:**

**LPPs:** Lipido fosfato fosfatasas

**SPP:** S1P fosfatasas

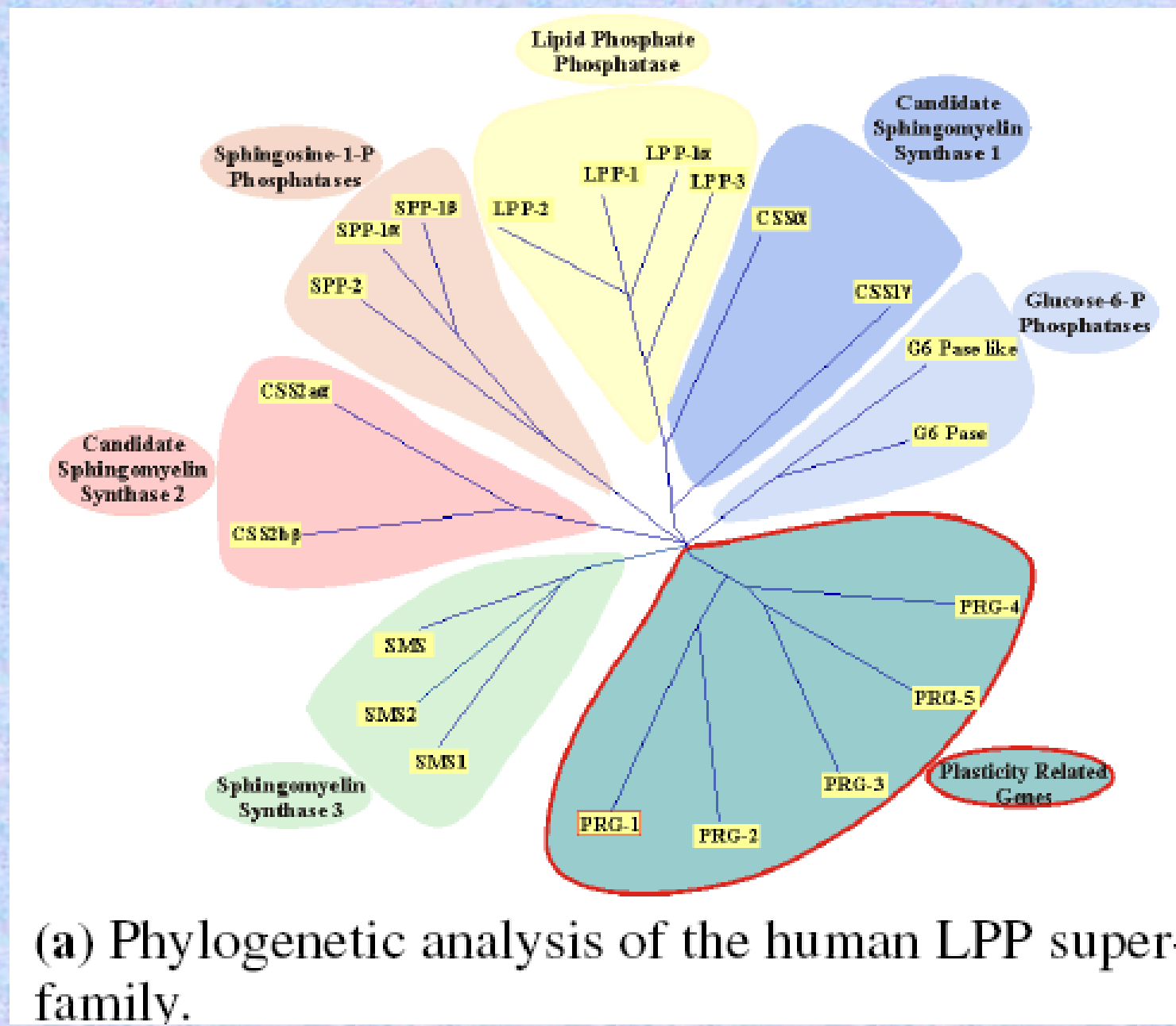
**SMS:** Esfingomieline sintasa

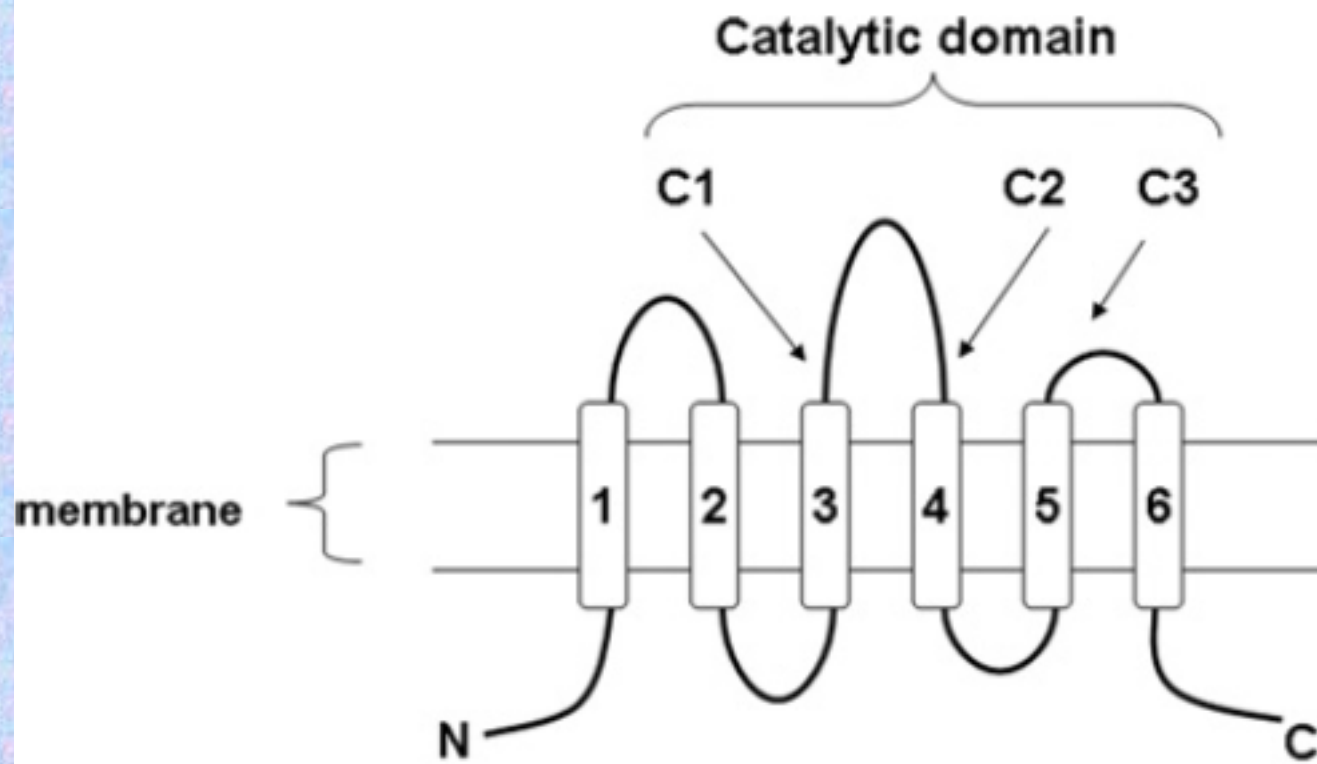
**CSS2:** Esfingomieline sintasa tipo 2

**LPR/PRG:** proteínas relacionadas a LPPasa ó genes relacionados a la plasticidad

**G6Pasa:** glucosa 6 fosfatasa







<b>gpLPP1</b>	120	- <b>K</b> YSIGRL <b>R</b> PHFLS-31-RLSFY <b>S</b> GHS-39-YVGLSRISDYK <b>H</b> HWSD	: 227
<b>hLPP2</b>	117	- <b>K</b> YMIGRL <b>R</b> PNFLA-31-RLSFY <b>S</b> GHS-39-YVGYTRVSDYK <b>H</b> HWSD	: 224
<b>hLPP3</b>	148	- <b>K</b> VSIGRL <b>R</b> PHFLS-31-RKSFF <b>S</b> GHA-39-YTGLSRVSDHK <b>H</b> HPSD	: 255
		<hr style="width: 20%; margin: 0 auto;"/> <div style="display: flex; justify-content: space-around; width: 100%;"> <span><b>C1</b></span> <span><b>C2</b></span> <span><b>C3</b></span> </div>	

Phosphatase Consensus:	C1 KXXXXXXRP	C2 SGH	C3 SRXXXXXHXKD
CPO	(353)KWEFEPWRP	(402)SGH	(489)SRIFLGVHWRFD
PgpB	(97)KDKVQEPKP	(161)SGH	(200)SRLLLGMHWPRD
DPP1	(118)KNWIGRLRP	(167)SGH	(216)SRTQDYRHHFVD
G6P	(76)KWILFGQRP	(117)SGH	(169)SRIYLAHFPHQ
SPP1	(178)KDIIRWPRP	(206)STH	(249)SRIYMGMSILD
SPP2	(136)KDVLEWPEP	(164)STH	(206)SRLYTGMHTVLD
LPP1	(125)KYSIGRLRP	(174)SGH	(221)SRVSDYKHHWSD
LPP2	(117)KYMIGRLRP	(166)SGH	(213)TRVSDYKHHWSD
LPP3	(148)KVSIGRLRP	(197)SGH	(244)SRVSDHKHHPSD
LPR1/PRG3	(146)PYFLTVCKP	(198)SKH	(245)NRVSEYRNHCSD
LPR2/PRG4	(148)PHFLSVCRP	(207)CKD	(154)VRVAEYRNHWSD
LPR3/PRG1	(197)QLSTGYQAP	(250)SQH	(296)TRITQYKNHPVD
LPR4/PRG2	(152)QLATGYHTP	(205)SQH	(279)TQITQYRSHPVD
CSS2 $\alpha$	(184)KGLVRRRRP	(212)SGH	(249)SRVFLGRHNVTD
CSS2 $\beta$	(163)QKLIKRRGP	(191)AGH	(228)SRVMIGRHHVTD
SMS1	Not Present	(283)SGH	(321)CILLAHDHYTVD
SMS2	Not Present	(227)SGH	(265)CILVAHEHYTID
	D1	D2	
SMS1	(167)PPLPD	(213)RRFCIVGTLYLYRCITMYVT	
SMS2	(111)PPLPD	(157)RRFCFIIGTLYLYRCITMYVT	

Abbreviation	Species	Name	GenBank Accession #
CPO	<i>C. inaequalis</i>	Vanadium chloroperoxidase	P49053
PgpB	<i>E. coli</i>	phosphatidylglycerol phosphate phosphatase	NP_309878
DPP1	<i>S. cerevisiae</i>	Diacylglycerol pyrophosphate phosphatase	NP_010570
G6P	<i>H. sapiens</i>	Glucose 6-phosphatase	NP_000142
SPP1,2	<i>H. sapiens</i>	sphingosine 1-phosphate phosphatase 1 and 2	NP_110418, NP_689599
LPP1,2,3	<i>H. sapiens</i>	lipid phosphate phosphatases 1-3	NP_795714, NP_808211, NP_003704
LPR/PRG1,2,3,4	<i>H. sapiens</i>	Lipid phosphate phosphatase related proteins/Plasticity related genes 1-4	AAH22465, AAH09378, NP_997182, NP_982278
CSS2 $\alpha,\beta$	<i>H. sapiens</i>	Candidate Sphingomyelin Synthases/Nuclear Lipid Phosphatases	NP_116117, BAB55210
SMS1,2	<i>H. sapiens</i>	Sphingomyelin Synthases	NP_671512, Q8NHU3

✓LPPs (**LPP1**, LPP2 y **LPP3**), Plasticity-related genes proteínas unidas a membranas con 6 segmentos transmembrana (31-36 Kd)

✓Membrana plasmática y membranas internas(RE,Golgi,endosomas)

✓LPP1 y **LPP3** en DRMs (**PLD2** y receptores de LPA yS1P)

✓Sitio activo hacia el espacio extracelular o luminal (permite entrada de formas desfosforiladas)

✓ Insensible a NEM y no dependiente de magnesio

✓ Pueden formar homo y heterooligómeros (**LPP2** y LPP3)(Act. Cat, mamif.)

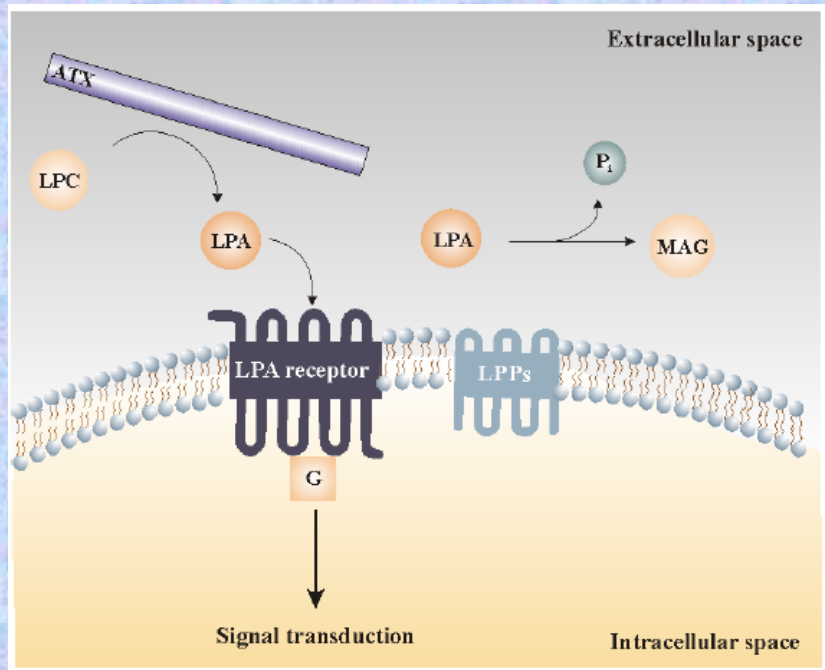


- ✓ Los oligómeros de LPPs regulan pooles compartamentalizados de PA y S1P
- ✓ Hidrolizan PA, LPA, S1P, C1P y DGPP
- ✓ LPP3 (PAP2b) se une a integrinas interacciones célula-célula (RGD,Arg, Gly, Aspartico) en el tercer loop extra membrana
- ✓ LPP2 y LPP3 colocalizan con SK1
- ✓ LPP3 y SK1 relocalizan en golgi por estímulo de PLD

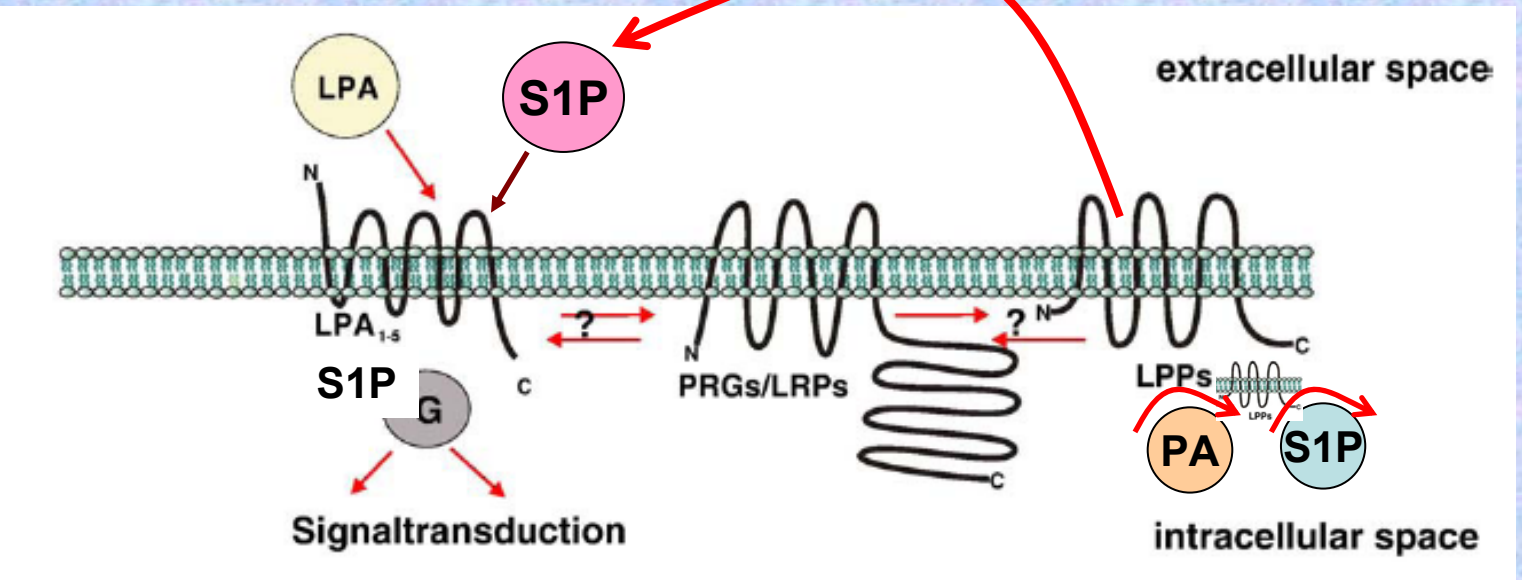
**Table 1 Expression of LPT family proteins in adult human tissues**

Expression profiles for the indicated genes were compiled from data available online at <http://www.ncbi.nlm.nih.gov/UniGene/>. The abundance of ES expressed as transcripts per million.

