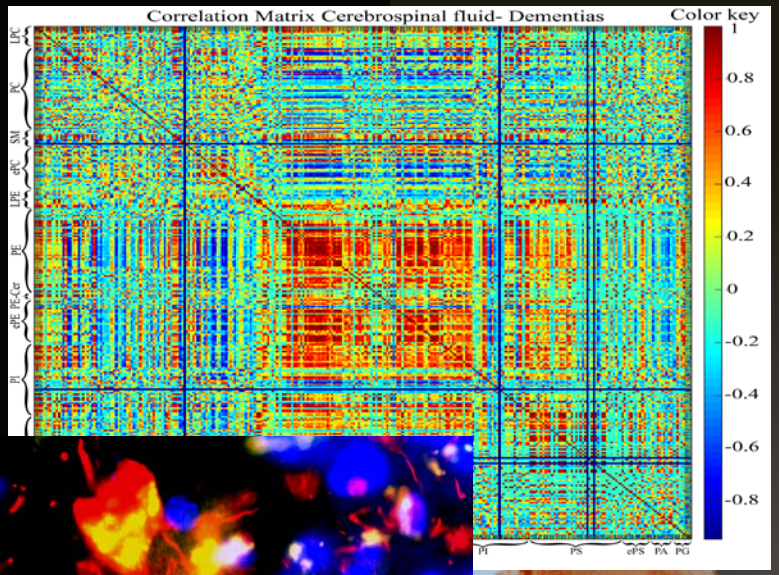

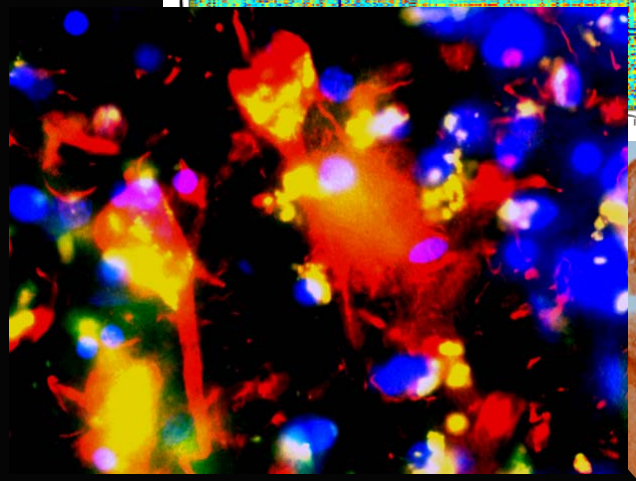

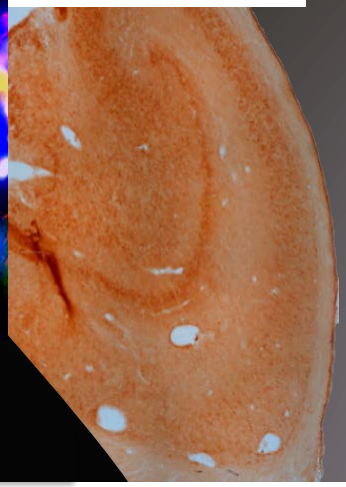

BACE 1 involved in taupathogenesis: A phospholipidic approach

GLORIA PATRICIA CARDONA-GÓMEZ Ph.D.

Cellular and Molecular Neurobiology Area

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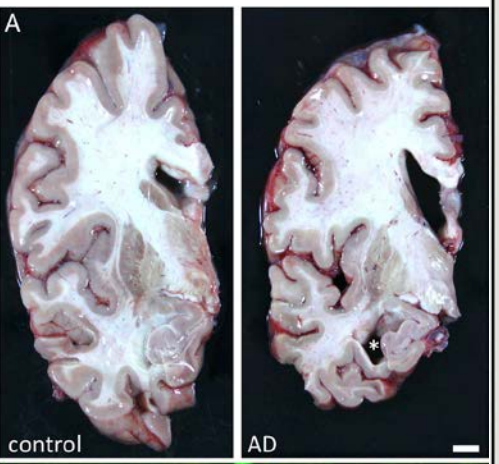
GNA
Grupo de Neurociencias\Universidad de Antioquia

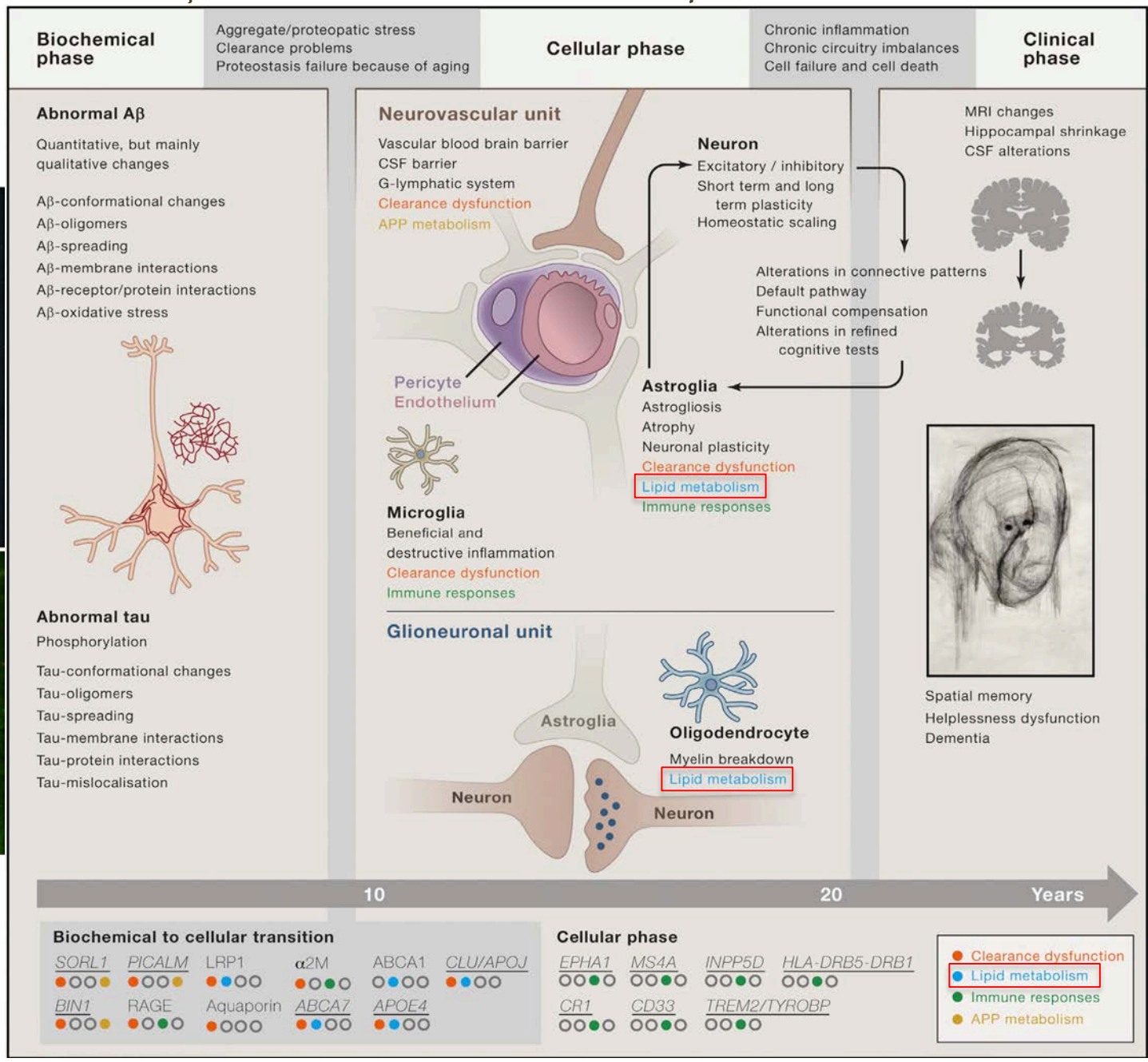
GLOBAL HEALTH CONFERENCE

May 7-9, 2019

Innovative Results. Global Solutions

The biochemical, cellular and clinical phases of AD- Focused in consequences not in the causes