	EST abundance (transcripts per million)								
	LPP			SPP		LPR/PRG			
	LPP1	LPP2	LPP3	SPP1	SPP2	LPR1/PRG3	LPR2/PRG4	LPR3/PRG2	LPR4/PRG1
Bladder	191	0	47	191	47	0	0	0	0
Bone	35	17	143	0	0	0	53	0	0
Bone marrow	27	0	136	54	0	0	0	27	0
Brain	107	30	166	35	19	48	181	17	124
Cervix	72	48	24	0	0	0	24	0	0
Colon	64	347	58	0	88	0	35	11	0
Eye	80	43	222	0	12	18	92	30	18
Heart	161	0	287	0	0	0	53	0	0
Kidney	172	44	202	37	112	29	7	0	0
Larynx	41	0	292	0	0	0	0	0	0
Liver	22	7	197	38	7	0	0	7	0
Lung	67	56	106	14	81	7	24	3	10
Lymph node	39	0	724	31	7	0	0	23	0
Mammary gland	132	24	490	0	33	0	41	0	0
Muscle	119	0	82	9	18	0	0	0	0
Ovary	63	116	21	0	31	10	116	10	0
Pancreas	74	211	161	0	12	0	87	12	0
Peripheral nervous system	318	0	238	0	39	0	159	0	0
Placenta	108	4	535	77	4	0	21	0	8
Pituitary	–	–	–	–	–	0	38	0	0
Prostate	483	38	576	7	15	0	42	0	–
Skin	30	12	6	24	24	0	0	0	0
Soft tissue	102	0	153	0	0	51	0	0	0
Spleen	0	0	0	0	0	0	0	0	0
Stomach	77	58	48	48	77	0	48	0	0
Tongue	36	0	36	0	145	0	0	0	72
Testis	60	7	68	7	15	7	7	15	15
Thymus	0	0	0	222	0	0	0	0	0
Uterus	196	156	214	0	17	0	11	5	0
Vascular system	154	0	656	0	38	0	0	0	0
Whole blood	105	0	39	13	13	0	52	26	0

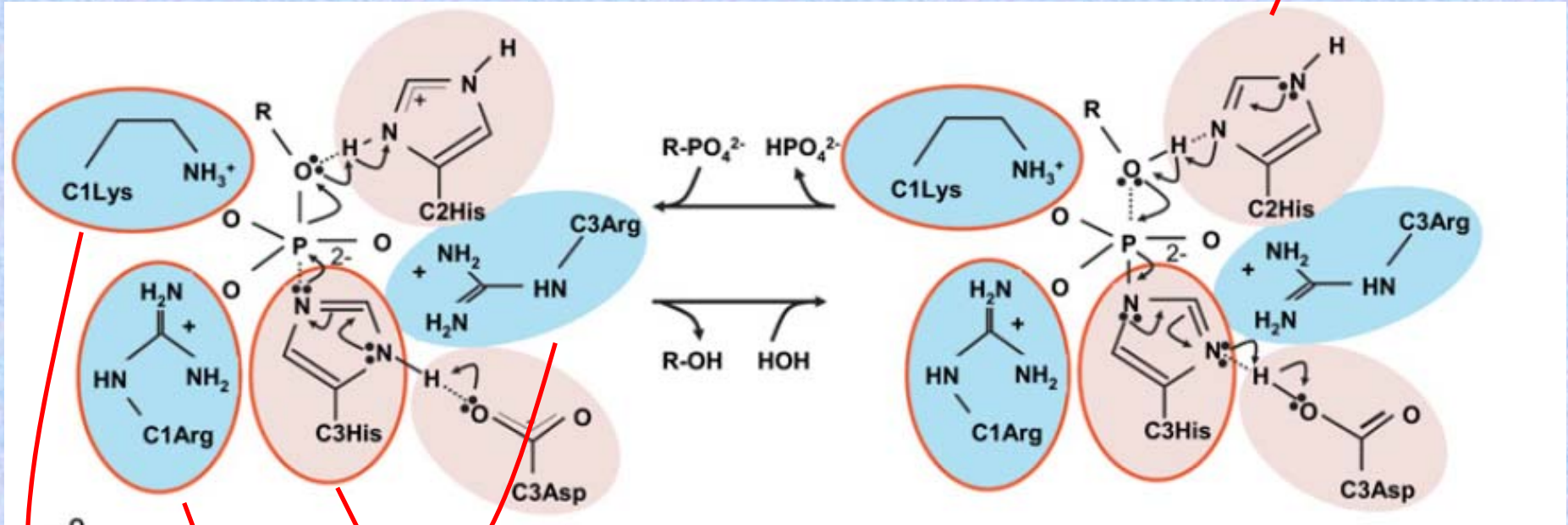


**Ectofosfatasas**



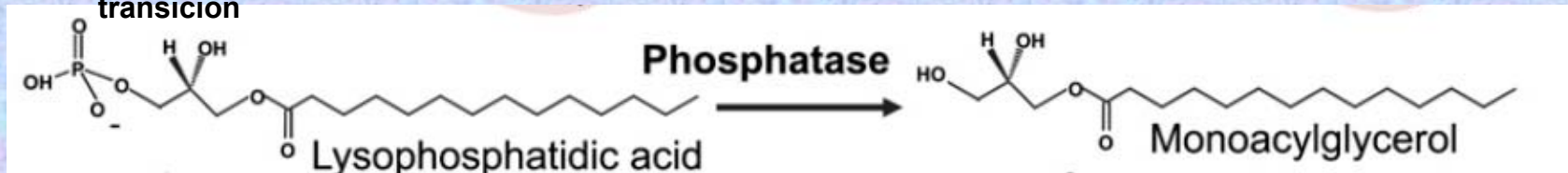


Favorece la liberación del fosfato

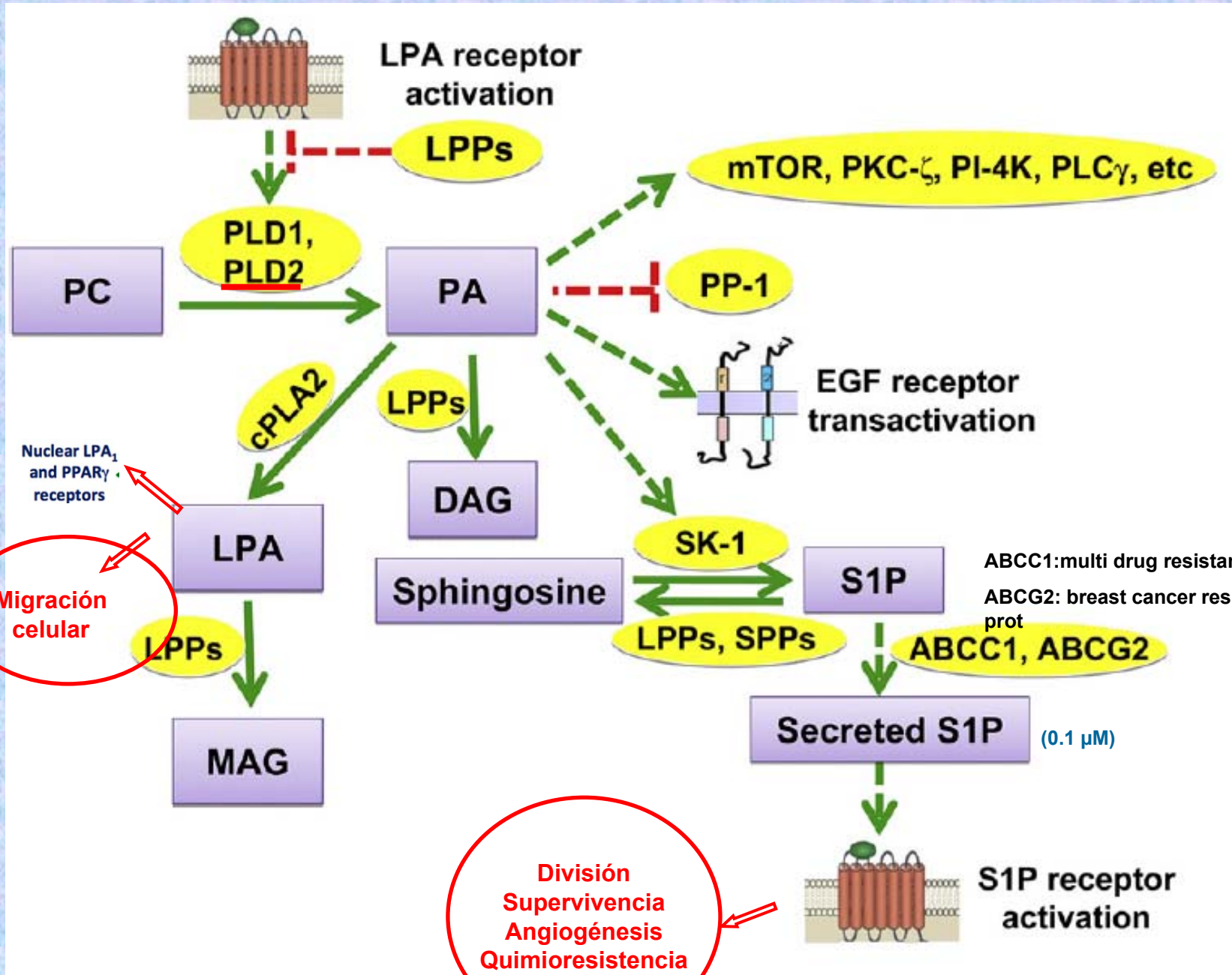


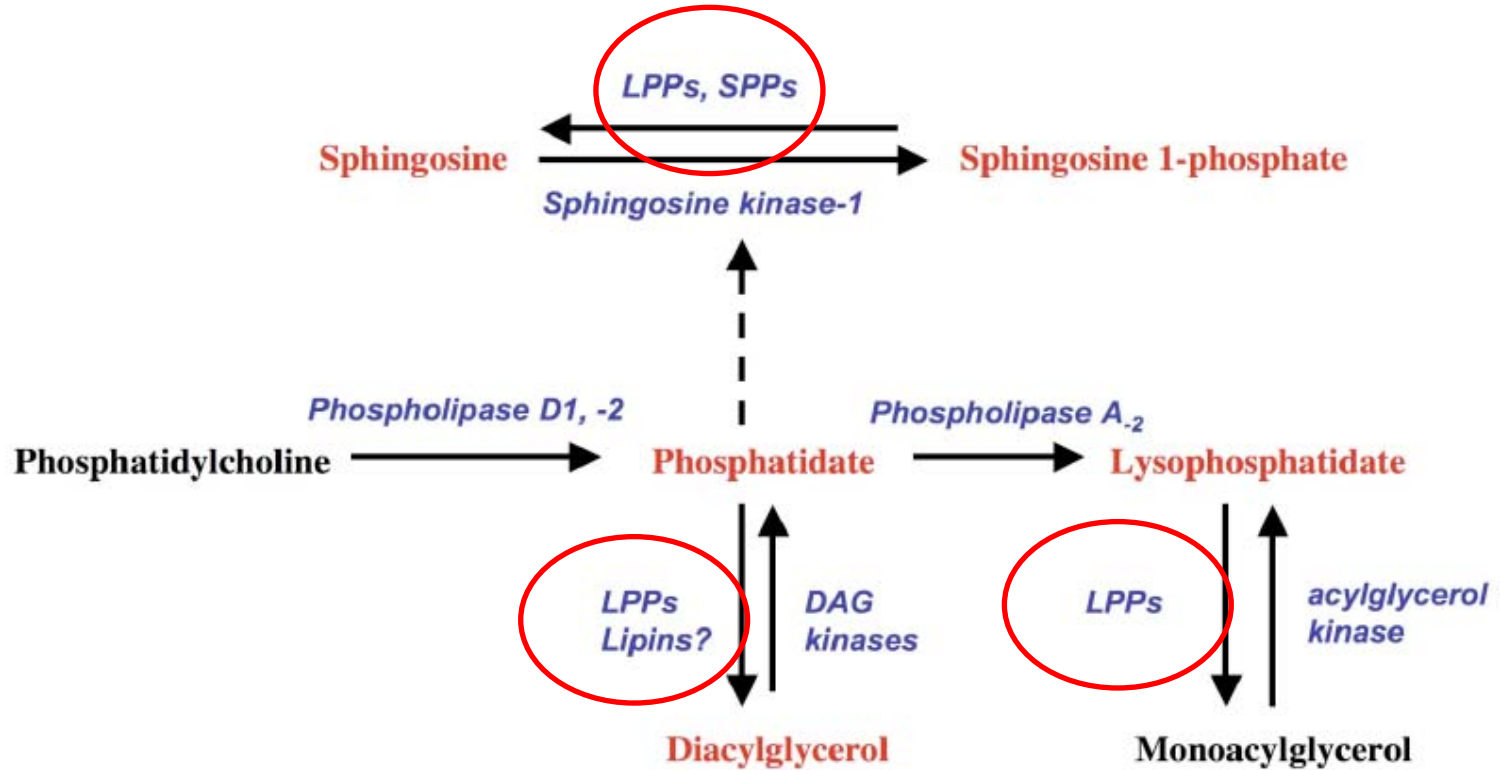
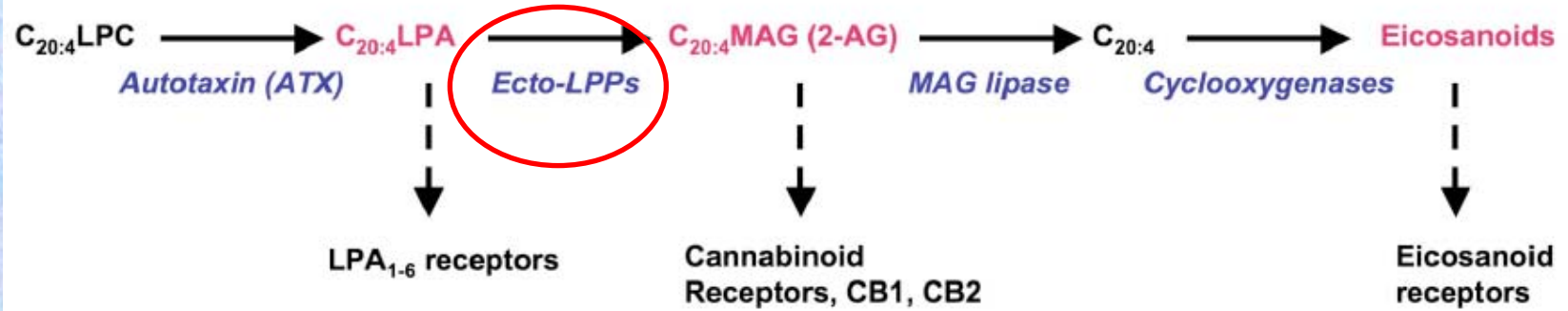
Donan H a los O del fosfato y estabilizan el estado de transición

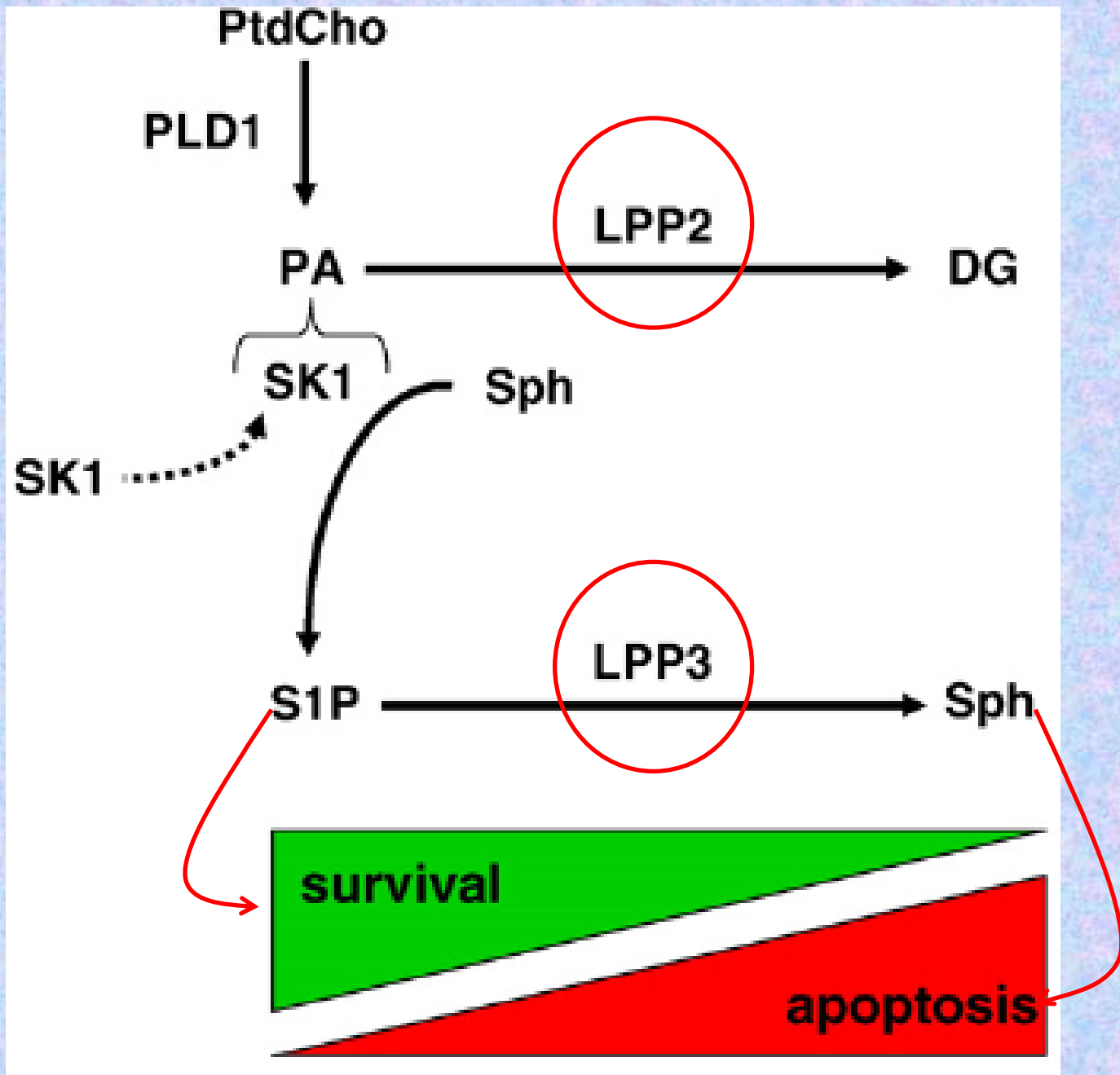
Relevo de cargas  
Histidina nucleófilo  
fosfohistidina



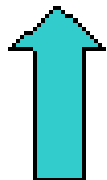








**Apoptosis**



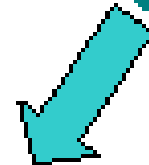
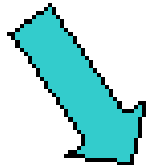
**Ceramida**  $\rightleftharpoons$  **Esfingosina**