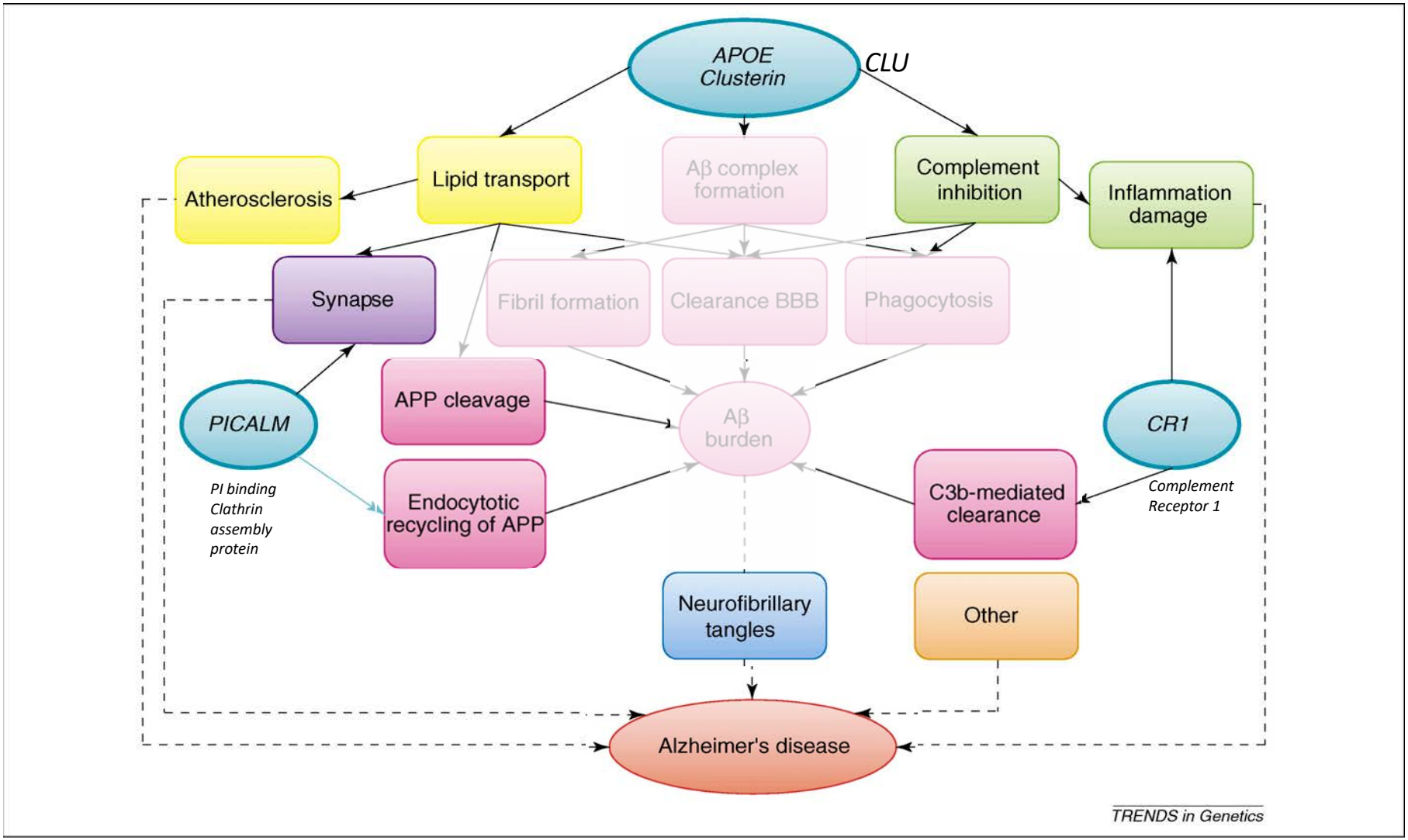




Spires-Jones and T Hyman. Neuron 82, May 21, 2014

De Strooper B and Karran E Cell 164, 2016

Genome wide association (strong) in AD- lipid role



Support existing hypotheses about the amyloid, lipid, chaperone and chronic inflammatory Pathways in AD pathogenesis. (*Sleeger, Trends in genetics 2009, 26:2*)

What is the implication of phospholipids in cell physiology?

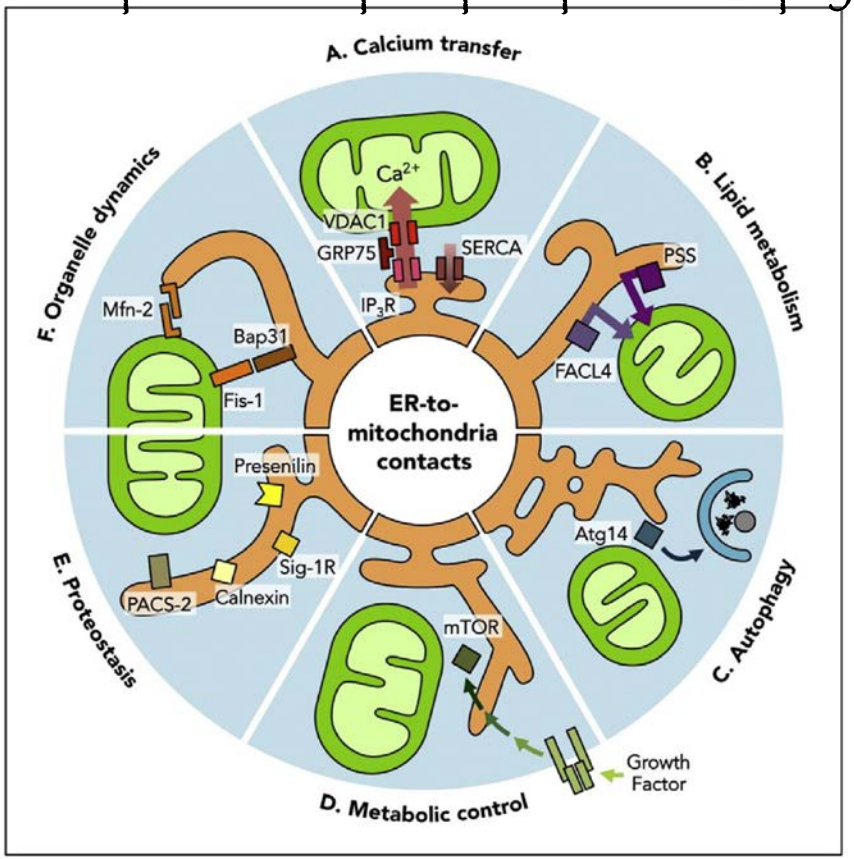


Fig. 2. ER–mitochondria contacts and cell physiology. A, Direct Ca^{2+} transfer occurs between ER and mitochondria via IP_3R and VDAC channels coupl

C. López-Crisosto et al. / Biochimica et Biophysica Acta 1852 (2015) 2096–2105

Table 2: Phospholipid composition of rat liver organelles (% total phospholipids)[a]

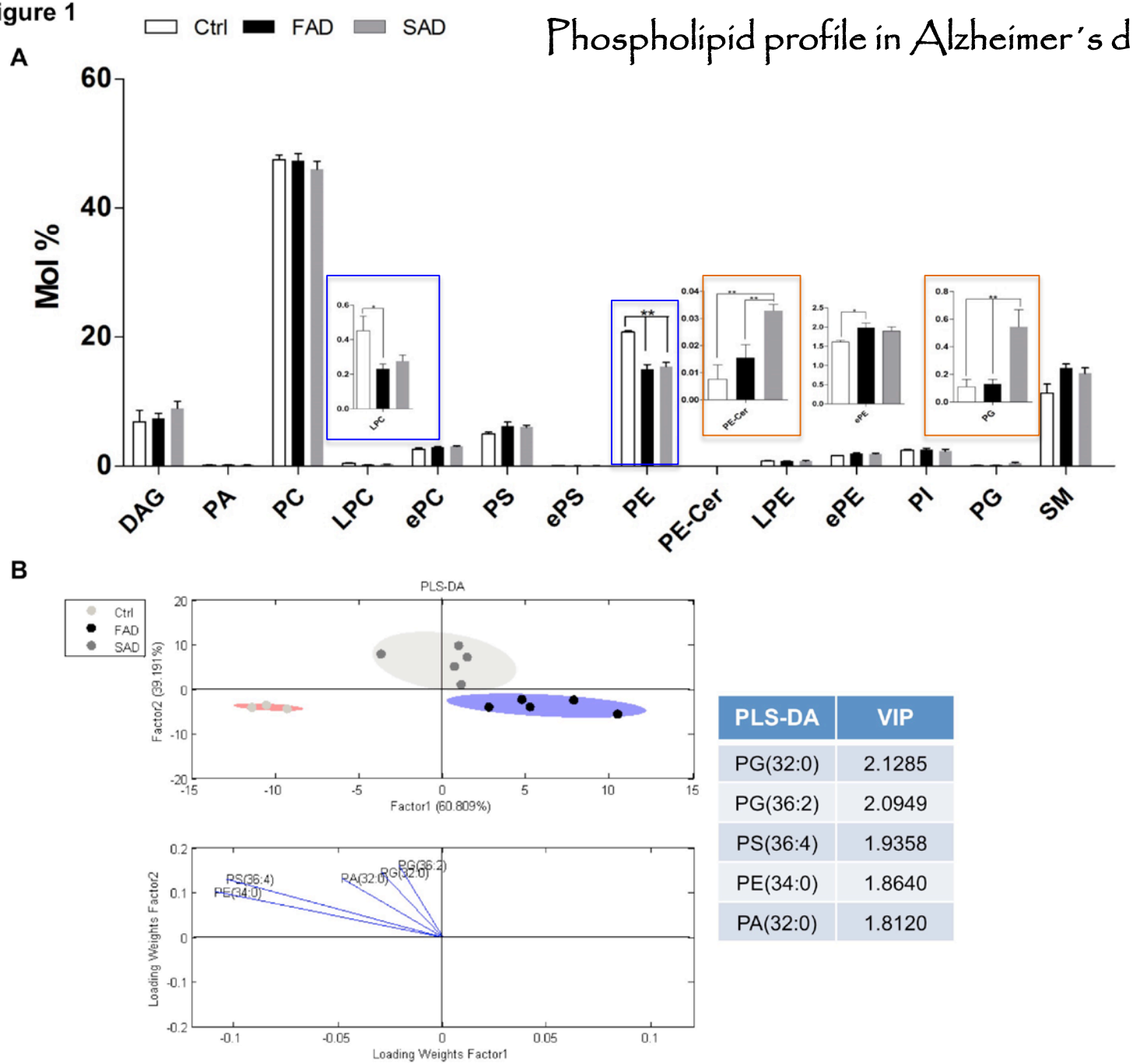
	Mitochondria						
Lipid	ER	Inner	Outer	Lysosomes	Nuclei	Golgi	Plasma membrane
PC	57	41	49	42	52	45	43
PE	21	38	34	21	25	17	21
SM	4	2	2	16	6	12	23
PI	9	2	9	6	4	9	7
PS	4	1	1	1	6	4	4
CL	0	16	5	0	0	0	0
Other	5	<1	<1	14	7	13	2
Chol/PL molar ratio	0.07	0.06		0.49		0.15	0.76

Approximate phospholipid content is given as % total lipid phosphorus.
Chol, cholesterol.
[a]Data are averaged from several sources.