**CerK**  $\updownarrow$  **LPPs**

**Sphk**  $\updownarrow$  **LPPs**

**Ceramida-1-P**

**Esfingosina-1-P**



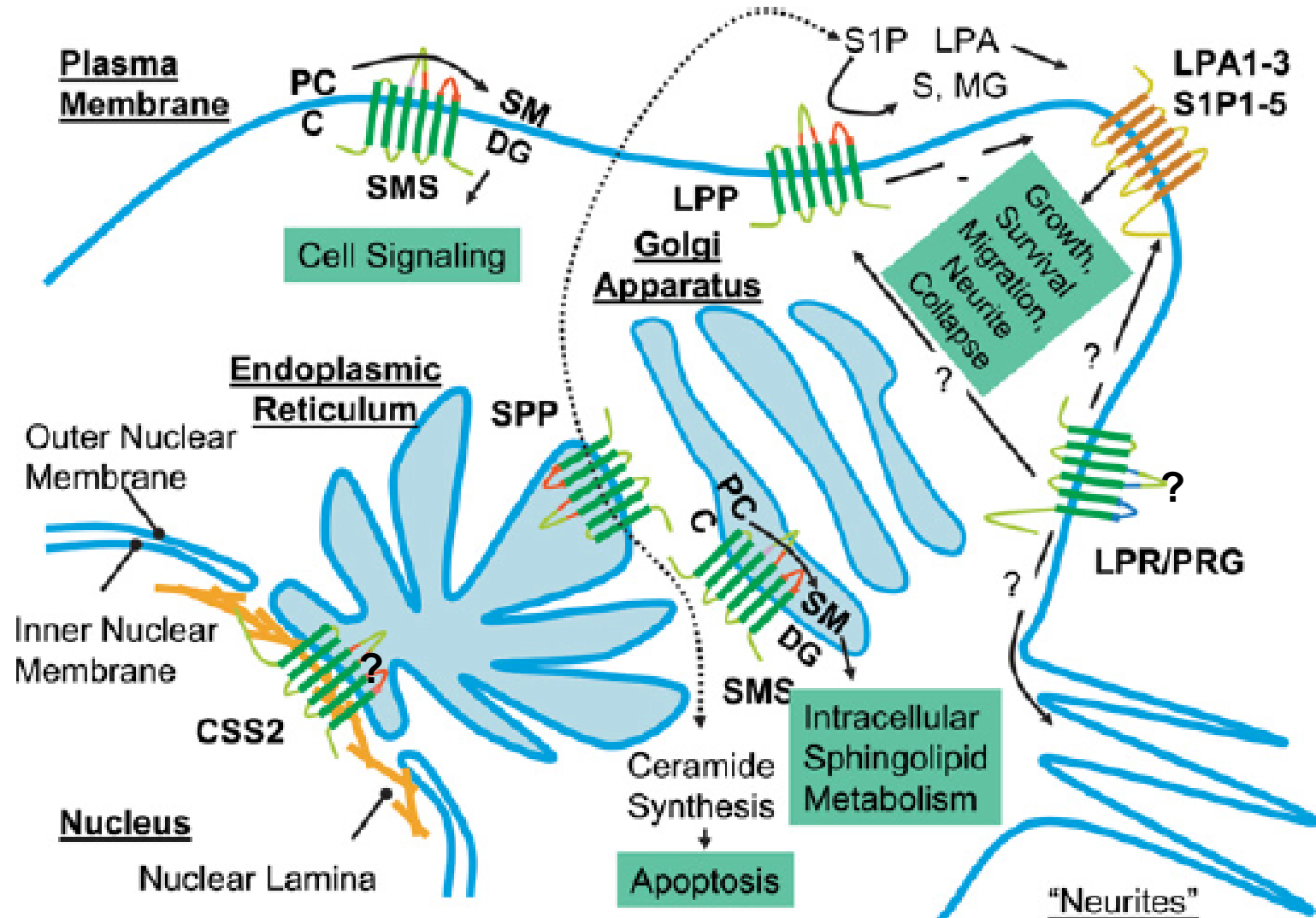
**Crecimiento celular**

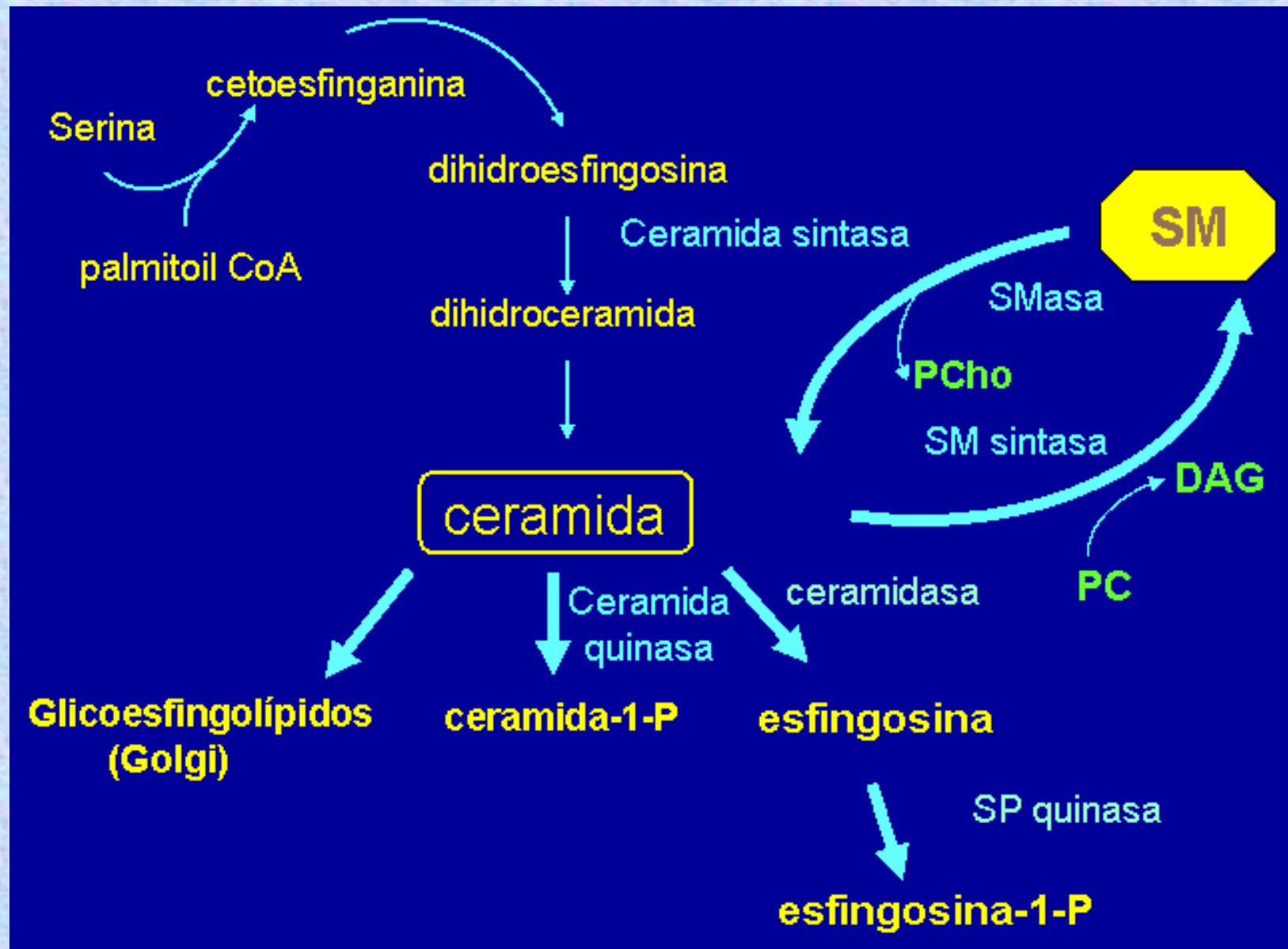


<b>Phosphatidate (PA)</b>
Stimulates NADPH oxidase, H <sub>2</sub> O <sub>2</sub> production, protein kinase C- $\zeta$ , phosphatidylinositol-4-phosphate kinase, phospholipase C- $\gamma$ ,
Activates Ras-GTP, Raf, ERK, mTOR and sphingosine kinase-1
Increases stress fiber formation
Inhibits protein phosphatase-1
Relative LPA and PA in membranes control their curvature, vesicle budding and transport
<b>Diacylglycerol (DAG)</b>
Stimulates of classical and novel protein kinase Cs.
Activation of RasGRP (guanine nucleotide releasing proteins)
<b>Lysophosphatidate</b>
Activates PPAR- $\gamma$ and nuclear LPA <sub>1</sub> receptors
<b>Sphingosine 1-phosphate</b>
Mobilizes intracellular Ca <sup>2+</sup> ,
Increases ERK activity, cell division and actin stress fiber formation
Protects against apoptosis
Increases COX-2 activity and eicosanoid synthesis
<b>Ceramide 1-phosphate (C1P)</b>
Involved in synaptic vesicle movement and neutrophil phagocytosis
Stimulates cell division and survival
Activates cytosolic phospholipase A <sub>2</sub> , production of arachidonate and prostaglandin E <sub>2</sub>
Blocks apoptosis by inhibiting acidic sphingomyelinase activity
<b>Ceramide</b>
Induces cell differentiation, apoptosis or senescence in most cells
Increases survival of fibroblasts, some neurons and other cells
Inhibits phospholipase D activity and vesicle movement
Stimulates serine/threonine kinase, protein kinase C- $\zeta$ and phosphoprotein phosphatase activities

**Las LPPs modifican el balance de moléculas de señalización**

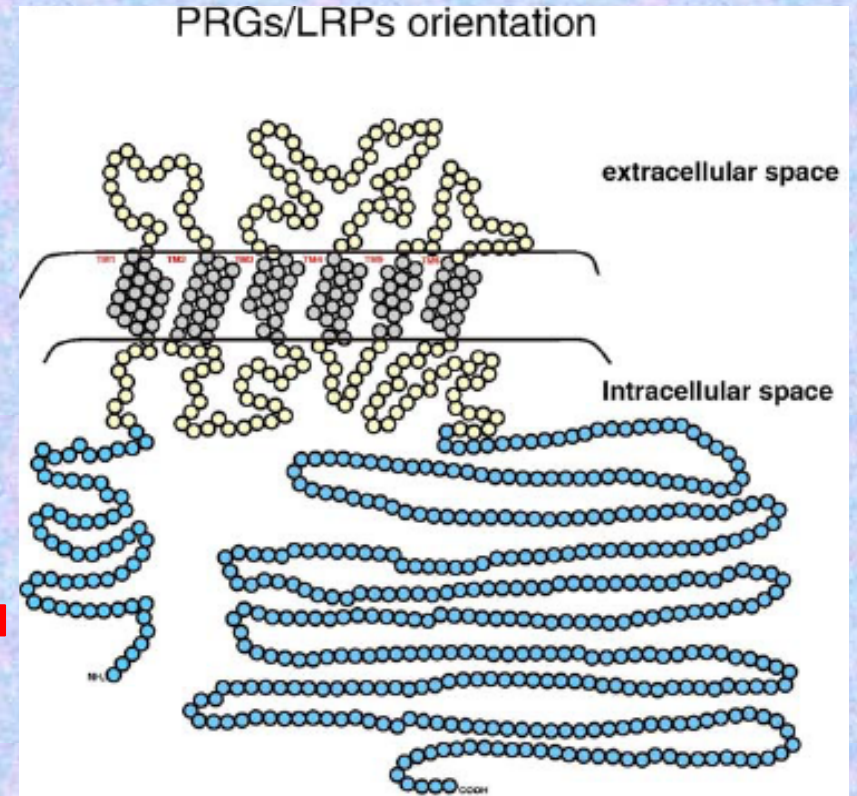
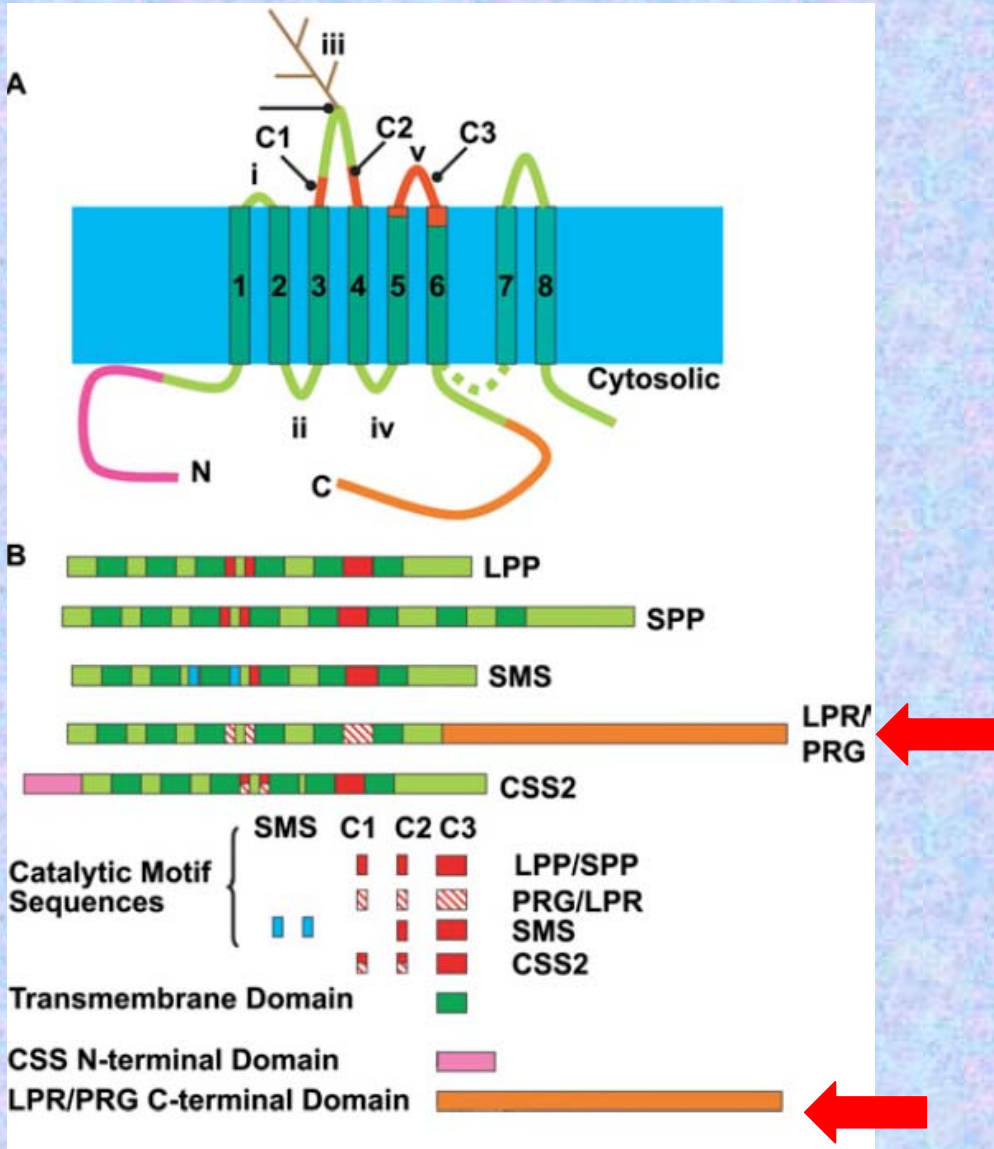
## Posible localización de LPTs







# Plasticity-related genes (PRGs/LRPs)



•5 isoformas en cerebro

•Expresadas diferencialmente en el desarrollo cerebral y en respuesta a la injuria

•Controla los niveles de LPA (LPR3)

•No usan el mecanismo de catálisis similar a las LPP



# **FOSFATIDATO FOSFATASAS (LIPINS)**

✓ El PA tiene funciones metabólicas y de señalización

✓ En mamíferos y vertebrados hay genes que codifican para Lip 1, 2 y 3

✓ GEN LIPIN 1 codifica para Lipin 1 $\alpha$  (nuclear),  $\beta$  (citoplasmática) y  $\gamma$  (LD).  
cerebro humano. A pre-adipocitos. B adipocitos maduros

✓ Un simple gen en nematodos, plantas y levaduras

✓ Lipins no son intrínsecas de membrana

✓ **115 KDa, homología del 44-48%**

✓ **Proteínas que interactúan y regulan PA. Motivos polibásicos en las proteínas que le permiten actuar con PA**

✓ **Esta interacción sería importante para orientar la enzima con el sustrato en la membrana celular**

✓ **Actúan sobre sustratos agregados en micelas**

✓ La actividad depende del número de micelas que contienen PA, de la concentración en la micela y de las moléculas de PA en la superficie de la micela

✓ La enzima interactúa con una molécula de PA antes de desfosforilar otra  
 $V_{max}$  de lipin1 >>lipin2>lipin3

✓ Inhibida por NEM y dependiente de magnesio. PA~Ca mal sustrato (inhiben la actividad soluble)

✓ PA generado a partir de acil-CoA y glicerol-3-fosfato sobre microsomas en presencia de  $Mg^{2+}$ , muy buen sustrato. Difícil de purificar (mamíferos) inestable térmicamente y sufre proteólisis



✓ **Gotas lipídicas (LD) en TAG y PC**

✓ **Transloca del citosol a la membrana, regulada por AG y fosforilación**

✓ **Lipina en organismos inferiores regula los niveles de LN y FL, la morfología de la membrana nuclear y del retículo y la desrepresión transcripcional de enzimas de la biosíntesis de FL**

✓ **Lipinas contienen un motivo polibásico (en las 3 lipinas) en el dominio amino terminal de unión al PA esto es crítico para el redireccionamiento retículo/núcleo**

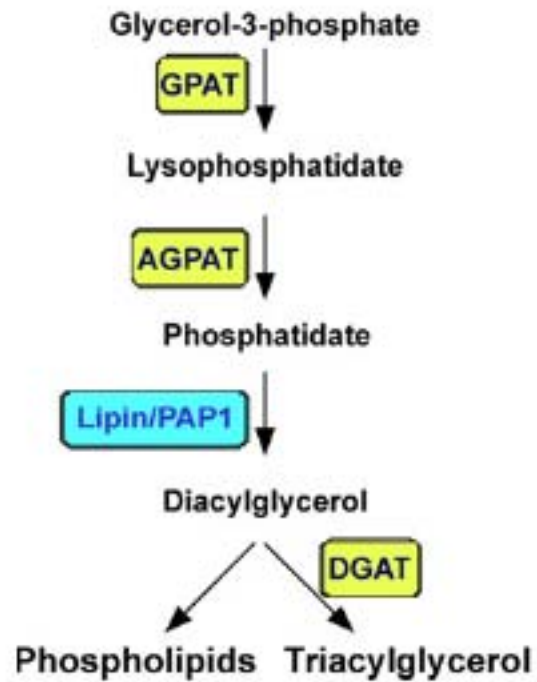
✓ **Los niveles de PA regulan la localización de la enzima del citosol al retículo (altos niveles) o al núcleo (bajos niveles) regulado hormonalmente**

- ✓ **A diferencia de organismos inferiores, donde la fosforilación modifica la actividad catalítica, en mamíferos se ve afectada la localización**
- ✓ **Algunos sitios de fosforilación en lipins de levaduras no se encuentran en los ortólogos de mamíferos**
- ✓ **En mamíferos la lipin1 está en forma nativa como dímero o tetramero**
- ✓ **Lipin 1 forma heterooligómeros con lipin2 y lipin3**
- ✓ **Se regula por transcripción génica, splicing del mRNA, fosforilación y degradación proteica**