Vance. Traffic 2015; 16: 1–18

Phospholipid profile in Alzheimer´s disease

Figure 1



PLS-DA	VIP
PG(32:0)	2.1285
PG(36:2)	2.0949
PS(36:4)	1.9358
PE(34:0)	1.8640
PA(32:0)	1.8120

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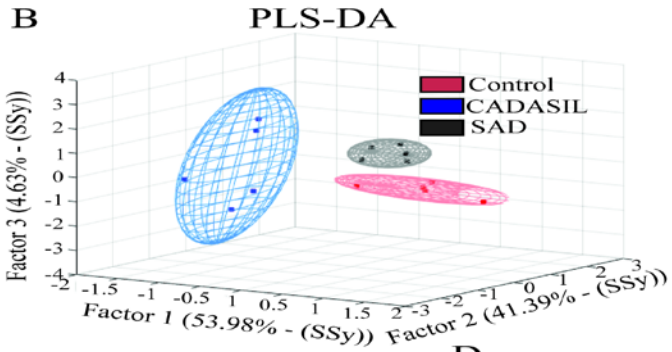
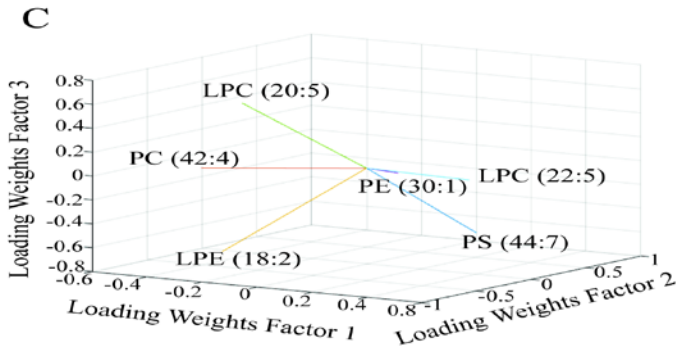
Villamil-Ortiz J et al. 2018 Journal of Alzheimer´s Disease. 61(1):209-219

Phospholipidic correlation in Frontal cortex of dementias

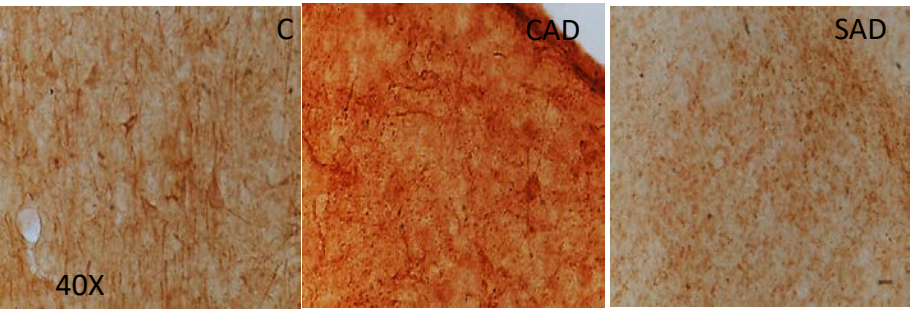


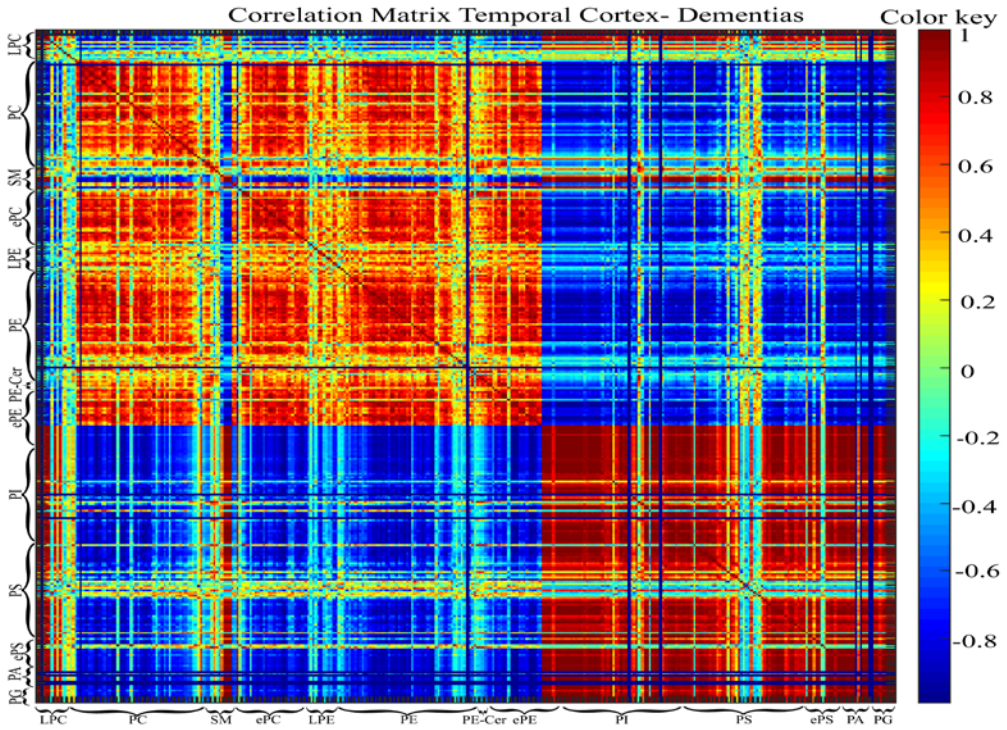


D

Species	sMC	VIP
PS (44:7)	13.7	1.0699
LPE (18:2)	9.20	1.0052
PC (42:4)	7.21	1.0104
PE (30:1)	5.84	0.9959
LPC (20:5)	5.02	0.9674
LPC (22:5)	4.85	0.9469

MAP2 L I-III





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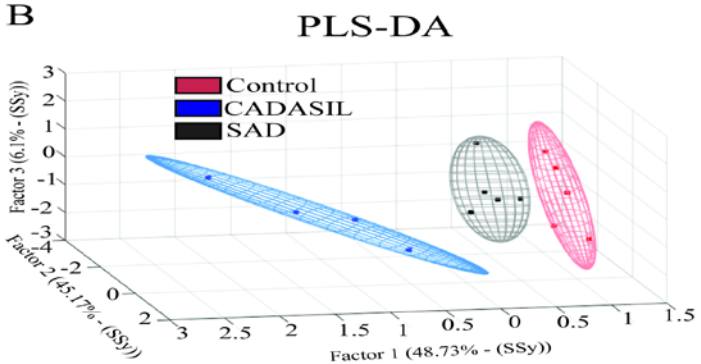
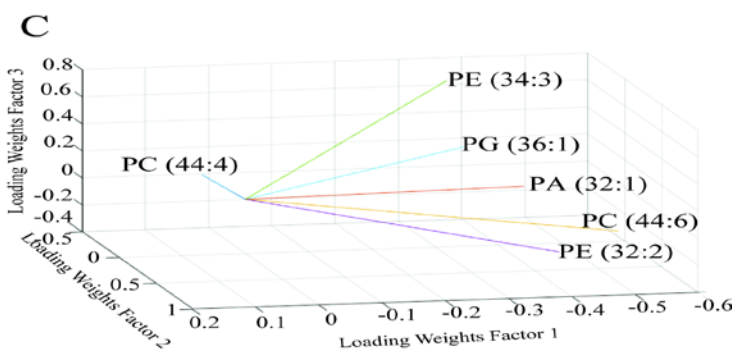
Sabogal-Guaqueta et al. In preparation

Phospholipidic correlation in white matter of dementias



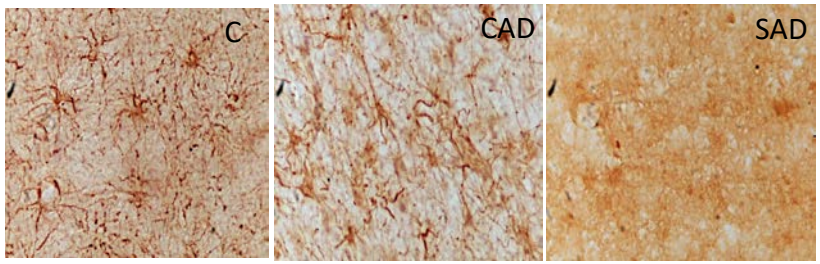


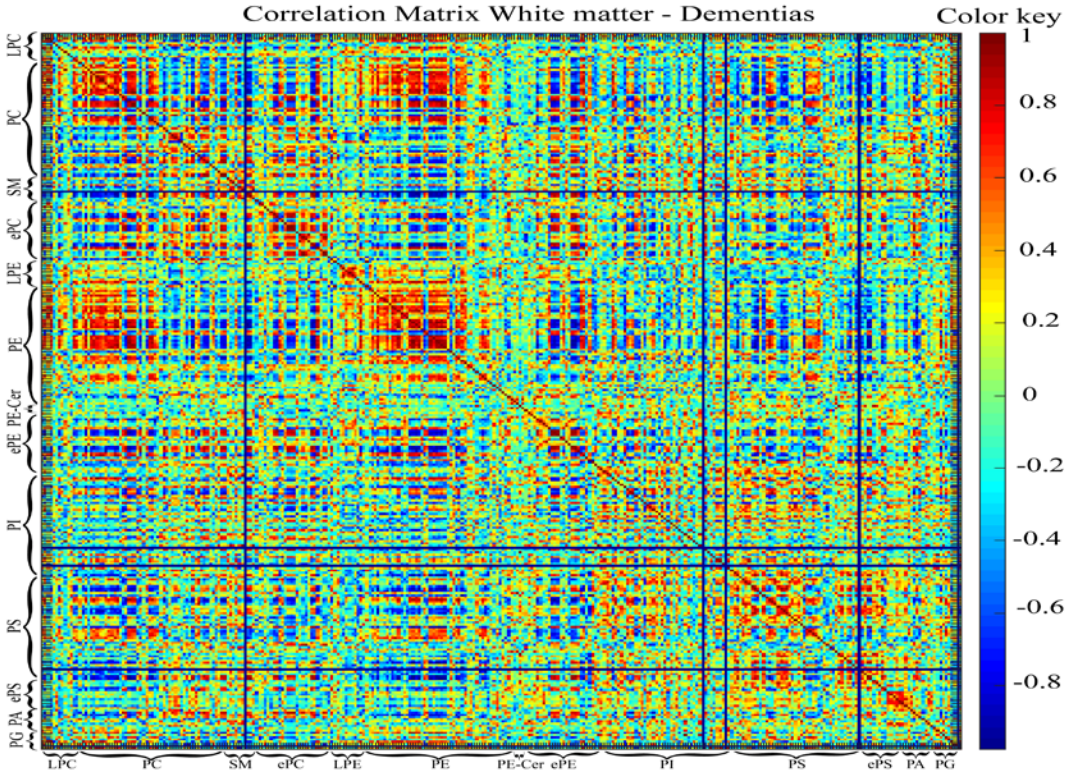
D

Species	sMC	VIP
PE (32:2)	13.79	0.9672
PC (44:6)	8.67	0.9954
PC (44:4)	6.83	1.1456
PA (32:1)	5.83	1.0849
PE (34:3)	4.05	0.9175
PG (36:1)	3.41	0.8617