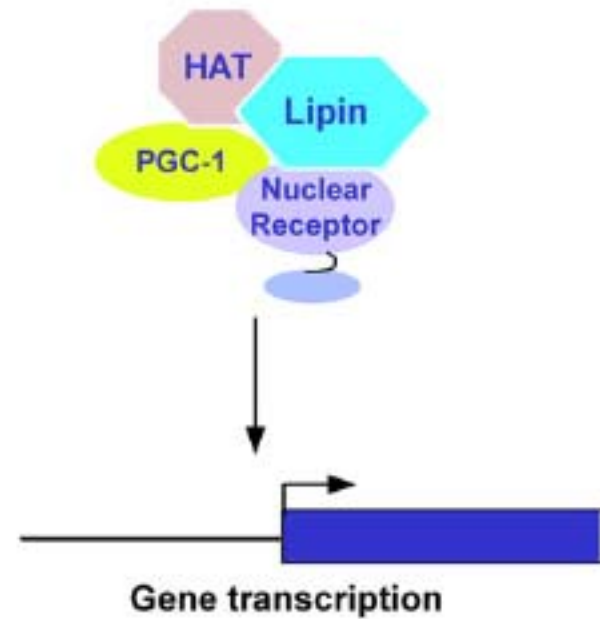
**Factor transcripcional**

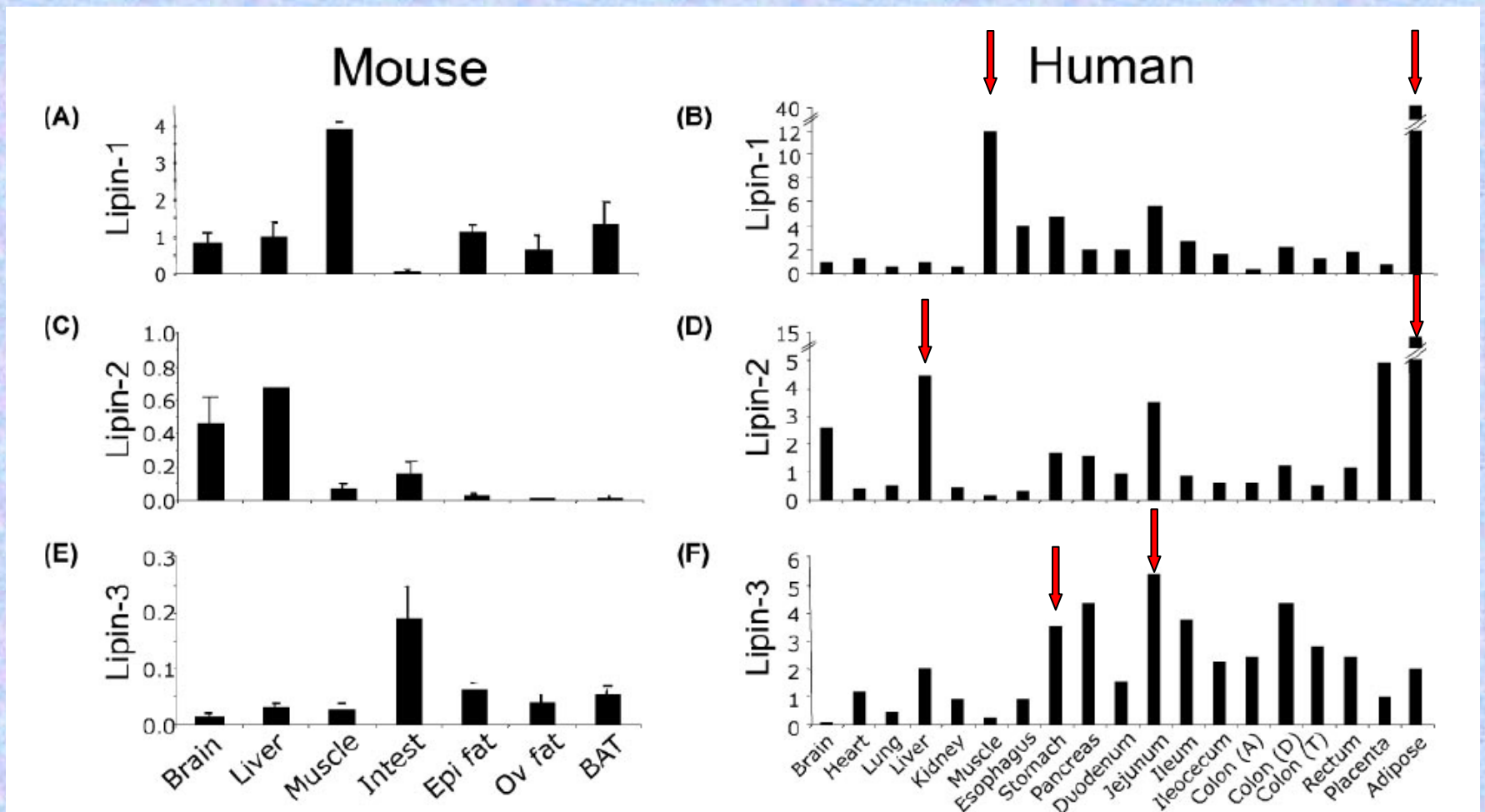
# Lipin

## Glycerolipid biosynthesis



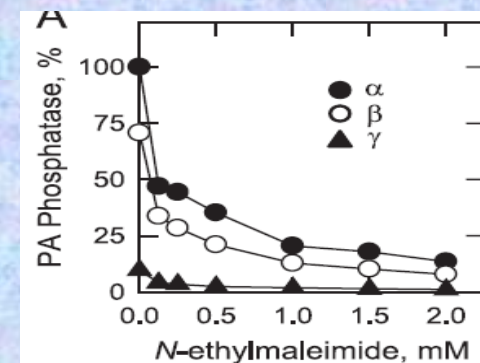
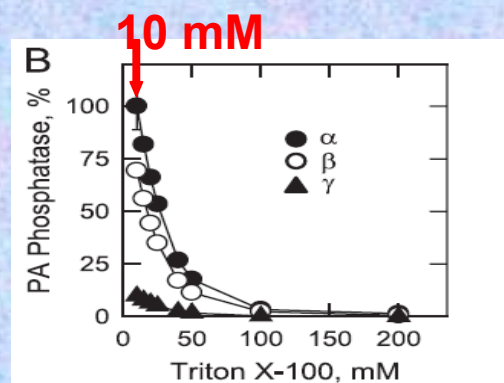
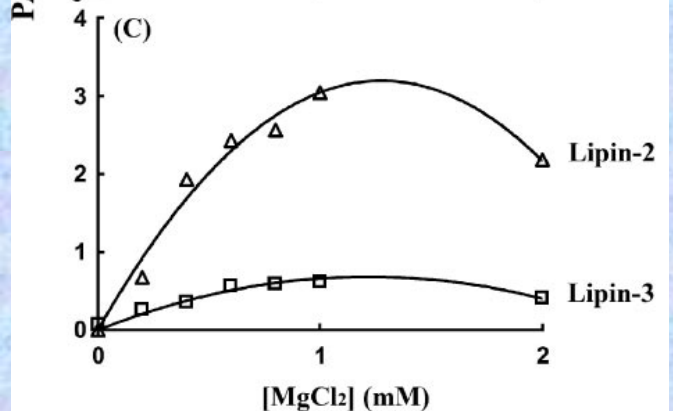
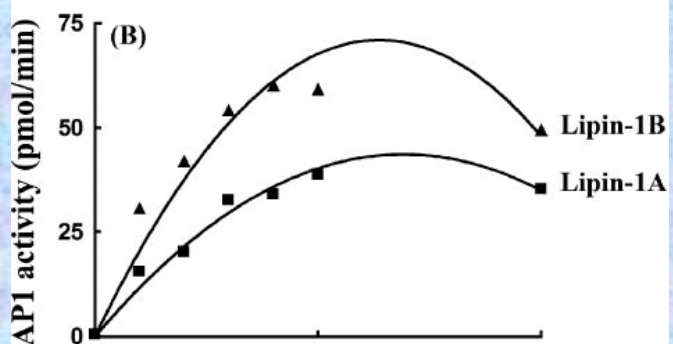
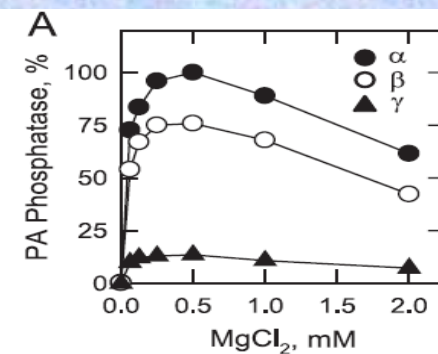
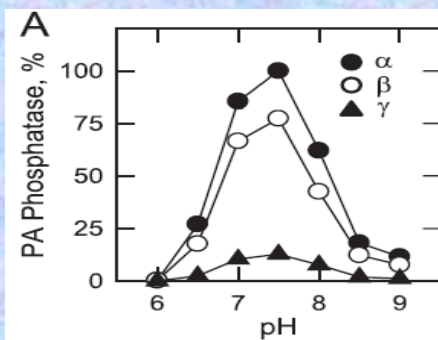
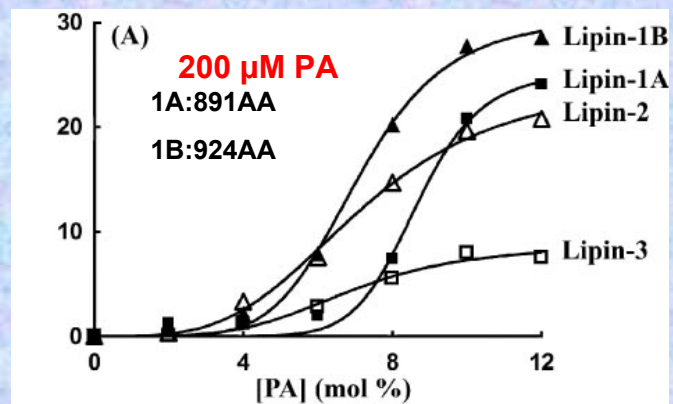
## Transcriptional coactivator





Expresión génica cuantificada por RT-PCR

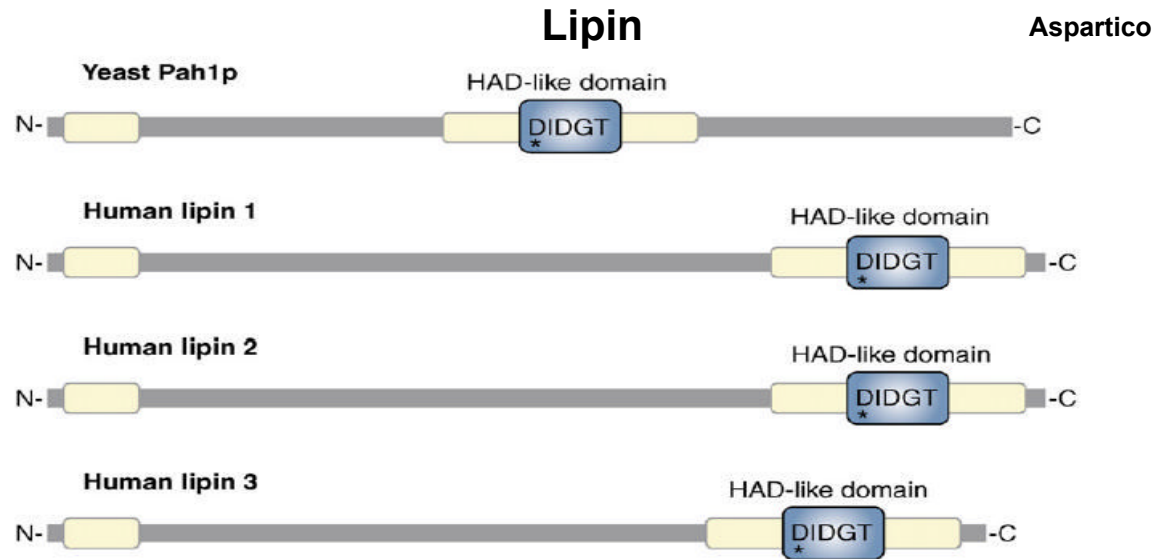




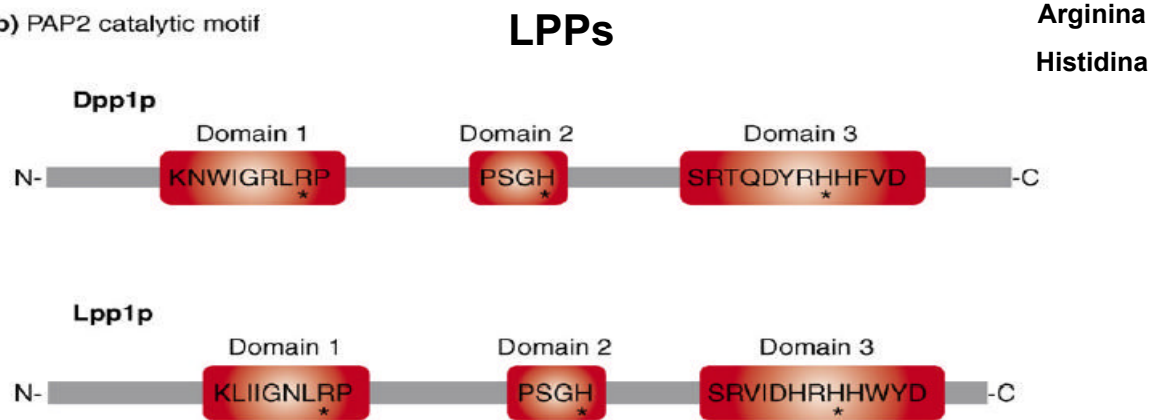
	Lipin-1A	Lipin-1B	Lipin-2	Lipin-3
$K_{50}$	$8.7 \pm 0.25$	$7.0 \pm 0.18$	$7.0 \pm 0.44$	$6.9 \pm 0.6$
$V_{max}$	$25 \pm 1.9$	$30.5 \pm 1.3$	$24.6 \pm 2.1$	$8.7 \pm 1$

293T cells transfectadas con constructos de lipinas

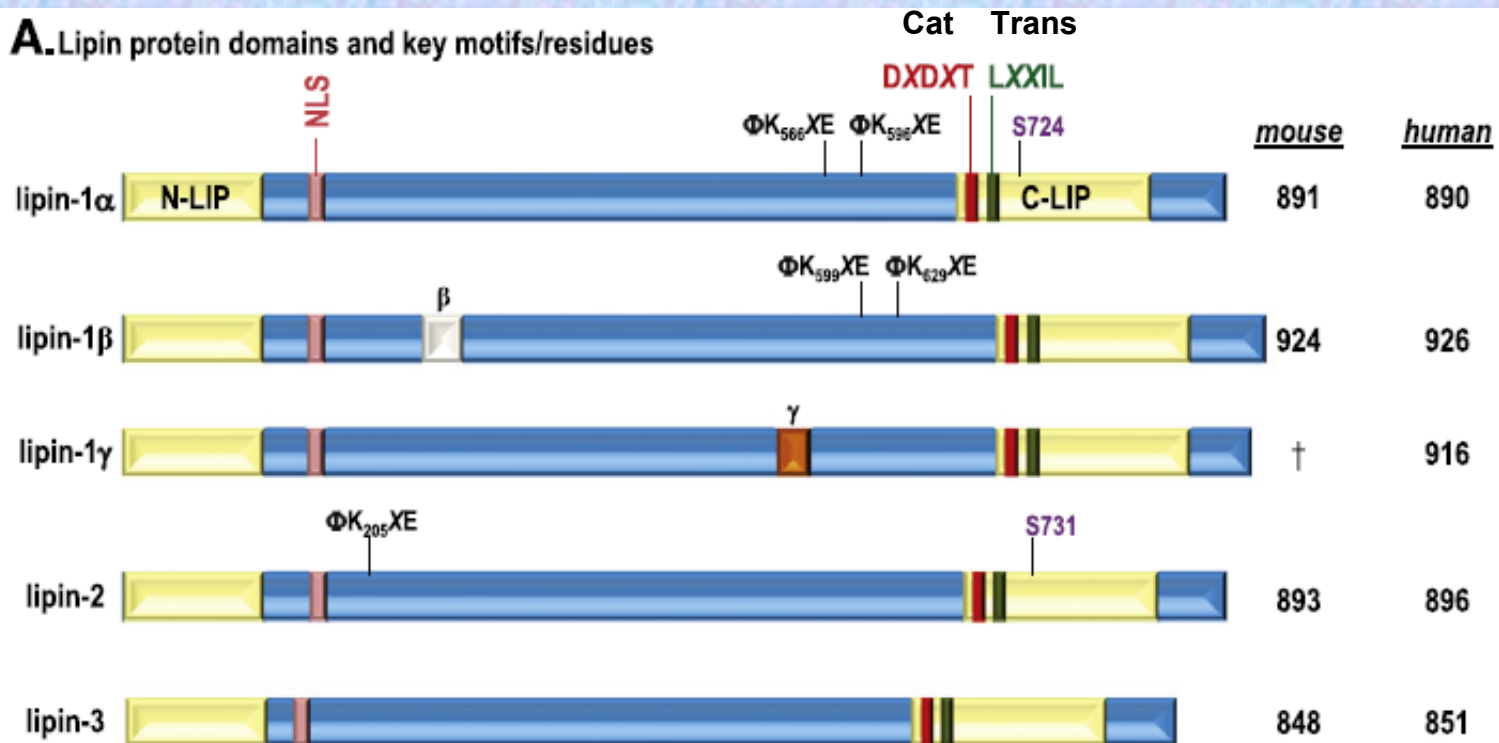
(a) PAP1 catalytic motif



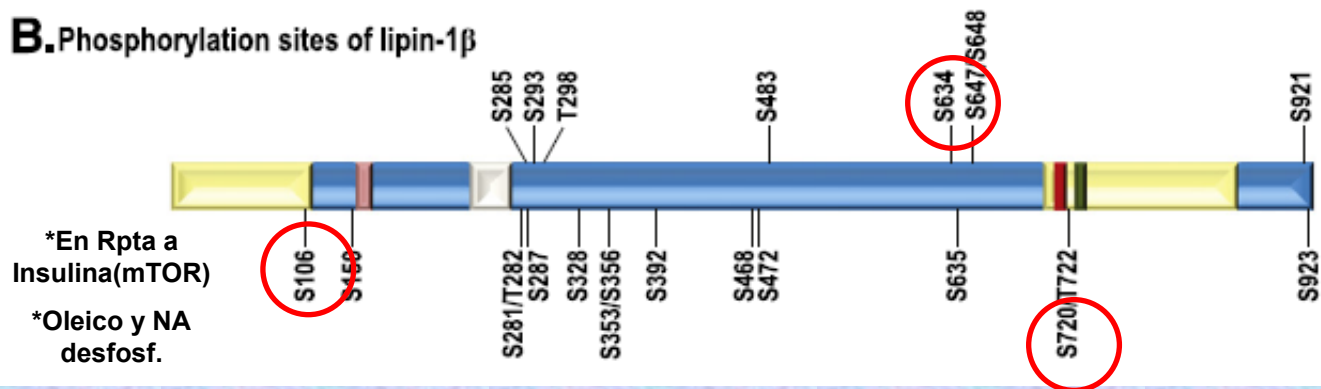
(b) PAP2 catalytic motif



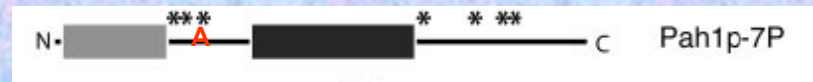
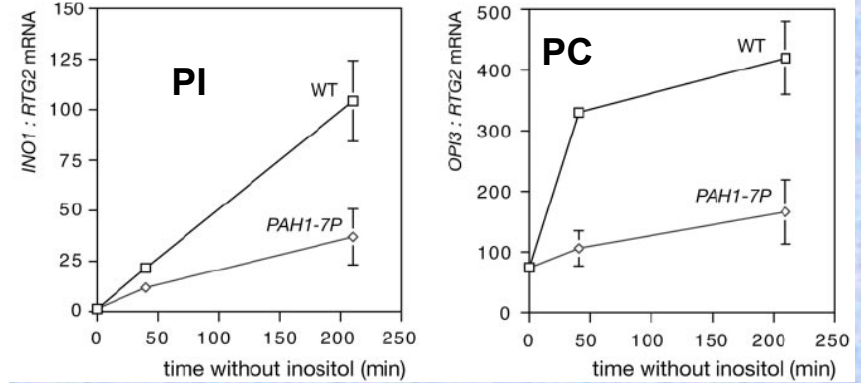
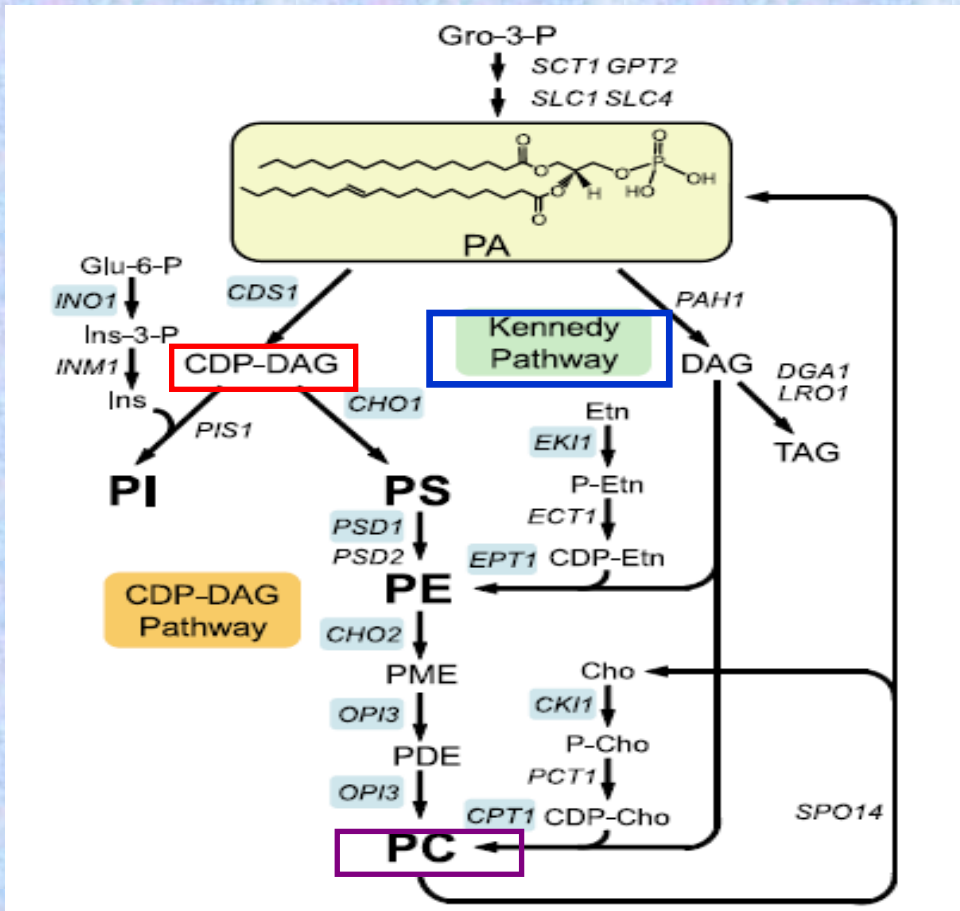
### A. Lipin protein domains and key motifs/residues