16:1 palmitoleic Acid
22:6 DHA

GFAP L VI-WM





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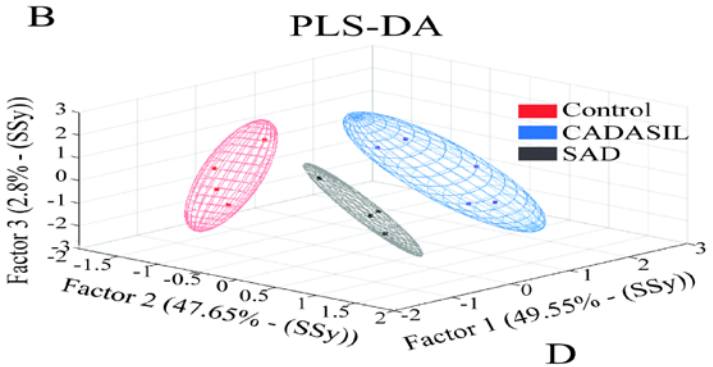
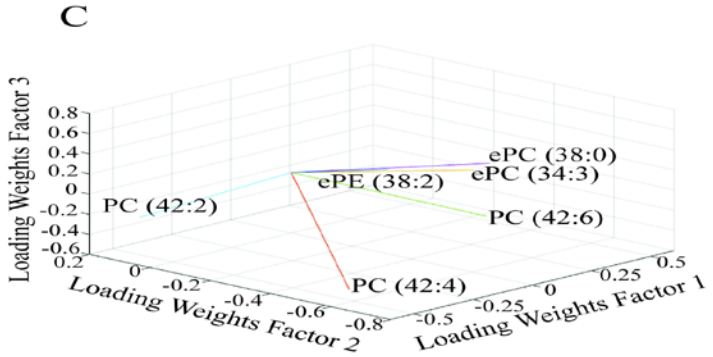
Phospholipidic correlation in CSF of dementias

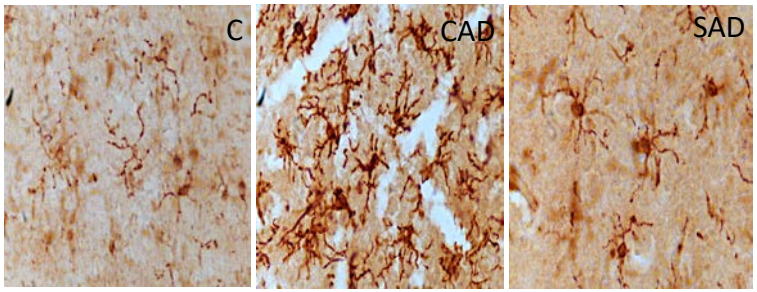


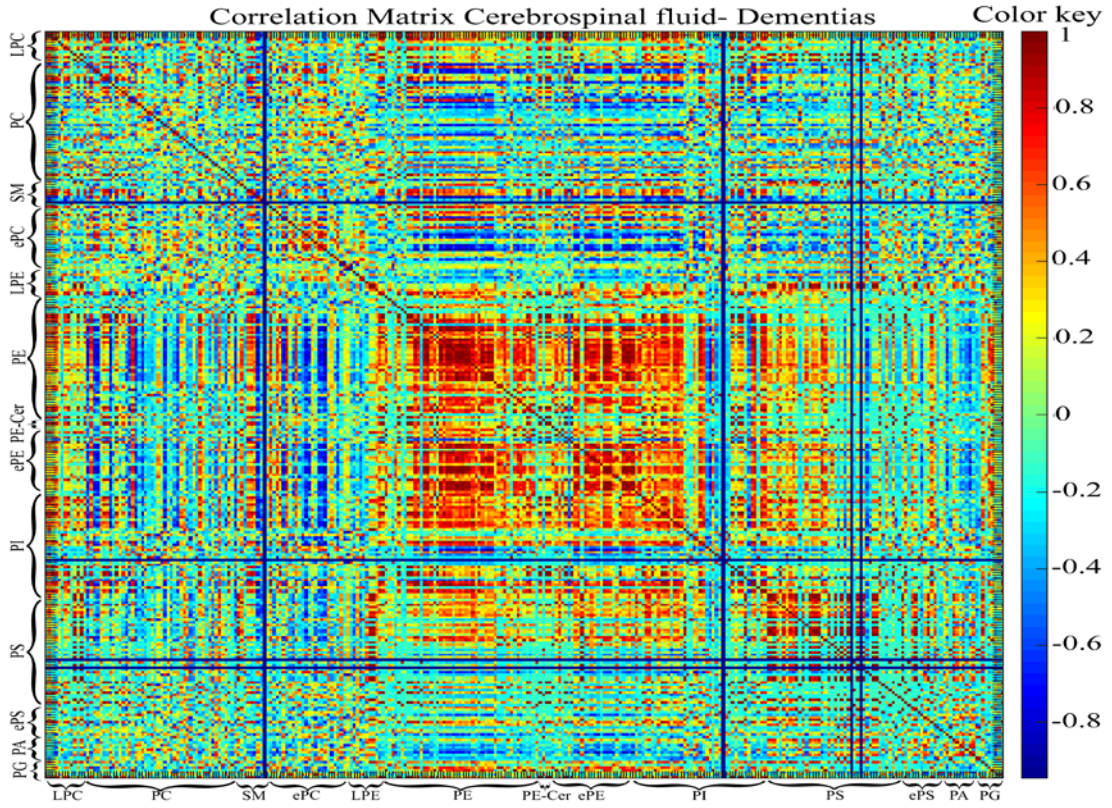


D

Species	sMC	VIP
ePE (38:2)	4.70	1.2240
ePC (34:3)	3.60	0.8937
PC (42:2)	3.08	0.7849
PC (42:4)	3.00	1.1651
ePC (38:0)	2.60	0.9769
PC (42:6)	1.99	0.8805

Iba1- L I-III





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Where is Phosphatydilethanolamine?

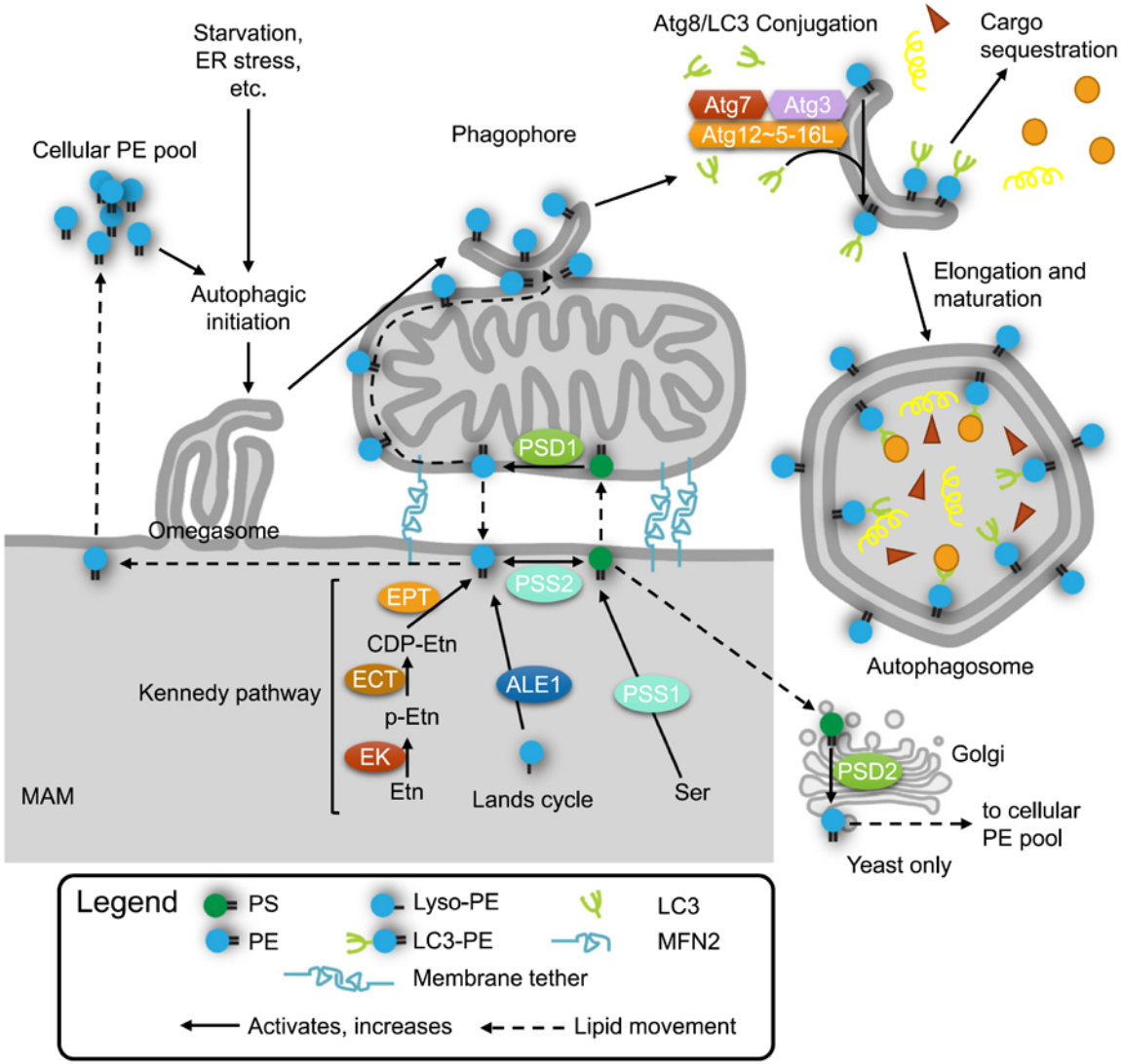
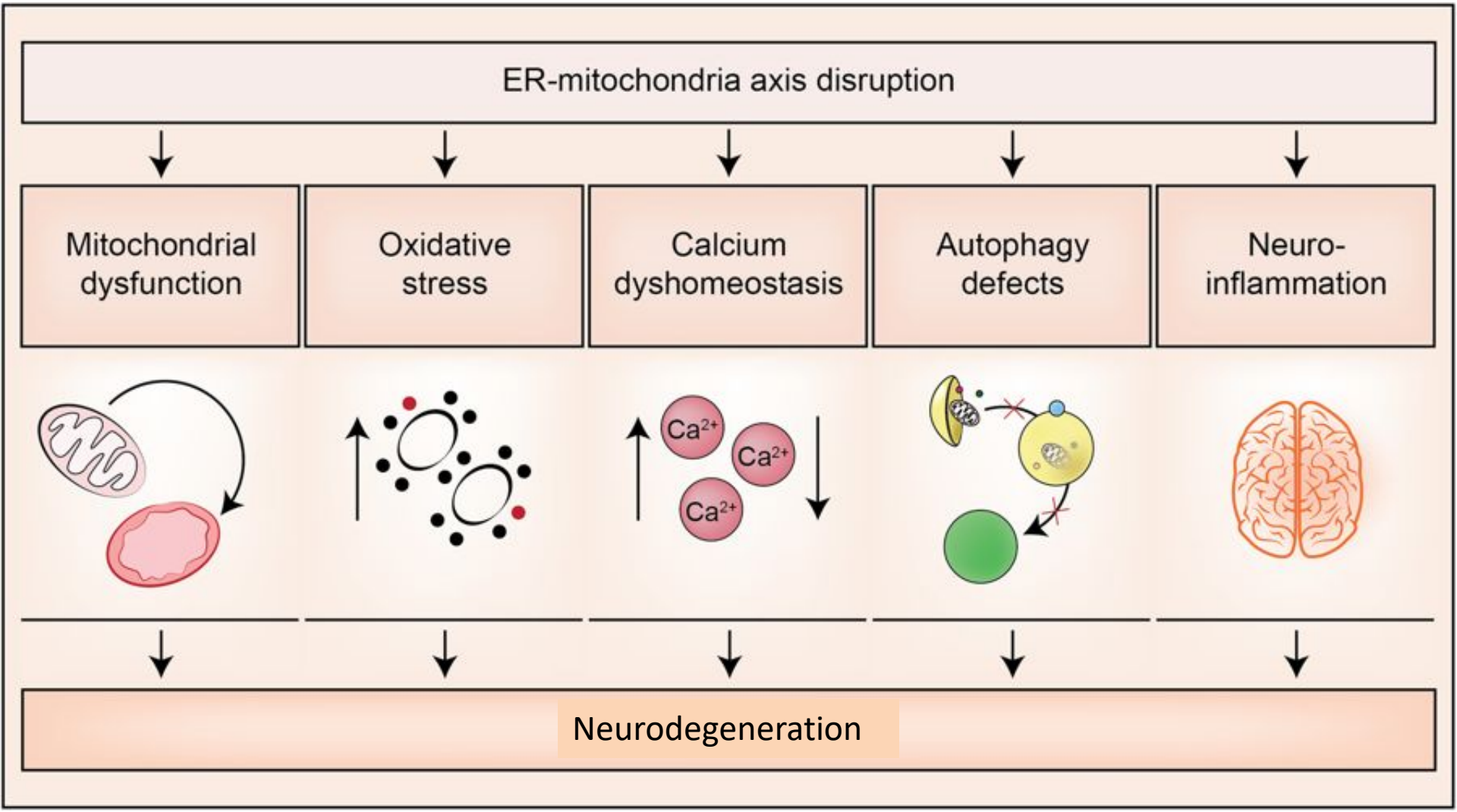