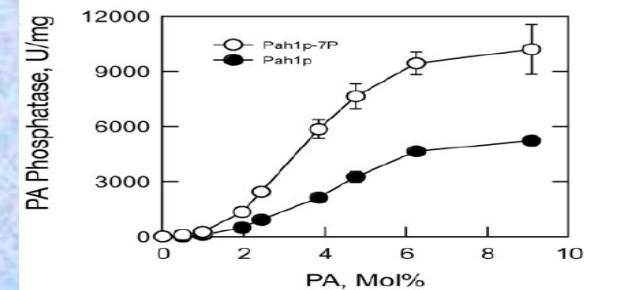
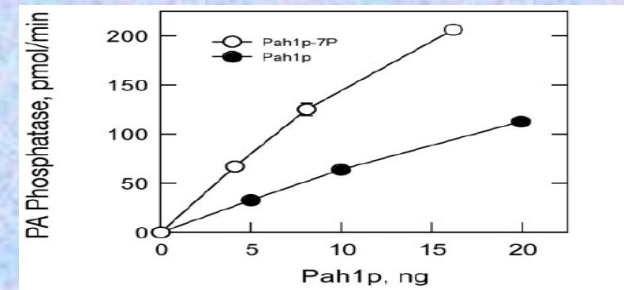
### B. Phosphorylation sites of lipin-1 $\beta$



# LEVADURAS



## Mutación de 7 sitios fosforilables (S/T a A)



	Pah1p	Pah1p-7P
$V_{max}$	6014 ± 21	10899 ± 1382
$K_m$	4.56 ± 0.04	3.63 ± 0.20

\*Fosf. Inhibe la actividad

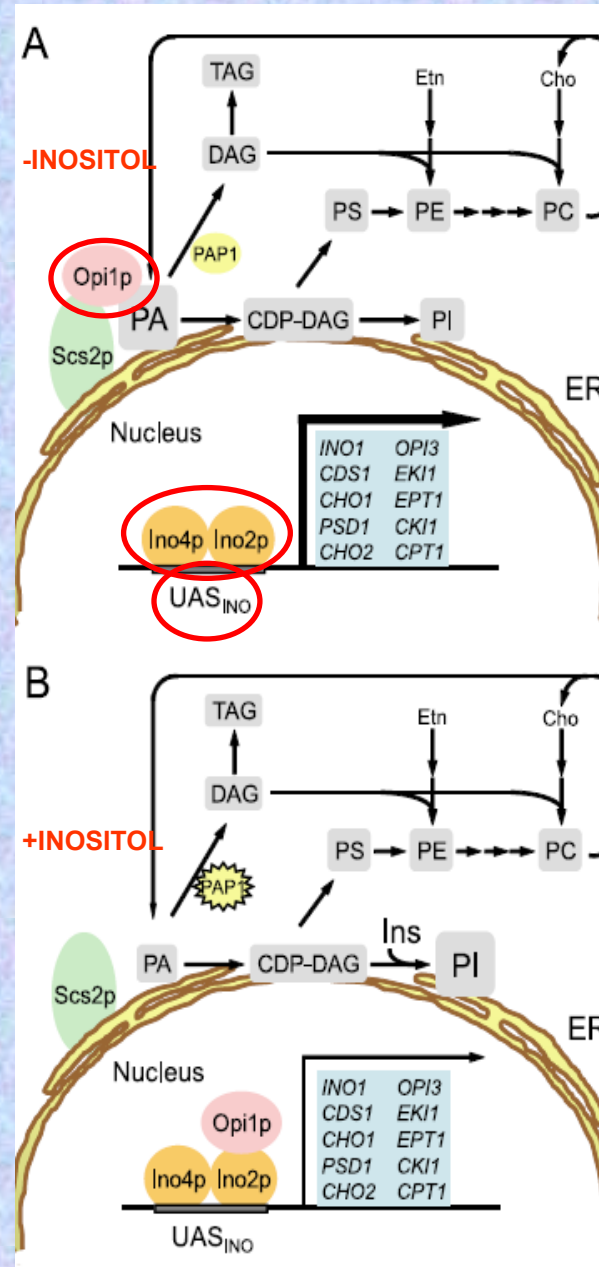
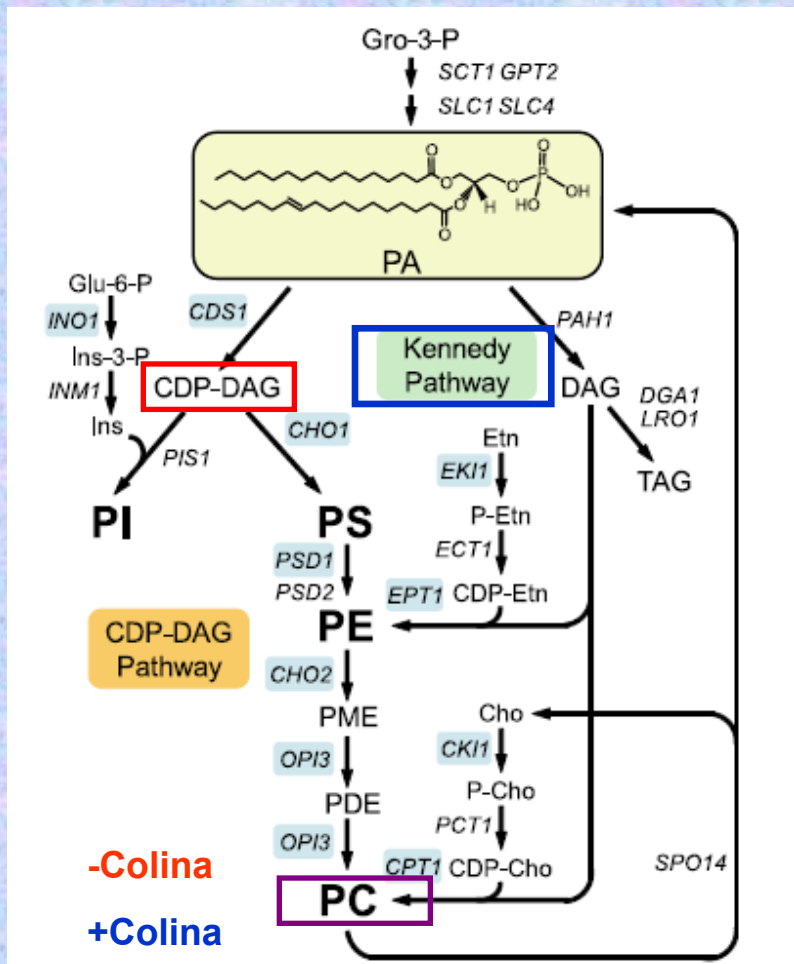
\*Represor transcripcional de síntesis de lípidos (Opi1p)





# Phosphatidic Acid Plays a Central Role in the Transcriptional Regulation of Glycerophospholipid Synthesis in *Saccharomyces cerevisiae*\*

Published, JBC Papers in Press, November 2, 2007, DOI 10.1074/jbc.R700038200  
 George M. Carman<sup>#1</sup> and Susan A. Henry<sup>5</sup>

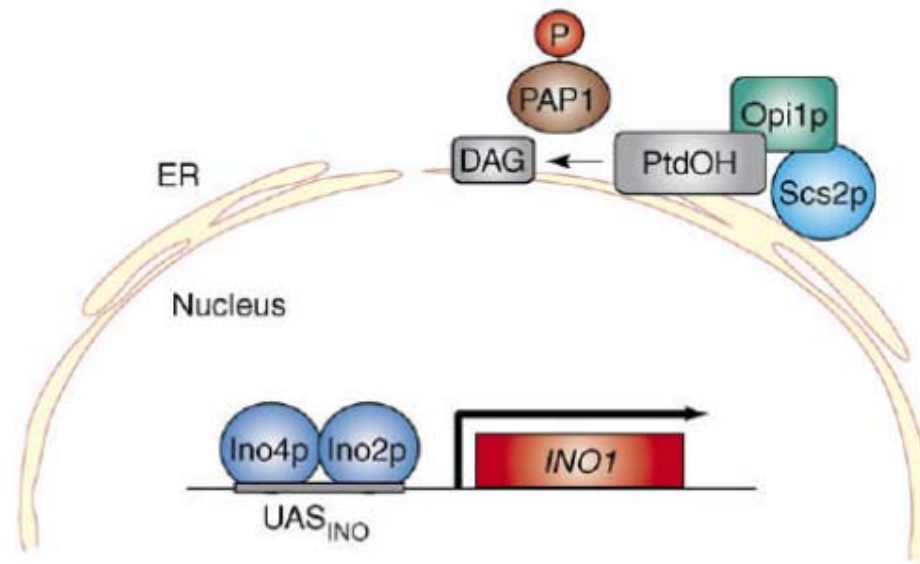


\* Regulación depende de 3 factores:  
 Secuencia en los promotores de genes (UAS<sub>INO</sub>), heterodímero Ino2p-Ino4p y Opi1p que une a PA.

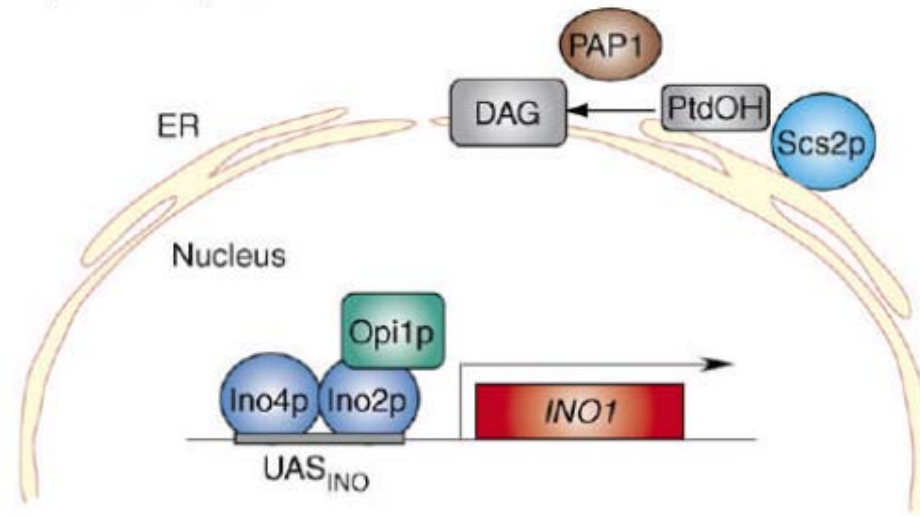
\* UAS<sub>INO</sub> (CATGTGAAT) para Ino2p-Ino4p (expresión de genes)

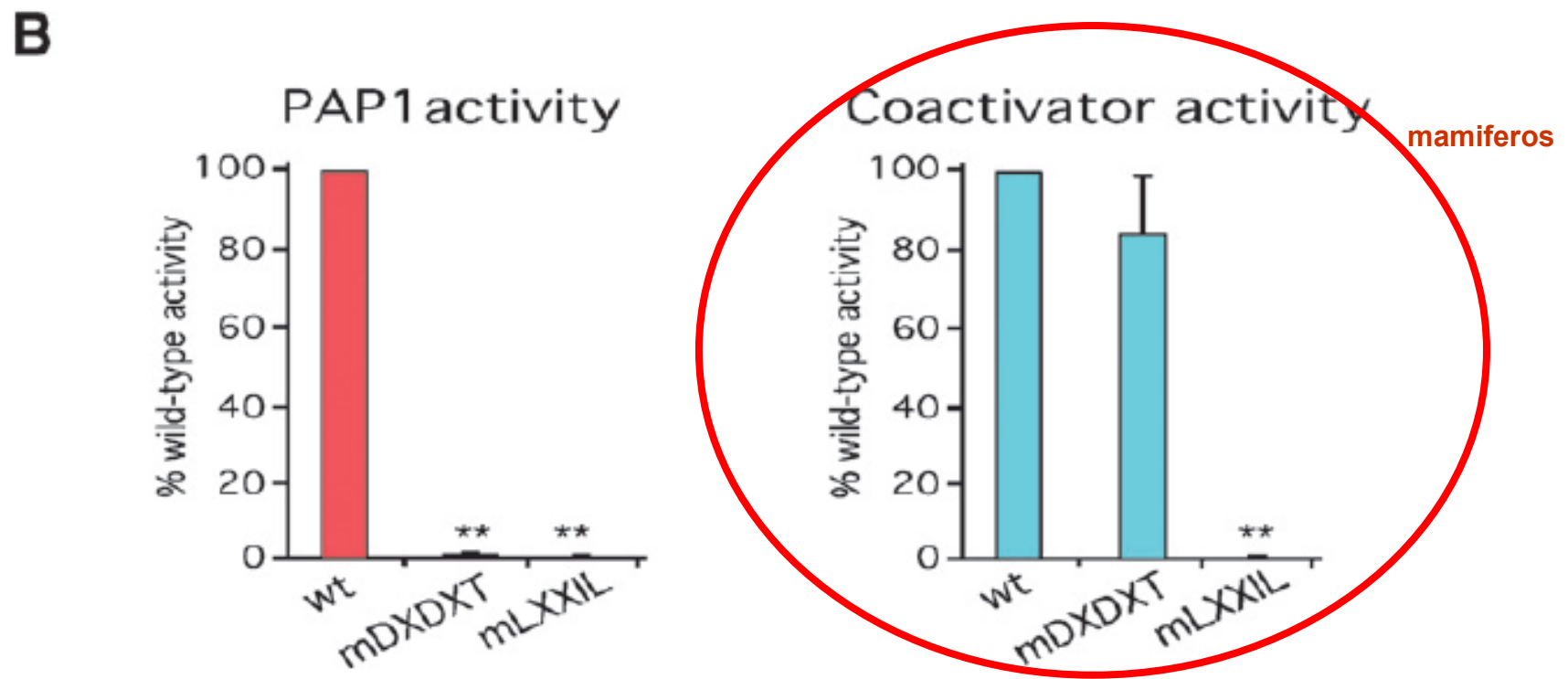
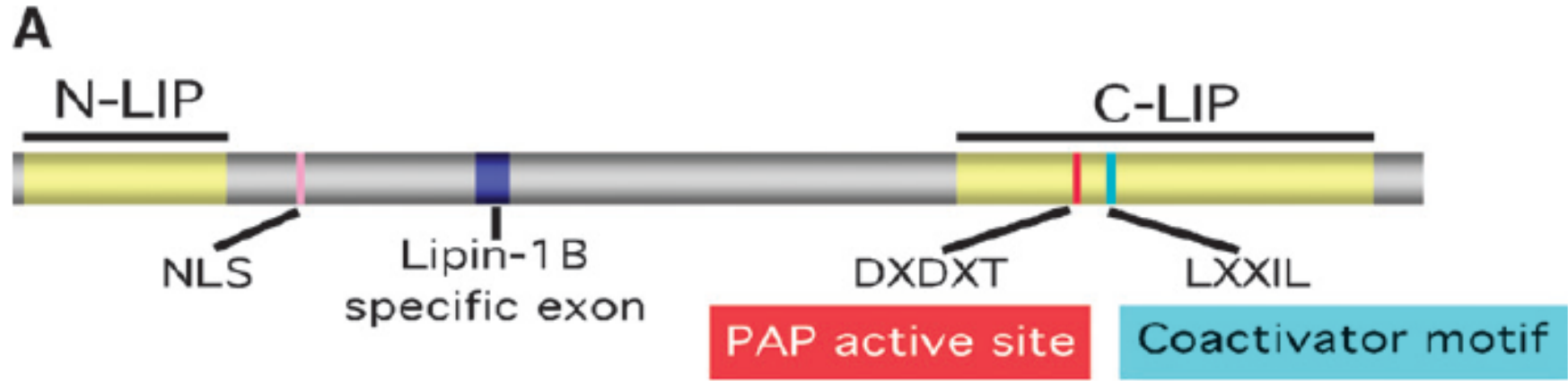
\* Los niveles de PA dependen de la disponibilidad de inositol, fase de crecimiento y de la depleción de nutrientes.

**(a) Maximum expression without inositol**

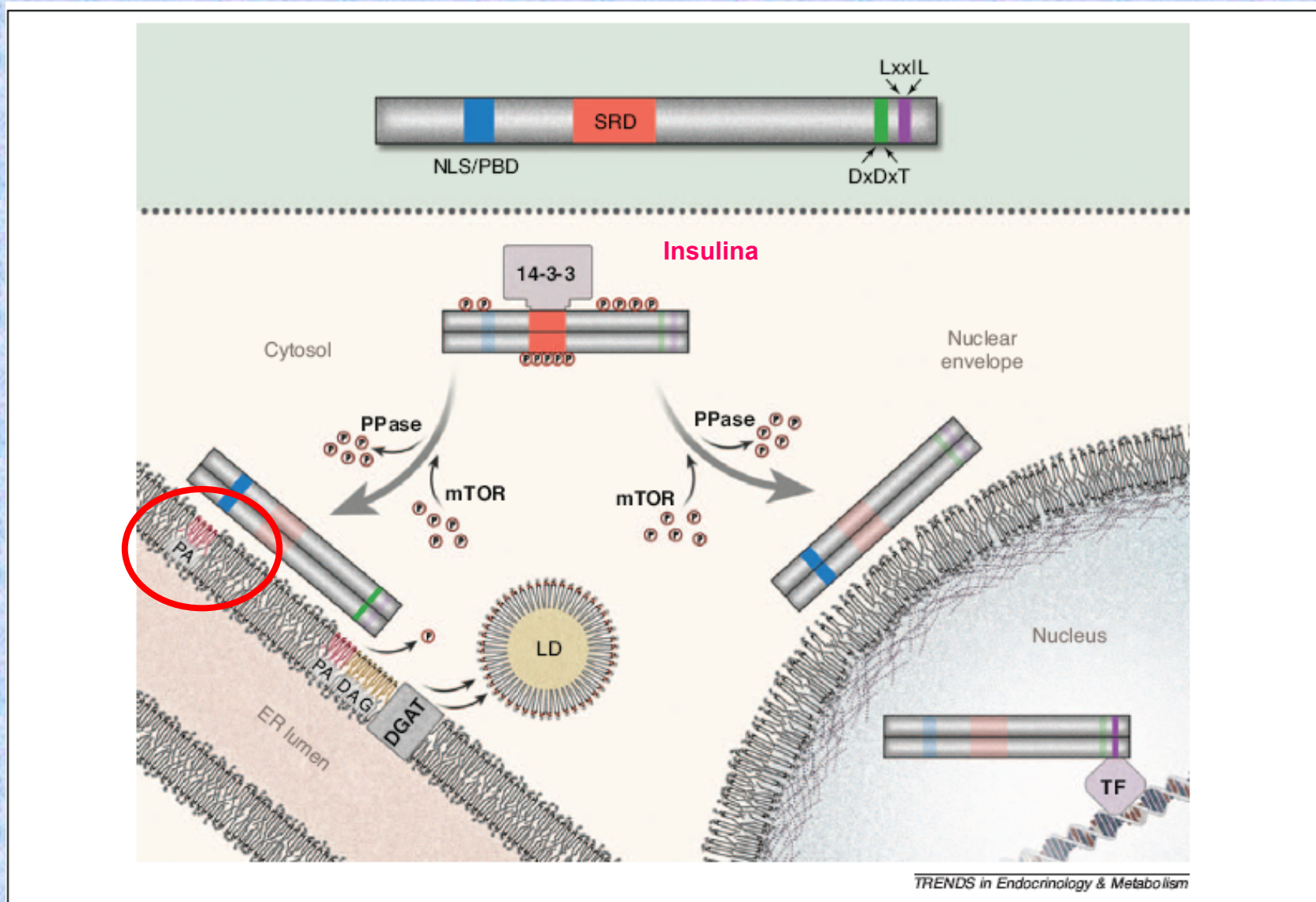


**(b) Repression by inositol**



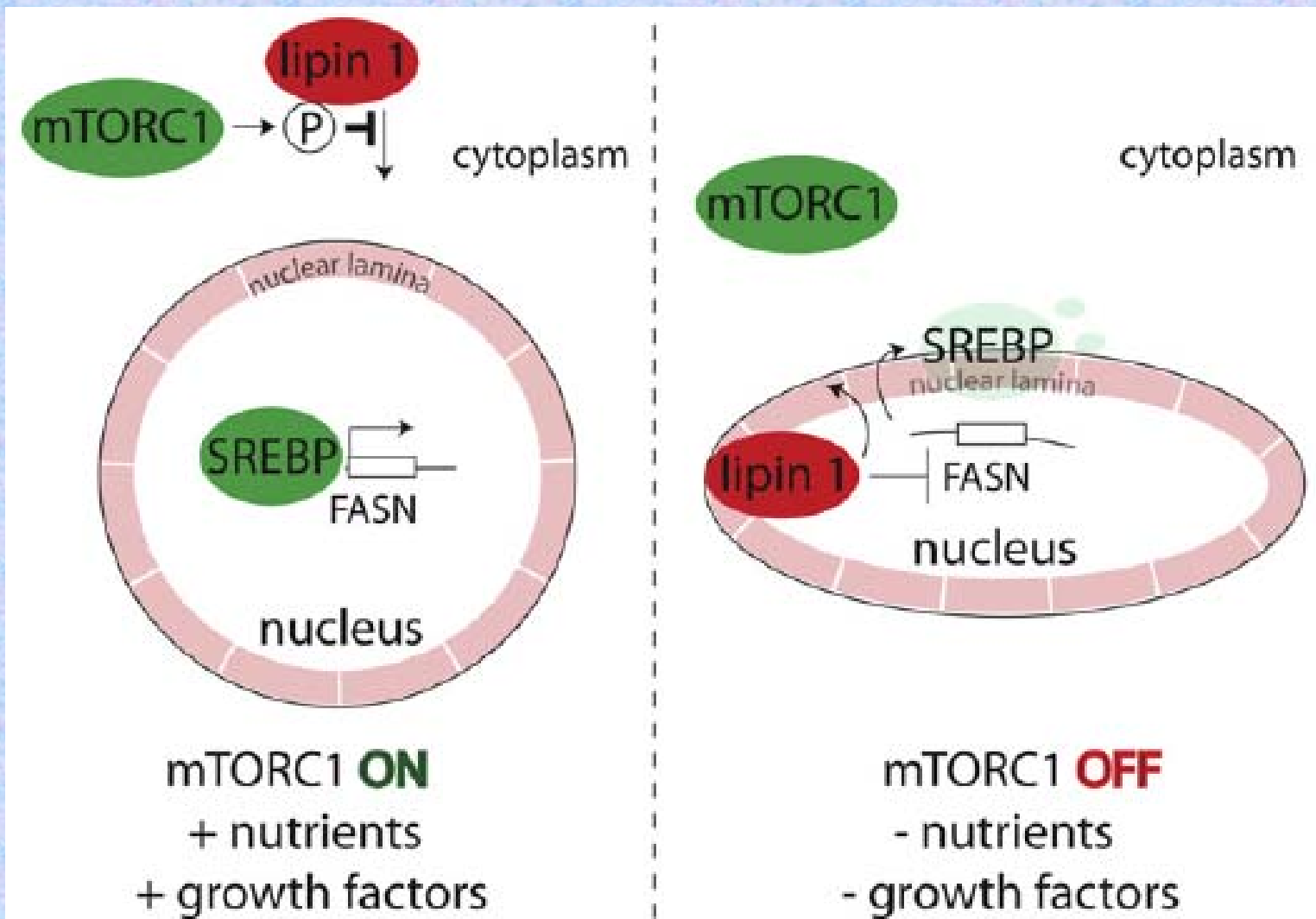




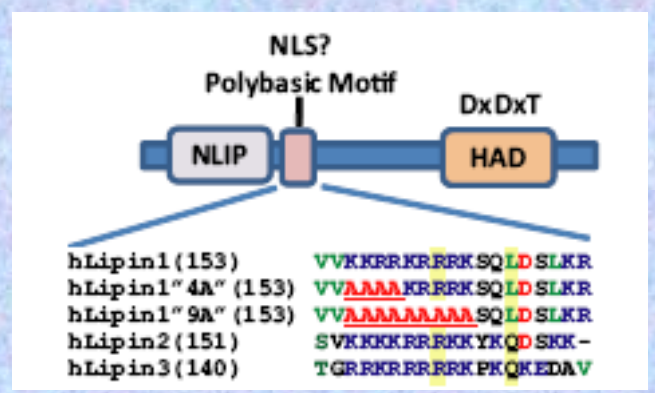
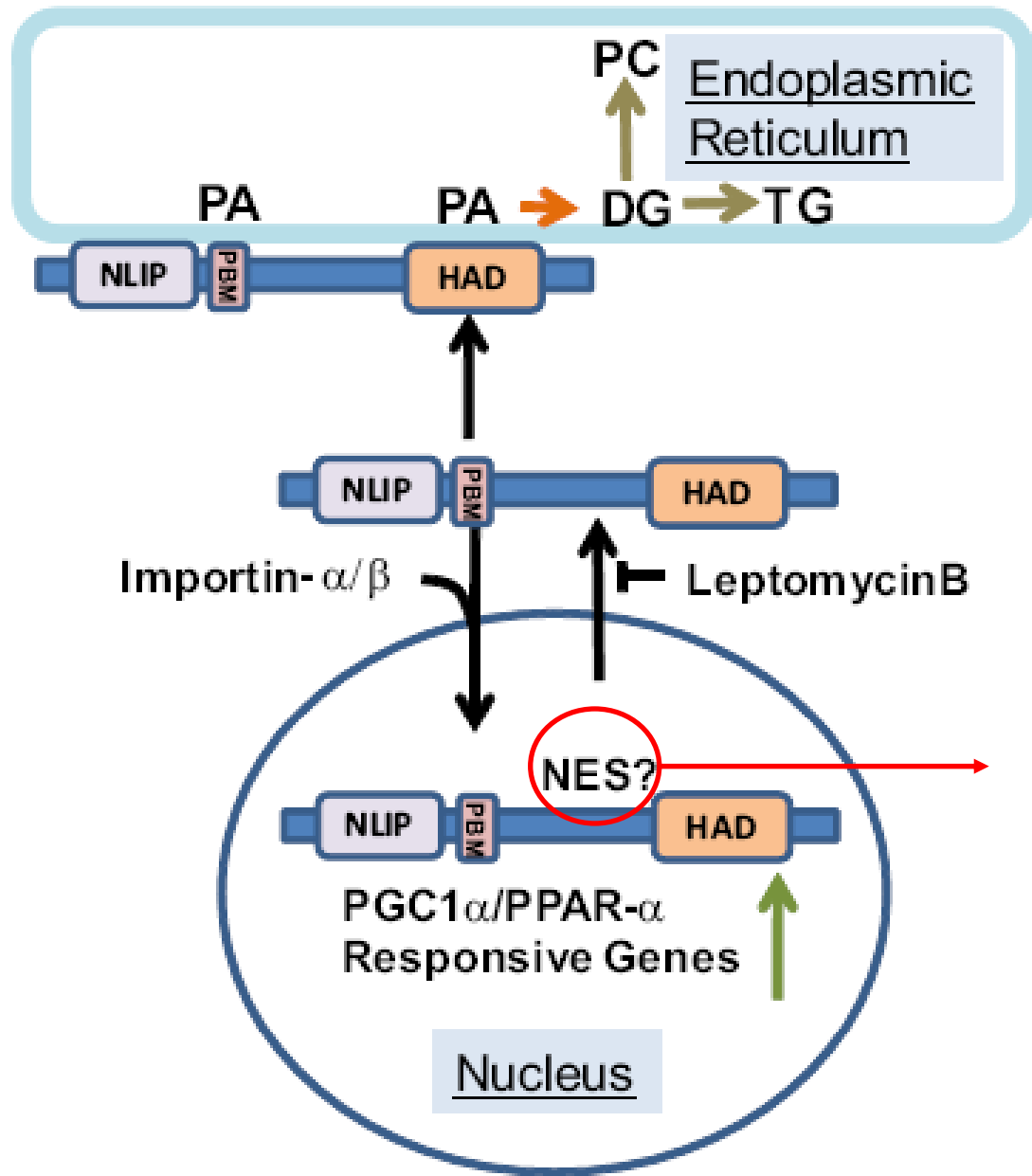


**Figure 3.** Intracellular trafficking of lipin 1 multimers. On top lipin 1 protein with domains described in Figure. 2 is shown. At centre hyperphosphorylation of the SRD of lipin 1 leads to associations with 14-3-3 proteins and cytosolic retention. mTOR has been identified as a kinase that phosphorylates lipin 1 and regulates its localization. Dephosphorylation by unknown protein phosphatase(s) (PPase) direct lipin to the nucleus or ER compartments. The NLS-PBD motif targets lipin 1 to PA-rich membranes, and the DxDxT catalytic motif is required for the dephosphorylation of PA to form DAG. DGAT then terminally acylates DAG to make TAG, and forms the core of nascent lipid droplets (LD). The NLS-PBD motif also mediates the nuclear localization of lipin 1. In the nucleus, lipin 1 interacts with DNA-bound transcription factors (TF) to regulate their activity.



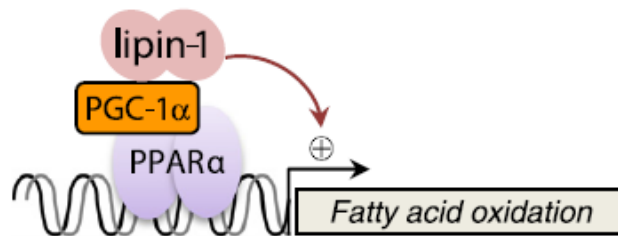


**Figure 7. Model of mTORC1/Lipin 1-Dependent Regulation of SREBP Transcriptional Activity**

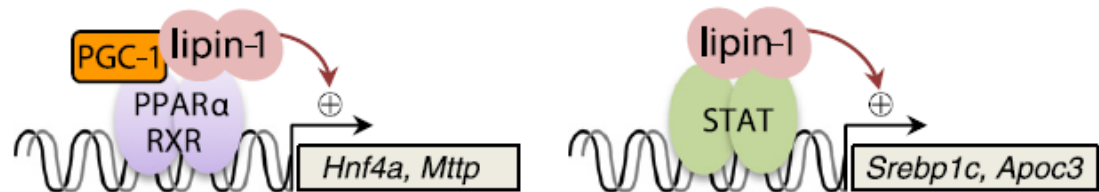


Secuencia de exportación nuclear

### A. Lipin activates fatty acid oxidation



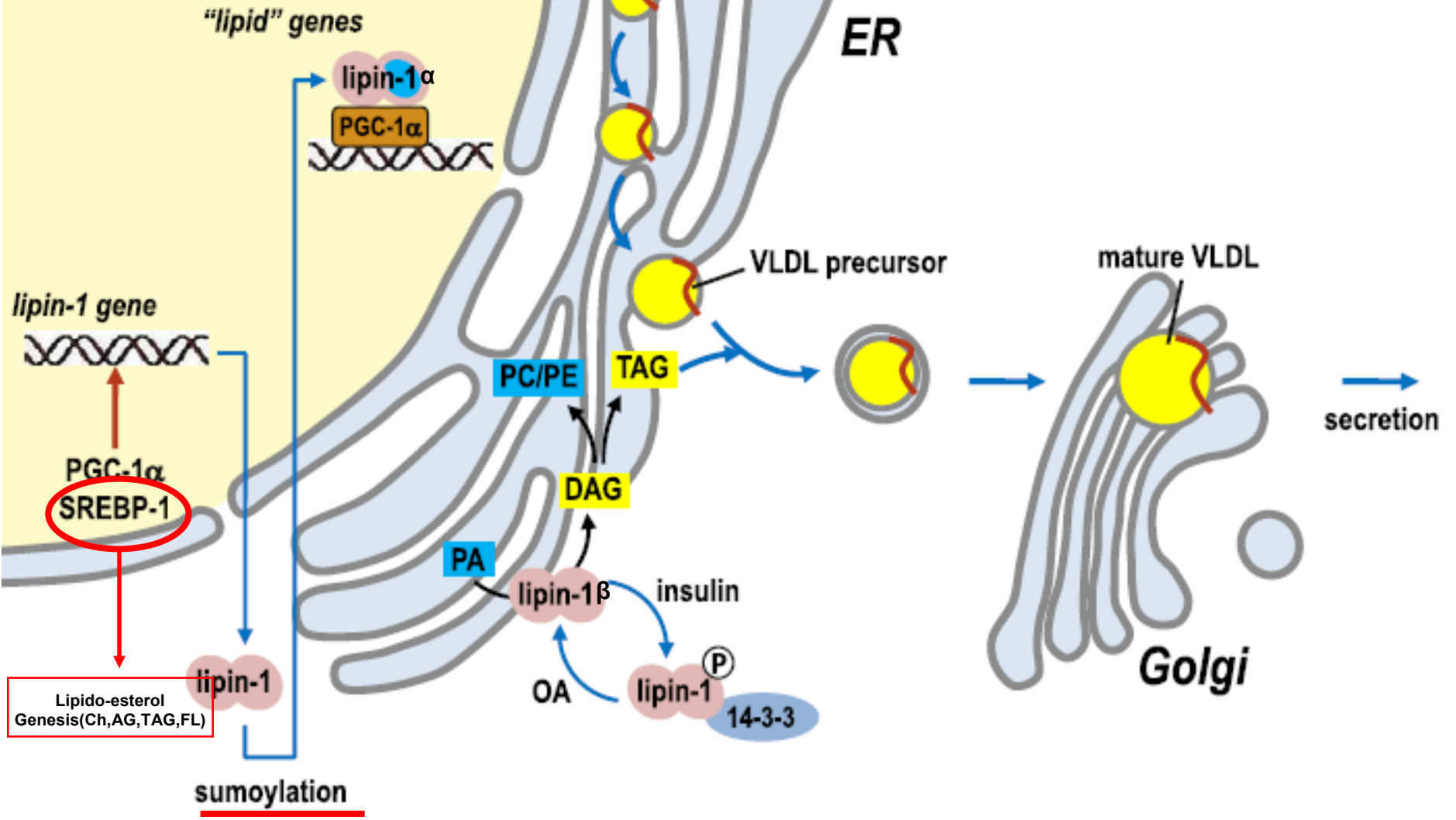
### B. Lipin activates lipid metabolism – bioinformatics



**Fig. 2.** Lipin and transcriptional regulation. A) Lipin-1 amplifies PGC-1 $\alpha$ /PPAR $\alpha$  regulatory circuits and mitochondrial fatty acid oxidation in the liver. B) Our bioinformatic analyses lead us to propose a model whereby lipin impacts transcriptional regulation of lipid metabolism genes either through interaction with PGC-1 $\alpha$ / $\beta$  or PPAR $\alpha$ , or through interaction with other transcription factors such as STAT proteins. *Abbreviations:* *Apoc3*, apolipoprotein C-III; *Hnf4a*, hepatocyte nuclear factor-4 $\alpha$ ; *Mttp*, microsomal triglyceride transfer protein; PGC-1 $\alpha$ / $\beta$ , proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) coactivator-1 $\alpha$ / $\beta$ ; PPAR, proliferator-activated receptor- $\alpha$ ; RXR, retinoid X receptor; *Srebp1c*, sterol regulatory element binding transcription factor-1c; STAT, signal transducer and activator of transcription.

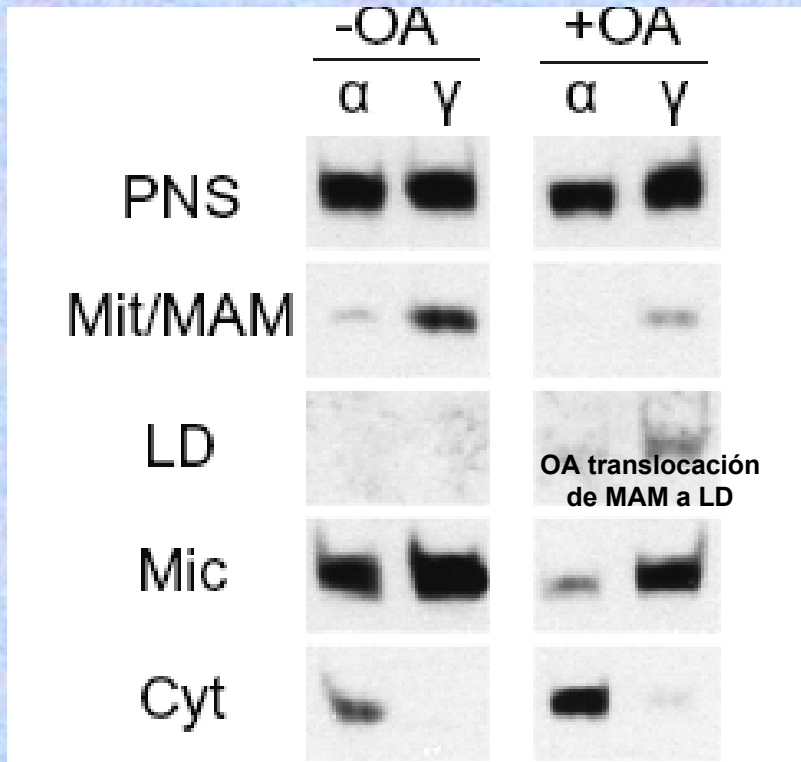
Represor transcripcional por reclutamiento de histonas deacetilasas