Fig. 3. Mitochondrial phosphatidylethanolamine (PE) is required for autophagy. PE is critical for the initiation of autophagy and elongation of autophagosomes. PE is synthesized through 4 pathways (5 for yeast): the CDP-ethanolamine/Kennedy pathway; base exchange by phosphatidylserine synthase 2 (PSS2); re-acylation of lyso-PE via the Lands cycle (ALE1/LPLAT2); decarboxylation of phosphatidylserine (PS) by phosphatidylserine decarboxylase in the mitochondria (PSD1) or in the Golgi (PSD2, yeast only). PS is synthesized by PSS1, which catalyzes a base exchange with phosphatidylcholine (not pictured). The mitochondrial PSD1 and Kennedy pathway are the major sources of cellular PE. The cellular PE pool is divided between PE as a major component of most lipid bilayers, glycosylphosphatidylinositol (GPI) anchor synthesis and Atg8/LC3 lipidation. When cellular PE is limited, GPI anchor synthesis and Atg8/LC3 lipidation compete for substrates. Atg8/LC3 lipidation occurs on the phagophore, where Atg7 (E1), Atg3 (E2), and the Atg5 complex (Atg12-Atg5-Atg16L1) (E3-like) covalently link Atg8/LC3 onto PE, forming LC3-II. LC3-II is required selective autophagy and links autophagy receptors with an LC3-interacting region to the inner surface of the autophagosome. Knockdown of PSD1 significantly impairs autophagy and LC3 lipidation, indicating the importance of mitochondria-derived PE in autophagy over other sources. Exogenous ethanolamine (Etn) and PE can restore autophagy in PSD1 knockouts, and can stimulate autophagy and increase longevity in wild-type cells.

Common dyshomeostasis involving phospholipids



Cell Death & Disease **volume 9**, 337 (2018)

BACE1 processing in a lipidic environment

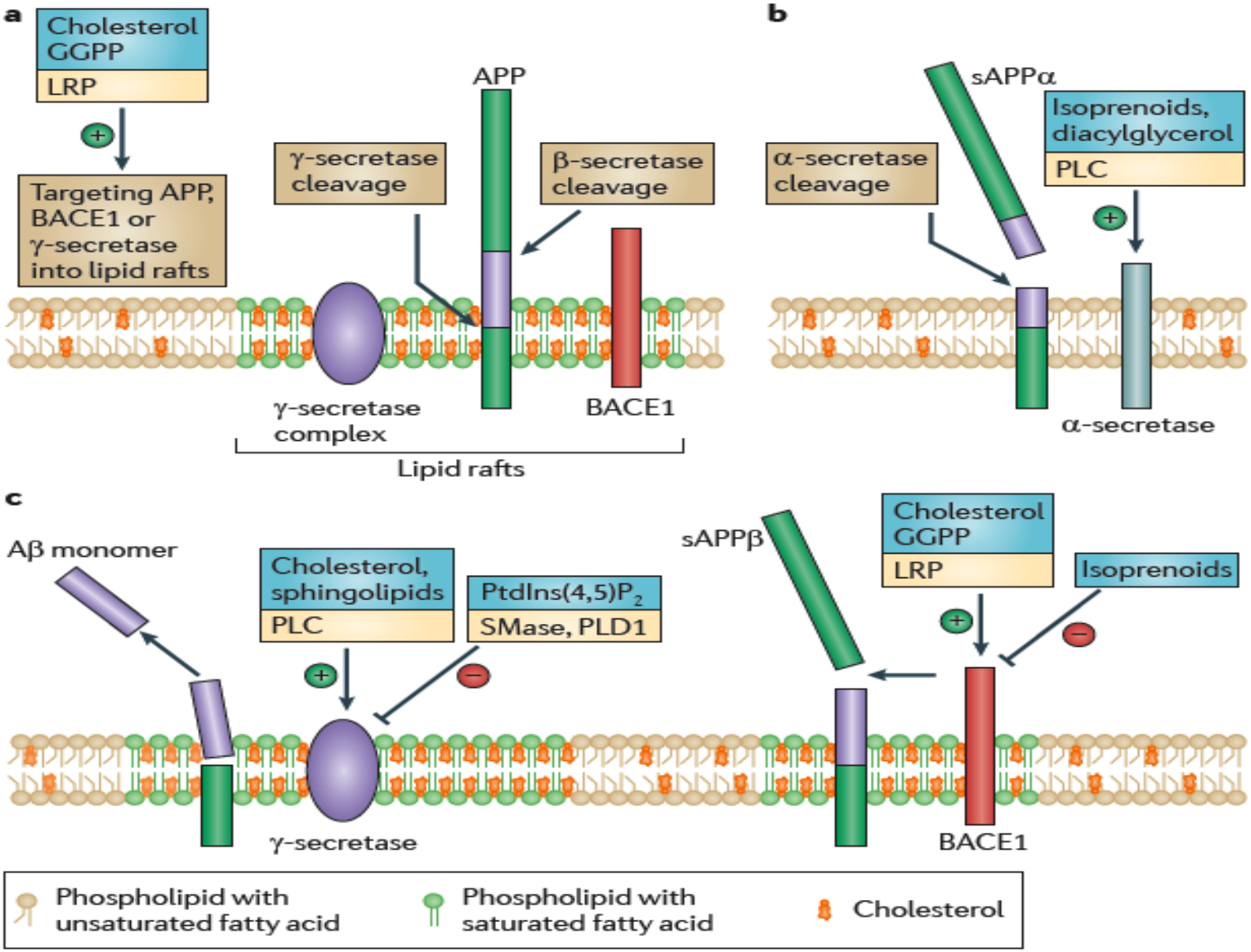
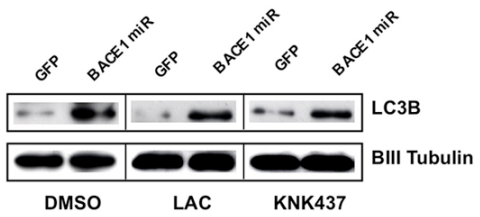
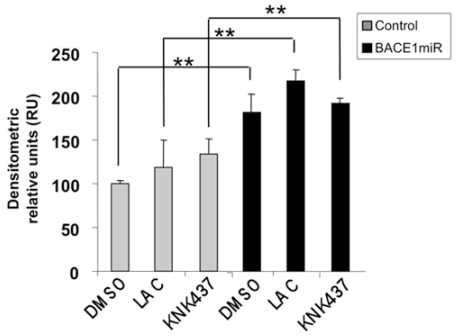
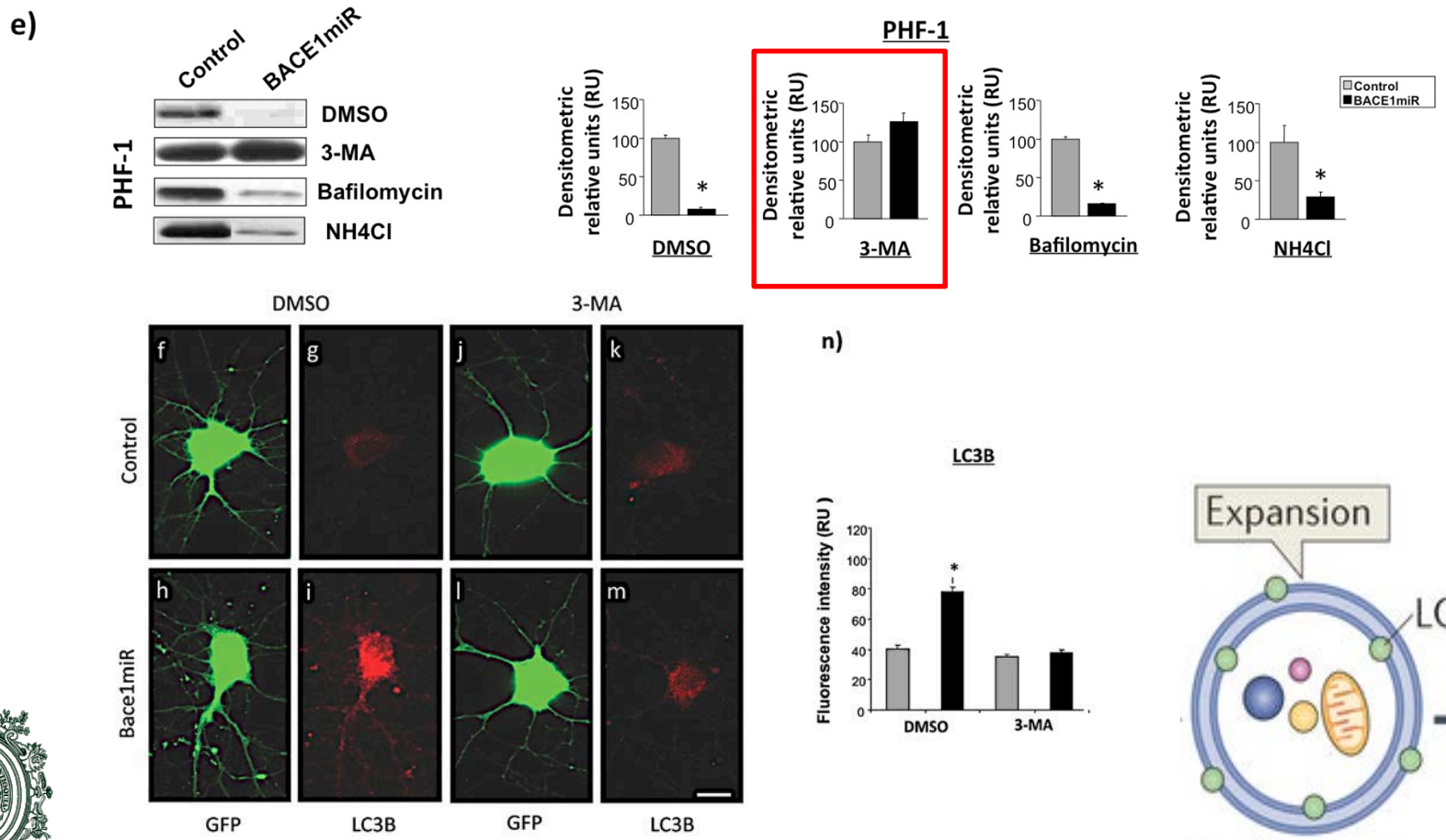


Figure 2 | **Modulation of proteolytic processing of amyloid precursor protein (APP) by lipids.** Several lipids (shown in blue boxes) and lipid metabolizing proteins (shown in

Inhibitor of PE lipidation (3-MA) reversed the effect of shBACE1 on phosphorylated tau clearance







Nature Reviews | Molecular Cell Biology

Piedrahita D et al. Front Cell Neurosci. 2016 Jan 8;9:498. doi: 10.3389/fncel.2015.00498.

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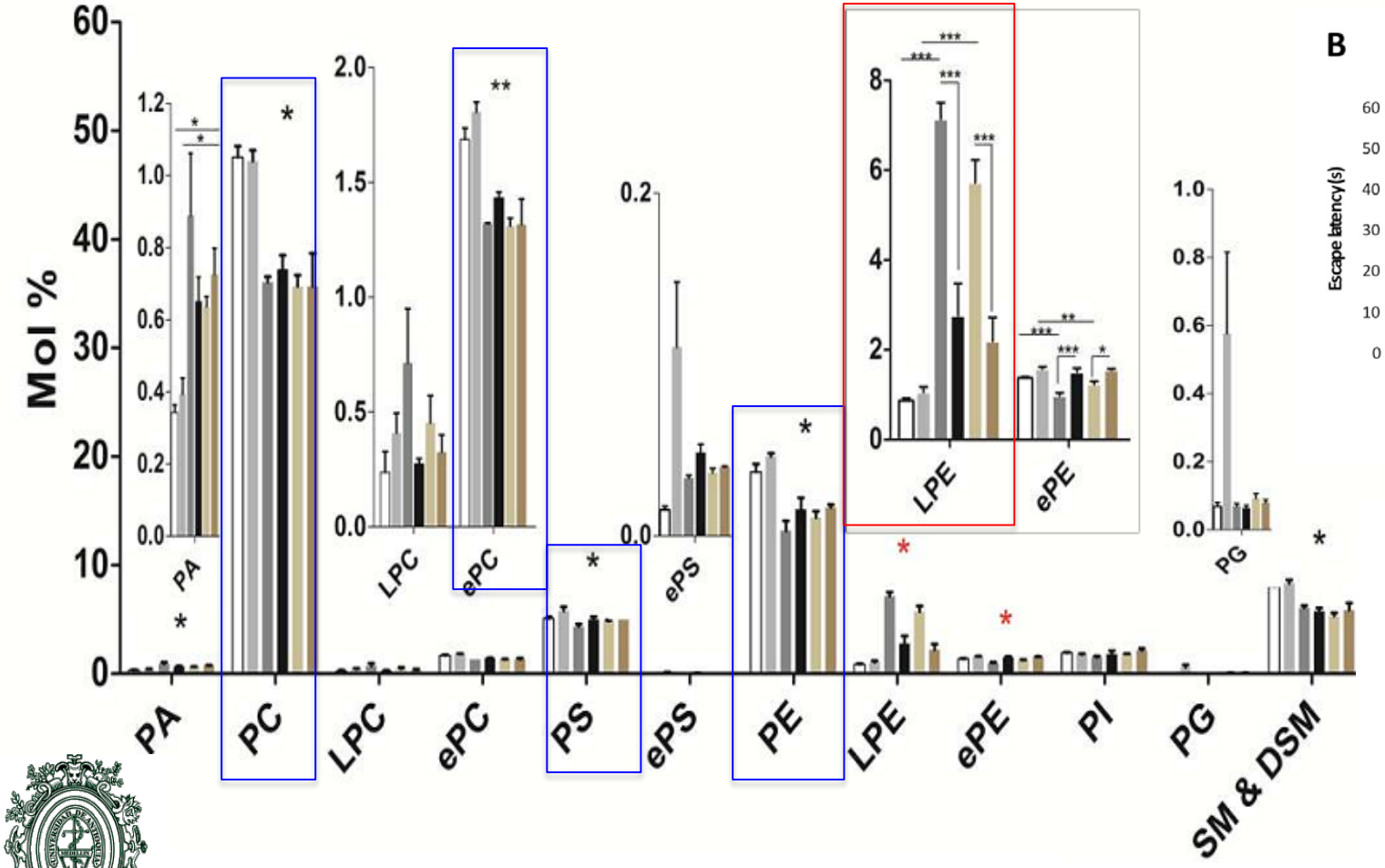
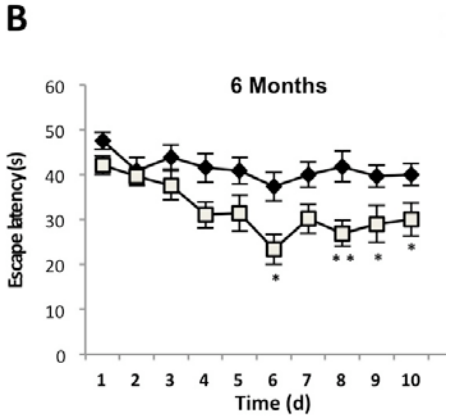
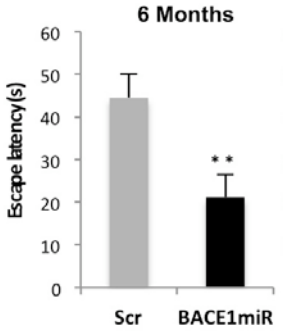
Lipid profile is altered in the hippocampus of 3xTg-AD mice

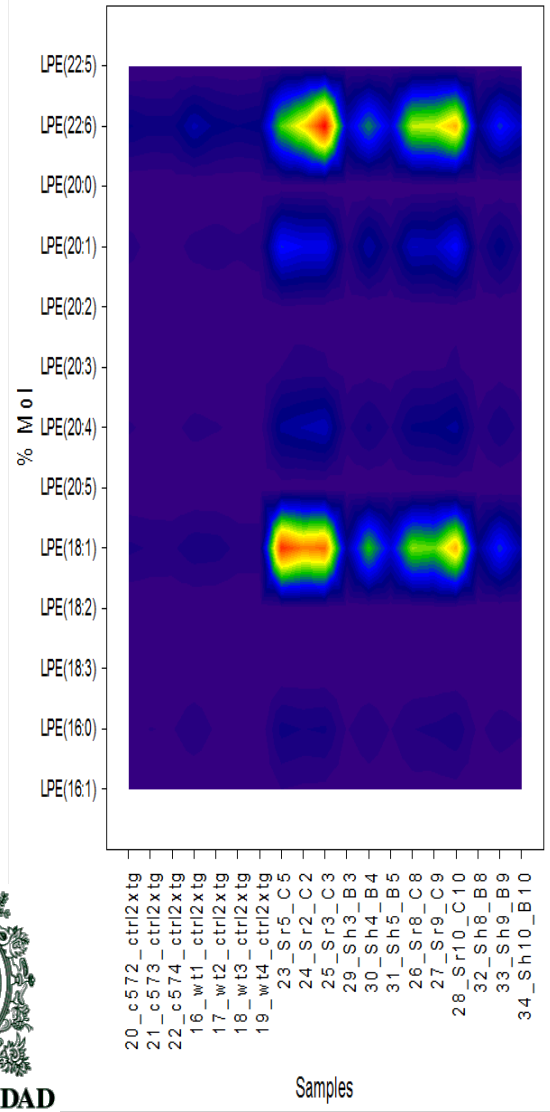


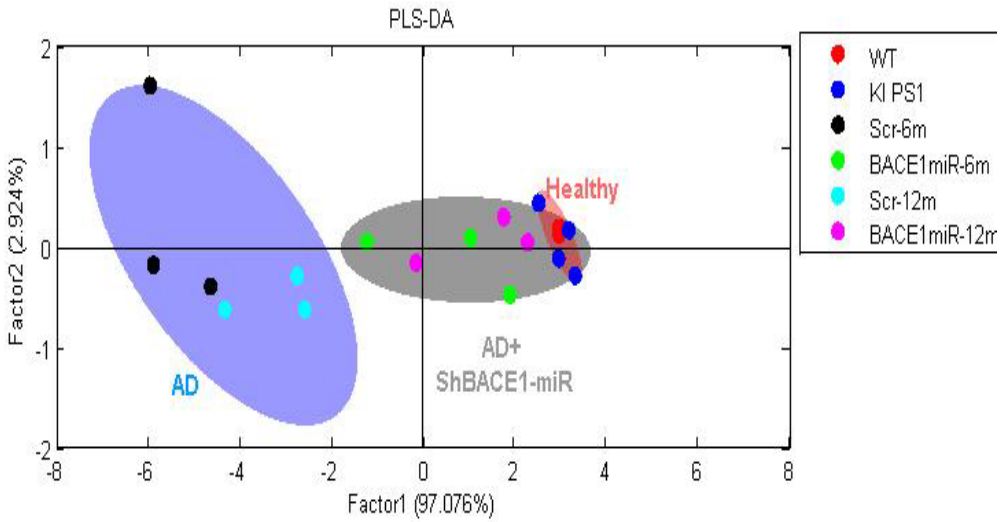




Villamil-Ortiz J et al. *Frontiers Cell Neurosci* 2016. 10:260.