# Nucleus





# Lipin 1 $\gamma$



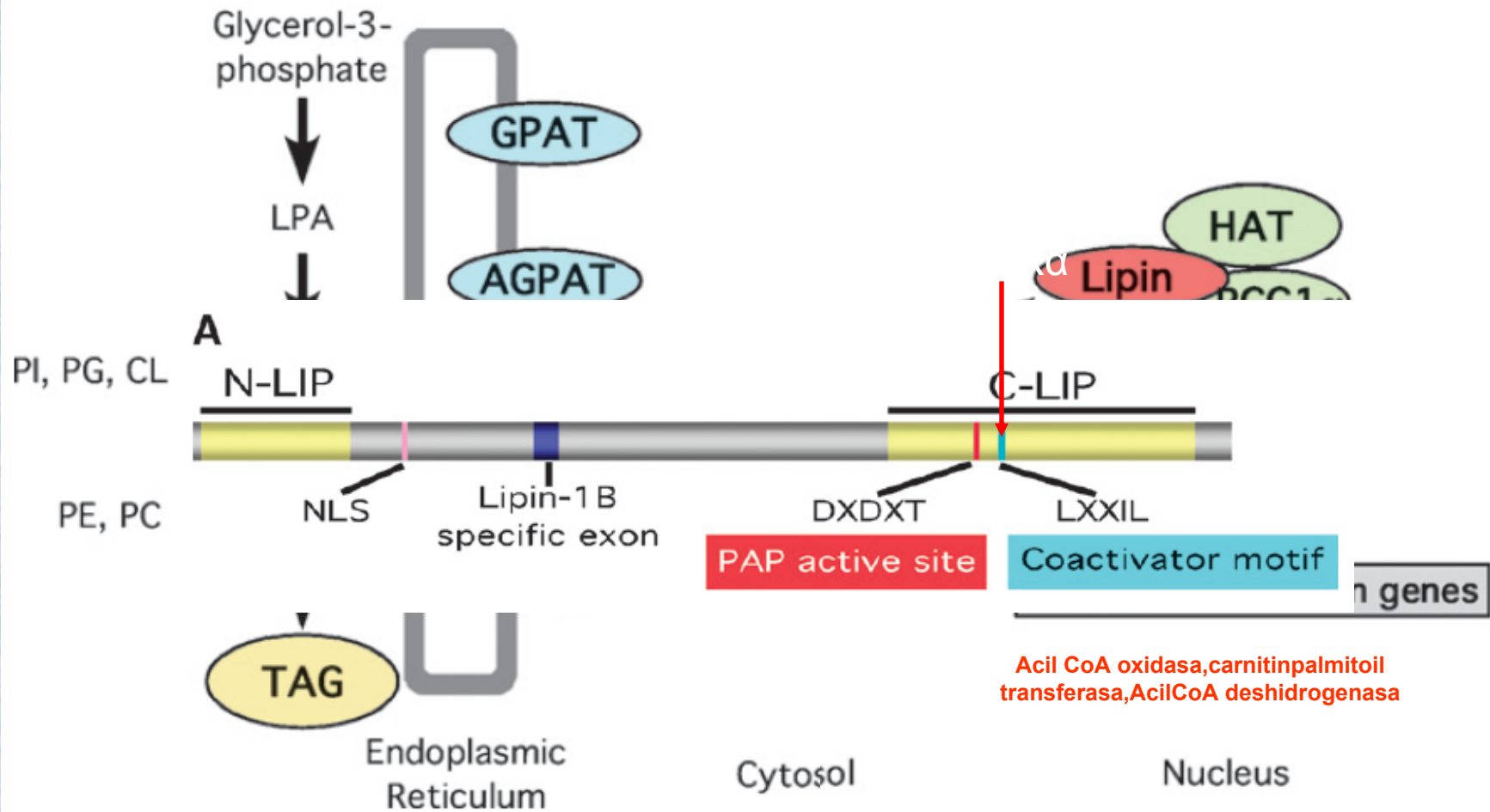
WB



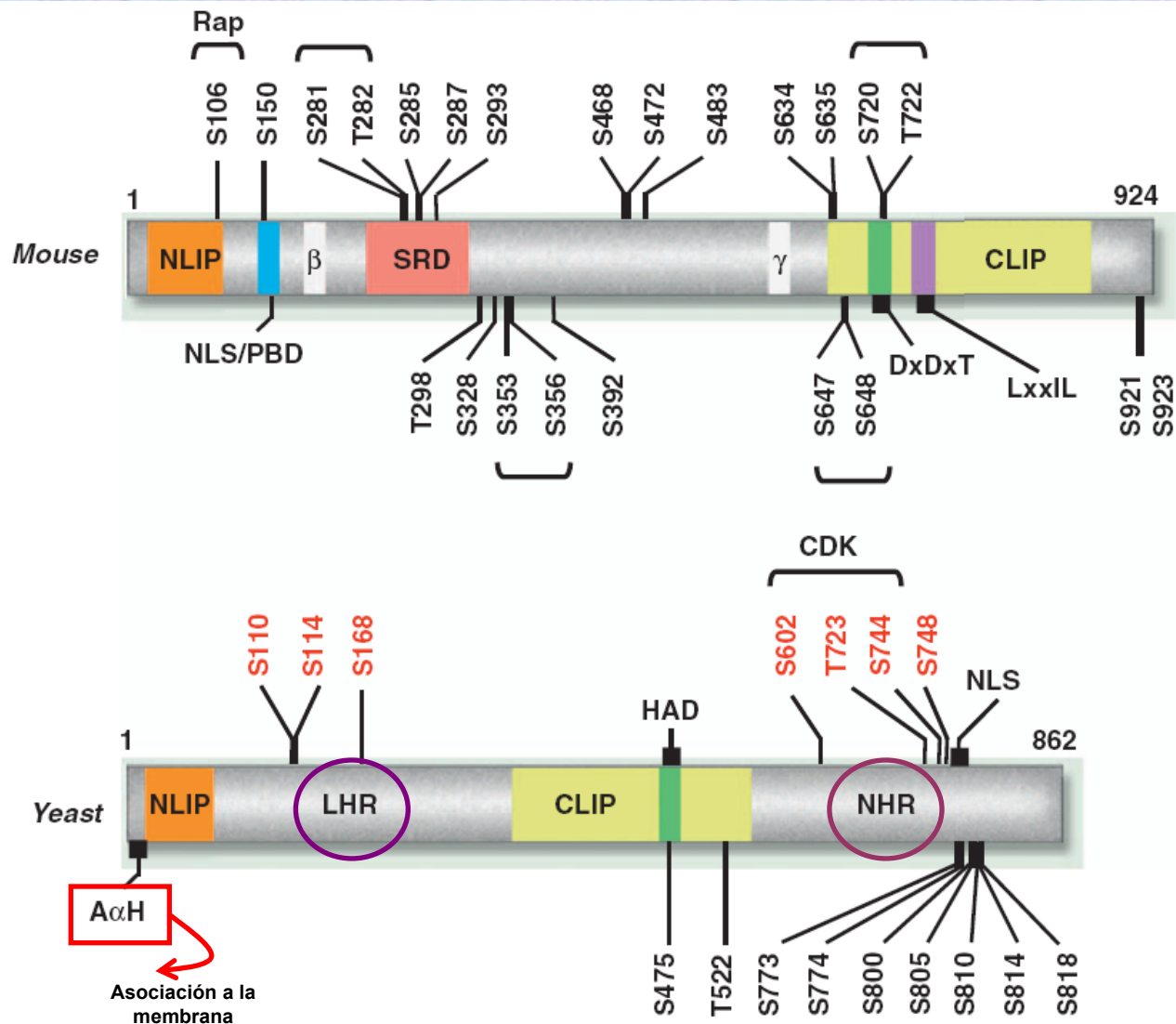
Expresión del mensajero

# Phosphatidate Phosphatase

# Transcriptional Coactivator

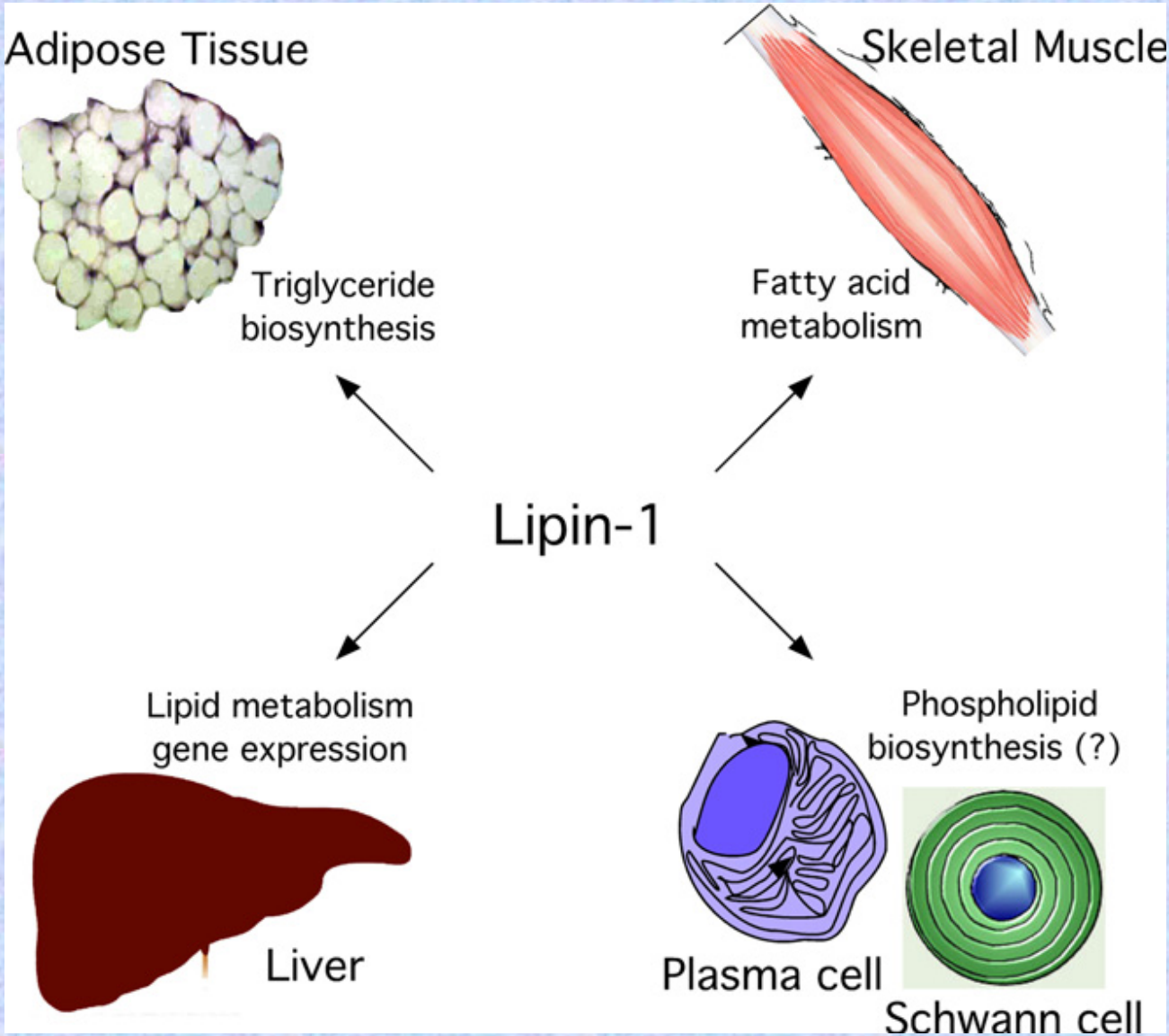


Esta función dual es única en las enzimas del metabolismo lipídico



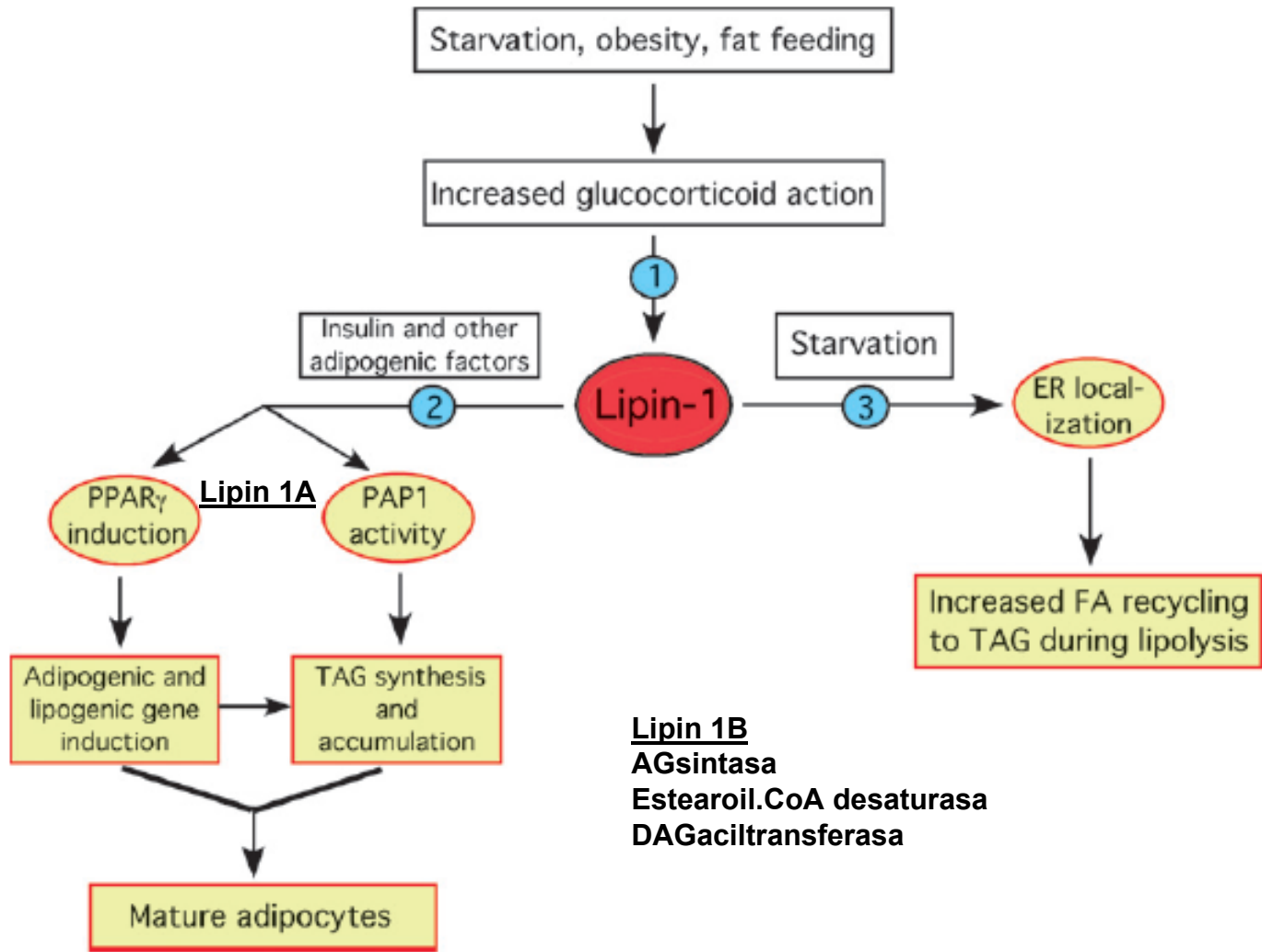
TRENDS in Endocrinology & Metabolism

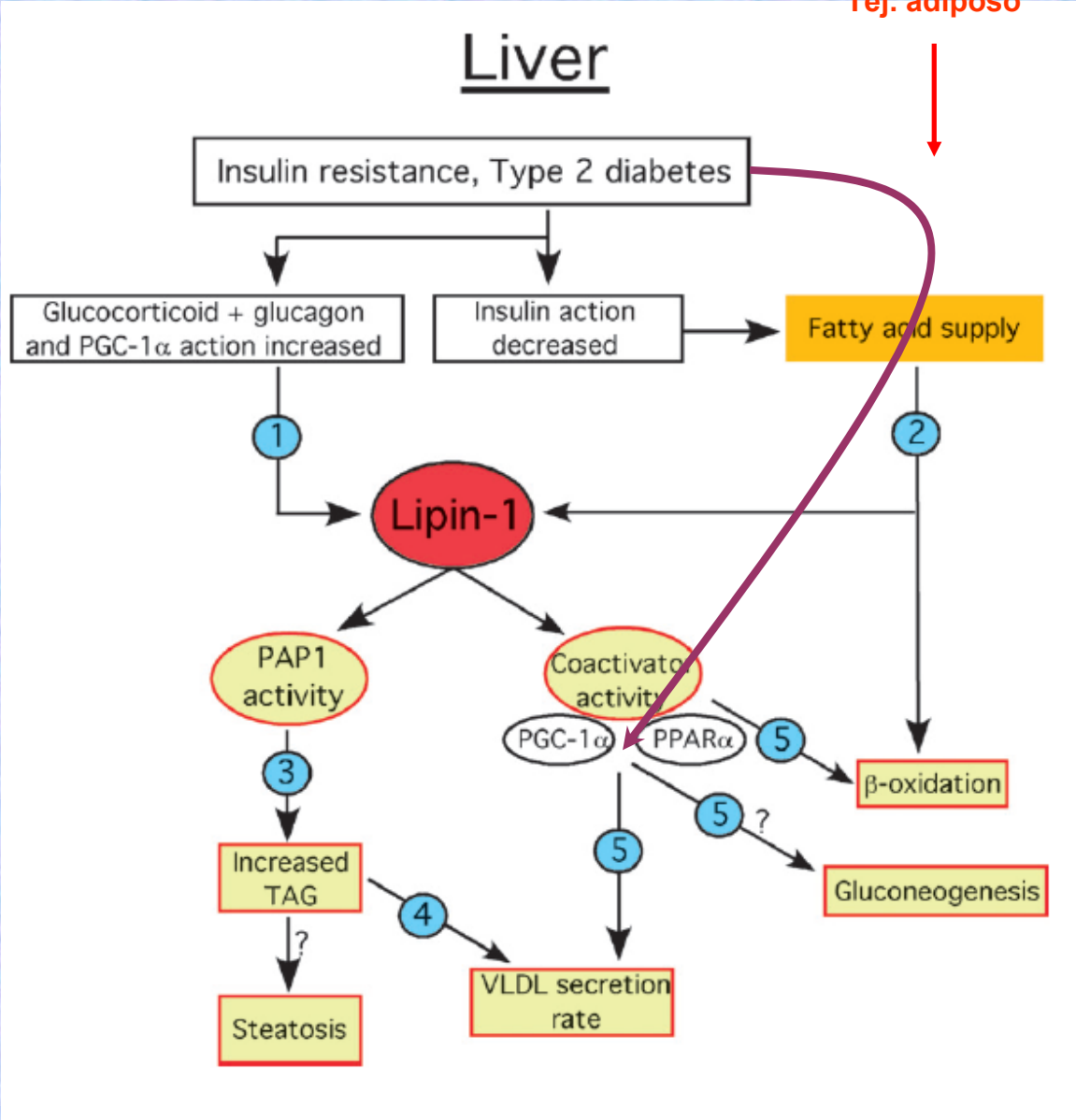
**Figure 2.** Mouse lipin 1 and *S. cerevisiae* Pah1p illustrating phosphorylation sites and domain features. NLIP and CLIP are conserved NH<sub>2</sub>- and COOH- lipin homology domains [4], LHR and NHR are the low-homology and no-homology regions within yeast lipin that have no homology with mammalian lipins [30],  $\beta$  and  $\gamma$  represent alternatively spliced exons, DxDxT is the haloacid dehalogenase domain [3], the nuclear-localization sequence (NLS) [4,17,40,59]–polybasic domain (PBD) is the PA-binding motif in mammalian lipins [40], the SRD mediates the interaction with 14-3-3 proteins [59], and A $\alpha$ H is the amphipathic  $\alpha$ -helix responsible for membrane association [19], residues in red are the amino acid residues mutated to alanine in PAH1-7A [19], CDK are the sites phosphorylated directly by CDK [20], Rap is the lipin 1 residue sensitive to rapamycin [30], and bracketed phosphosites within lipin 1 indicate that either site might be phosphorylated. Figure adapted from Harris *et al.*, 2007.