shBACE1-miR restores the basal levels of LPE at 6 and 12 months post-treatment in 3xTgAD mice





PLS-DA	VIP
LPE(18:1)	1.2029
LPE(22:6)	1.0157
LPE(20:1)	0.4374
LPE(20:4)	0.2626
LPE(16:0)	0.1153

18:1 Oleic Acid
22:6 DHA

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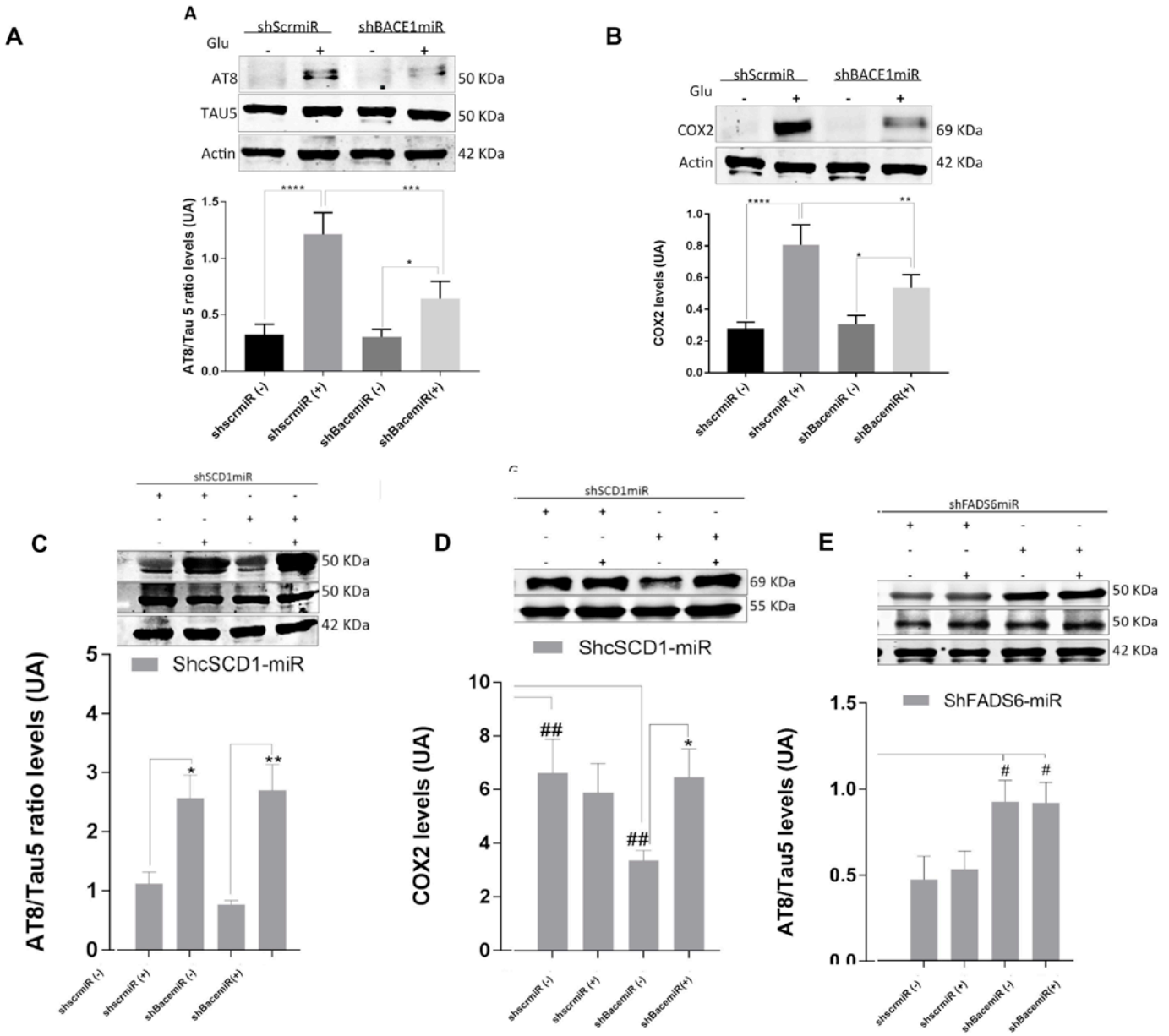
Villamil-Ortiz J et al. *Frontiers Cell Neurosci* 2016. 10:260.

Silencing of desaturases block the anti-inflammatory effect of shBACE1



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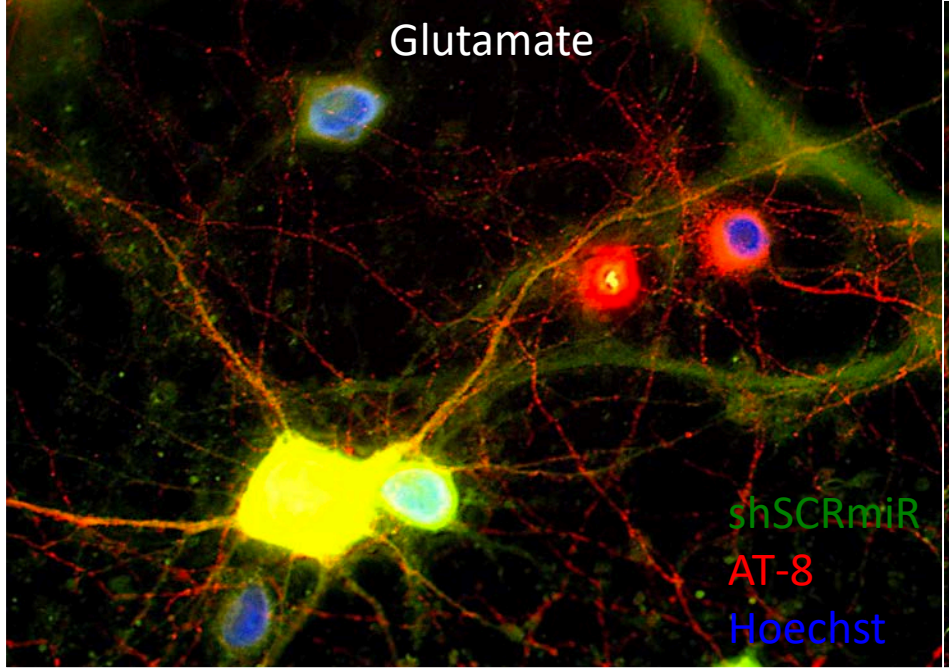
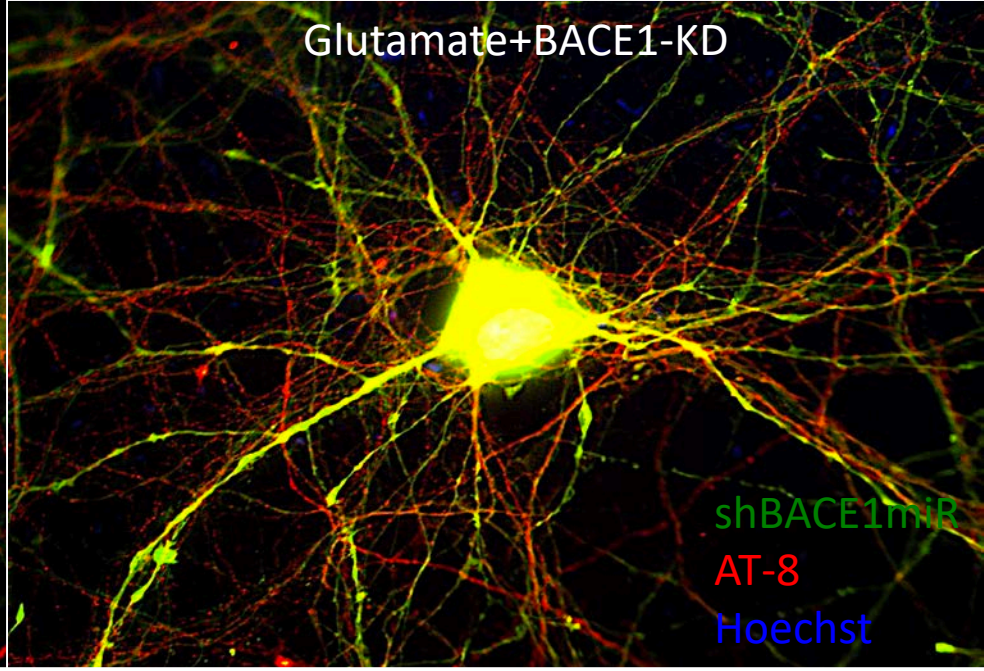
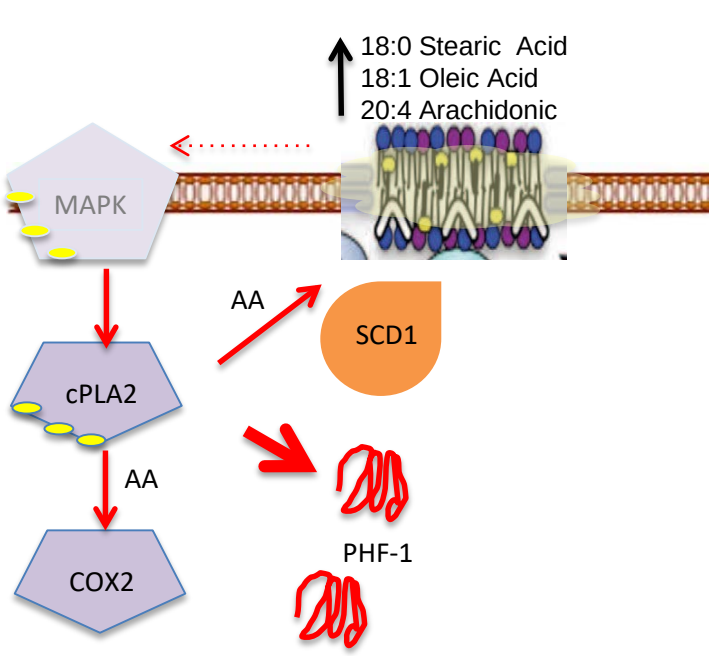
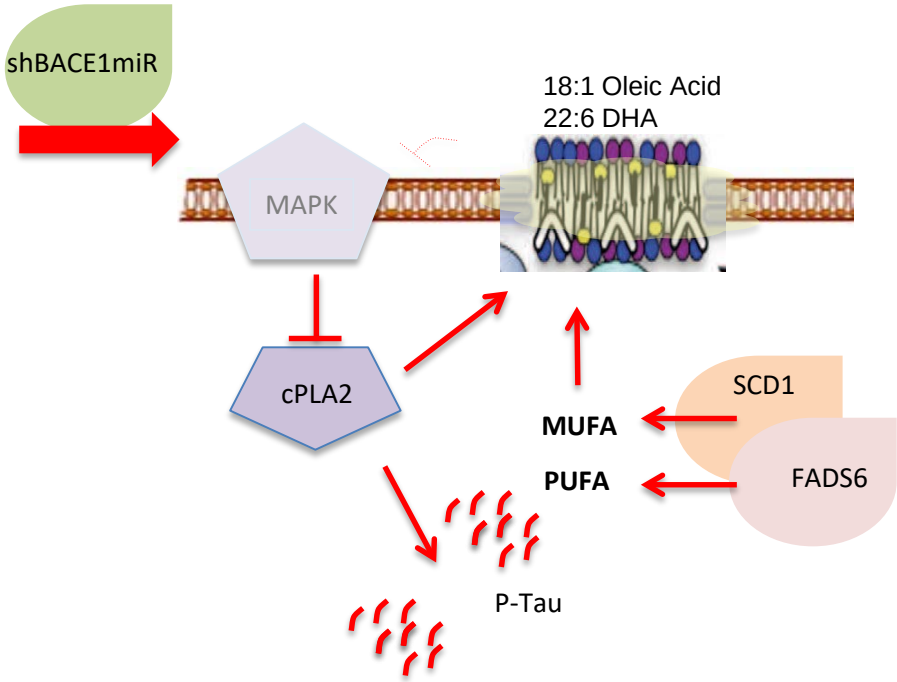
Villamil-Ortiz J et al. BBA 2018