# Adipose Tissue





**ADIPOGENESIS Y  
REGULACIÓN DEL  
ALMACENAJE LIPÍDICO**



**RESISTENCIA A INSULINA  
DIABETES  
DISLIPEMIAS  
HIPERTENSIÓN  
ENFERMEDADES CORONARIAS**

**Adipocitos**

**Leptina: Promueven saciedad (hipotálamo)**

**Regulan gasto energético**

**Regulan la producción de gsa en hígado**

**Adiponectina: Incrementa captación de gsa muscular**

**Reduce la producción de gsa hepática**

**(1981) MUTACIÓN RECESIVA ESPONTANEA**

**NORMALES AL NACER**

**RETARDO EN EL CRECIMIENTO**

**HÍGADO GRASO (crónico en humano)**

**HIPERTRIGLICERIDEMIA**

**25% MENOS DE PESO CORPORAL**

**NEUROPATÍAS: TEMBLORES, DEFECTOS MOTORES (en algunos humanos)**



***Fld (fatty liver dystrophy )***

**CARECEN DE TEJIDO ADIPOSO**

**ALMACENAN EL DOBLE DE GNO  
EN HÍGADO Y MUSCULO**

**MAYOR SINTESIS DE AG EN  
HIGADO**

**RESISTENCIA A LA INSULINA**

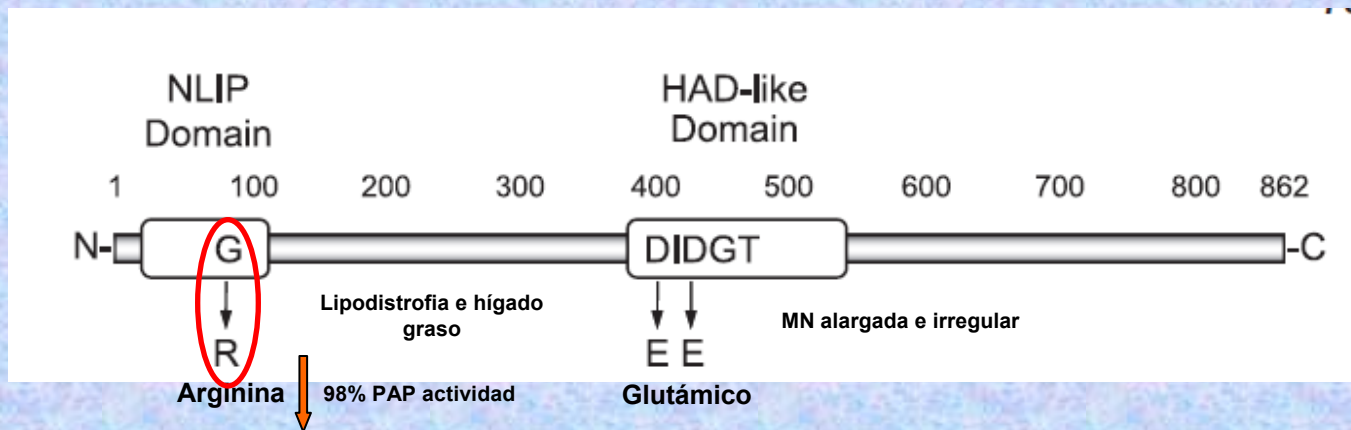


# LIPINAS ??????????

2001, GEN AFECTADO EN *fld*

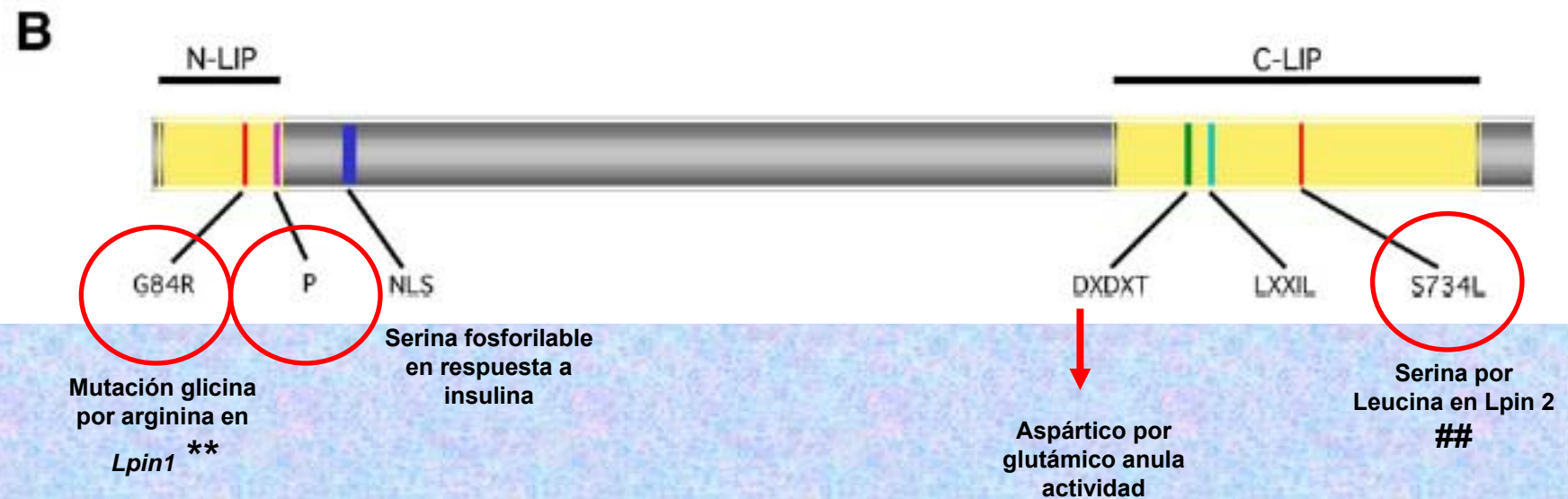
*Lipin1*

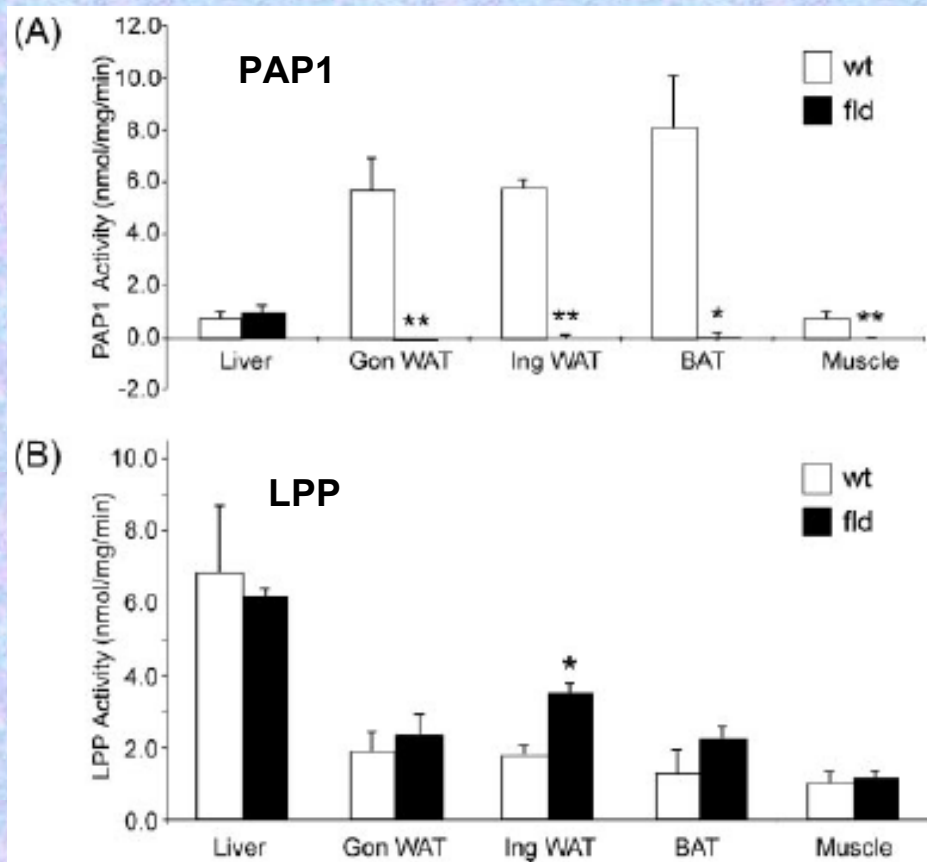
**Células de Schwann (alteraciones y degradación de mielina)**



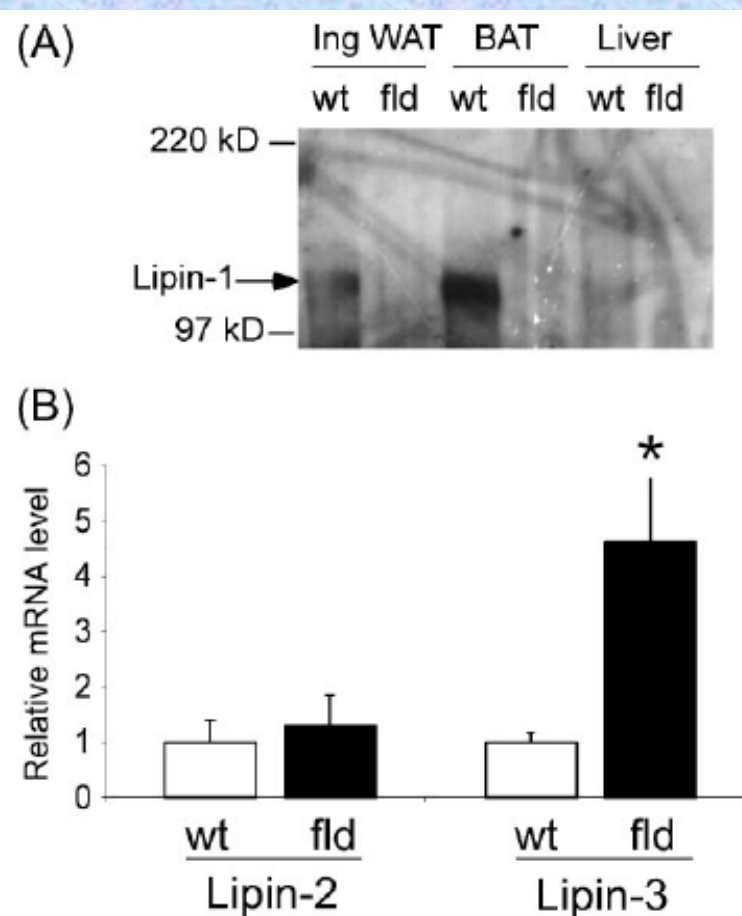
**A**

	Human	Mouse	Tissue Expression	Associated Disease
Lipin-1A	890	891	Muscle, Adipose tissue > Liver, Brain, Other	Lipodystrophy (mouse) **
Lipin-1B	923	924	Liver, Brain > Other	Majeed Syndrome ##
Lipin-2	896	893	Intestine > Liver	???
Lipin-3	851	848		





**FIGURE 1. Absence of PAP1 activity in adipose tissue and muscle of lipin-deficient *fld* mice.** Tissues prepared from *fld* and wild-type (*wt*) littermates were assayed for (A)  $Mg^{2+}$ -dependent PAP1 activity and (B)  $Mg^{2+}$ -independent LPP1 activity. Activity is normalized to protein content of tissue extracts and represents the mean values  $\pm$  S.D. for tissues from three mice of each genotype. *Gon WAT*, gonadal white adipose tissue; *Ing WAT*, inguinal subcutaneous white adipose tissue; *BAT*, interscapular brown adipose tissue. \*, different from corresponding *wt* tissue at  $p < 0.005$ ; \*\*,  $p < 0.001$ .



**FIGURE 2. Absence of lipin-1 protein and enhanced lipin-3 expression levels in liver of *fld* mice.** A, Western blot of lipin-1 present in liver, inguinal white adipose (*Ing WAT*), and brown adipose tissue (*BAT*) of wild-type (*wt*) and *fld* mice. Each lane contains an equal protein load. B, hepatic lipin-2 and lipin-3 mRNA levels in wild-type and *fld* mice determined by real-time RT-PCR.  $n = 5$  mice for each genotype; \*,  $p < 0.005$  versus wild-type.



## **\*Deficiencia de Lipina-1 falla en acumular TAG**

**\*Lip1A en preadipocitos (nuclear) induce PPAR  $\gamma$  y Lip 1B en maduros (citosol) induce genes de AG sintasa, esteroil CoA desaturasa y DAG aciltransferasa**

**\**fld* afectan depósitos de tej. adiposo**

**\*Mayor expresión de enzima promueve obesidad**

**\*Humanos obesos disminución de la expresión de Lip.-1 en tej. adiposo**

## **Ratones transgénicos (Lip.1)**

**\*Aumento de TAG y expresión de genes lipogénicos**

**\*Bajos niveles de gsa e Insulina**

**\*Sensibles a Insulina:**

**???????????**

**1. Lip.-1 promueve la expresión del transportador de gsa (GLUT4) y aumento de captación de gsa**

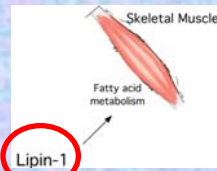
**2. Favorece almacenaje de TAG en tejido adiposo evitando el almacenaje ectópico (músculo) que contribuye a la lipotoxicidad y a la resistencia a la Insulina**

**(aumento de la expresión de LIP.1 en adipocitos, menor contenido lipídico en miocitos)**

**3. Promueva oxidación de AG**

**(aumento de mensajero de Lip se correlaciona con expresión de PPAR $\alpha$  y Acil-CoA deshidrogenasa)**





**\*Sobreexpresión de lipina altera balance energético**

**\*Obesos con dieta normal (70%) e hiperobesos con dieta grasa**

**\*Reduce consumo energético (15%) y disminución en la oxidación de ácidos grasos**

**\*Aumento masa de tejido adiposo**

**\*Resistencia a Insulina**

**\*Deficiencia en lipina aumento consumo energético**

**\*Ratones fld pueden normalizar su fenotipo reconstituyendo la expresión de la proteína en músculo**

**\*Ejercicio aumenta la expresión y coincide con la expresión de genes oxidativos**



**\*Sobreexpresión de lipina en ayuno**

(Metabólica: síntesis de TAG en rpta. a alta entrada de AG)

Factor de transcripción: coactivador de genes de oxidación de ácidos grasos)

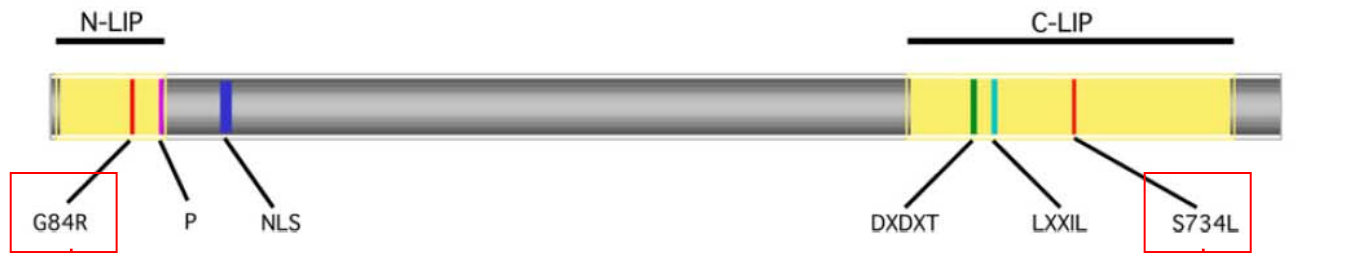
**\*Regula la secreción de TAG en VLDL**

**\*Hepatocitos de *fld* alta secreción de VLDL-TAG y altos niveles de estearoil CoA-desaturasa (regulador de la secreción de VLDL)**

**A**

	Human	Mouse	Tissue Expression	Associated Disease
Lipin-1A	890	891	Muscle, Adipose tissue > Liver, Brain, Other	Lipodystrophy (mouse)
Lipin-1B	923	924		
Lipin-2	896	893	Liver, Brain > Other	Majeed Syndrome
Lipin-3	851	848	Intestine > Liver	???

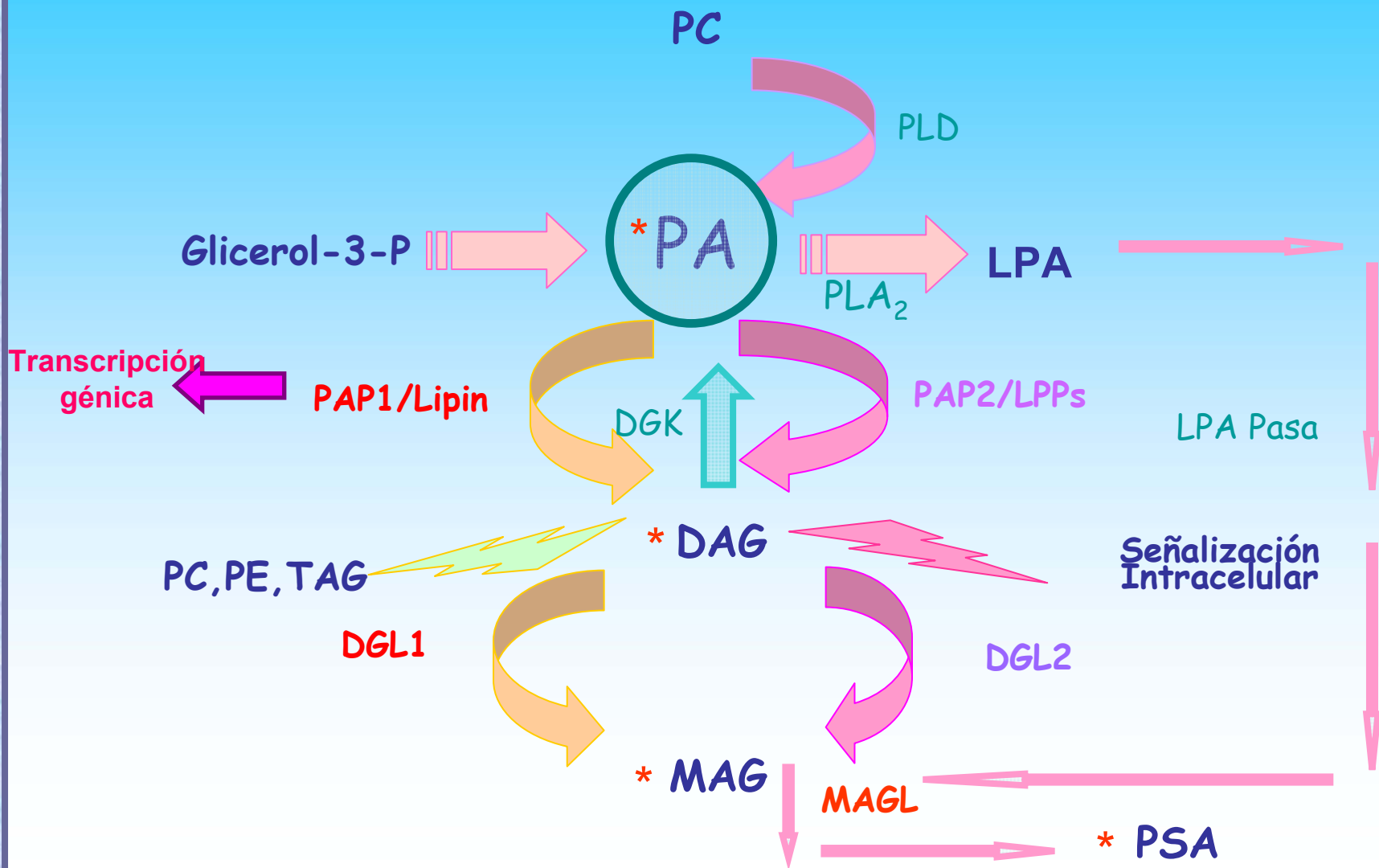
Inflamatorio  
Osteomielitis  
Anemia

**B**

Glicina por Arginina

Serina por Leucina  
(anula la actividad,  
no la asociación a  
RE)

# METABOLIZACIÓN DE ÁCIDO FOSFATÍDICO POR FOSFATIDATO FOSFOHIDROLASAS







MUCHAS GRACIAS !!!