Glutamate
shSCRmiR
AT-8
Hoechst


Glutamate+BACE1-KD
shBACE1miR
AT-8
Hoechst


18:0 Stearic Acid
18:1 Oleic Acid
20:4 Arachidonic
MAPK
AA
SCD1
cPLA2
AA
COX2
PHF-1


shBACE1miR
18:1 Oleic Acid
22:6 DHA
MAPK
cPLA2
SCD1
MUFA
PUFA
FADS6
P-Tau

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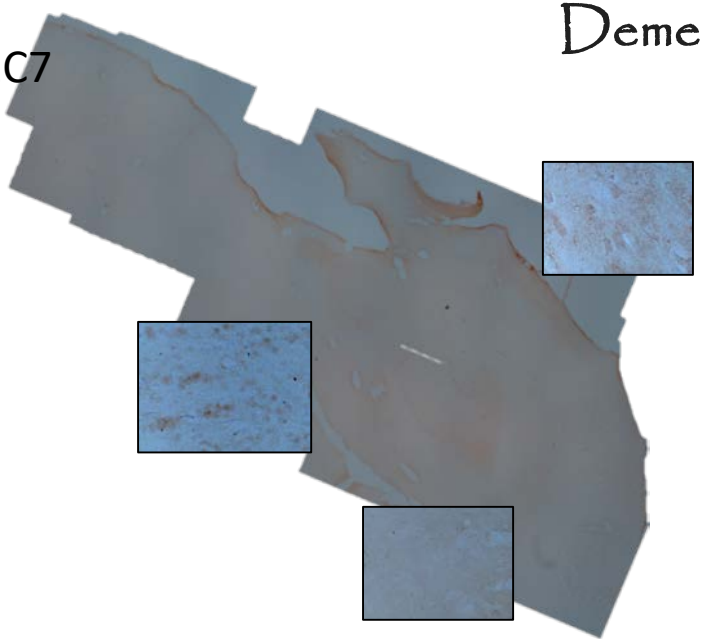
SCD1 are increased in the hippocampus of different types of Dementias in humans

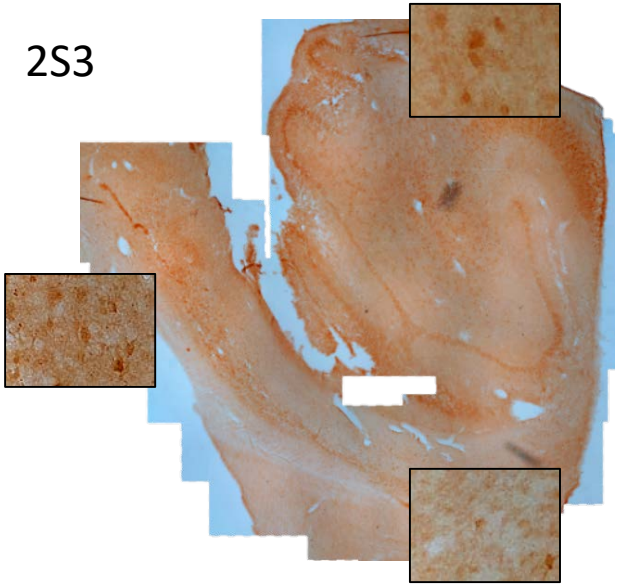
SCD-1

2C7

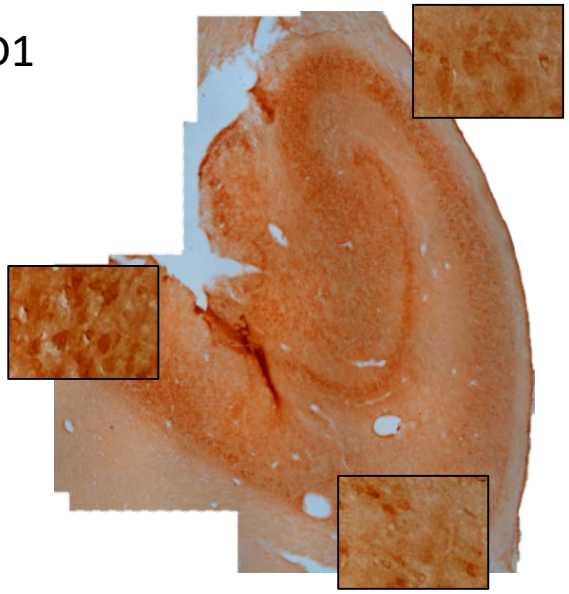


2F2

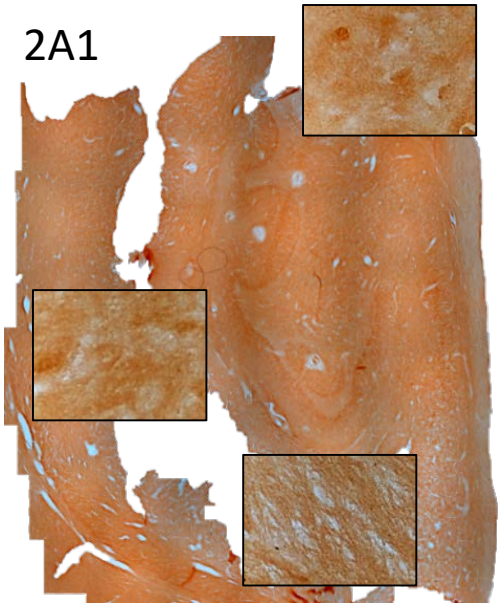
2S3



2D1

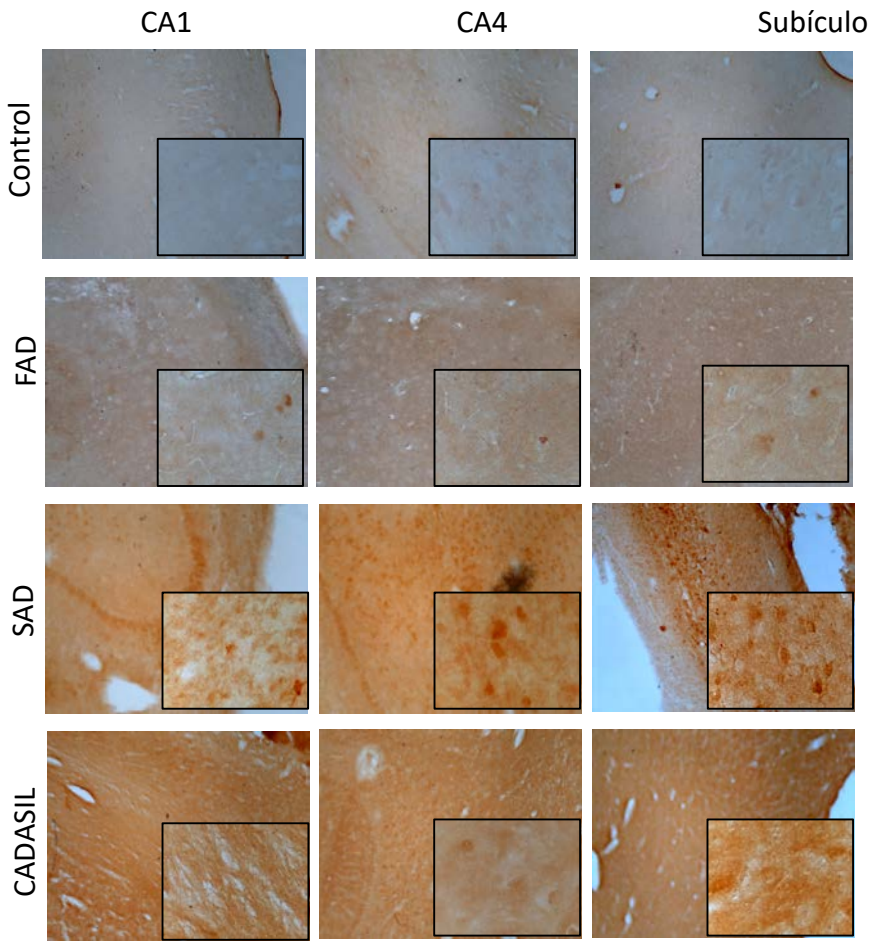


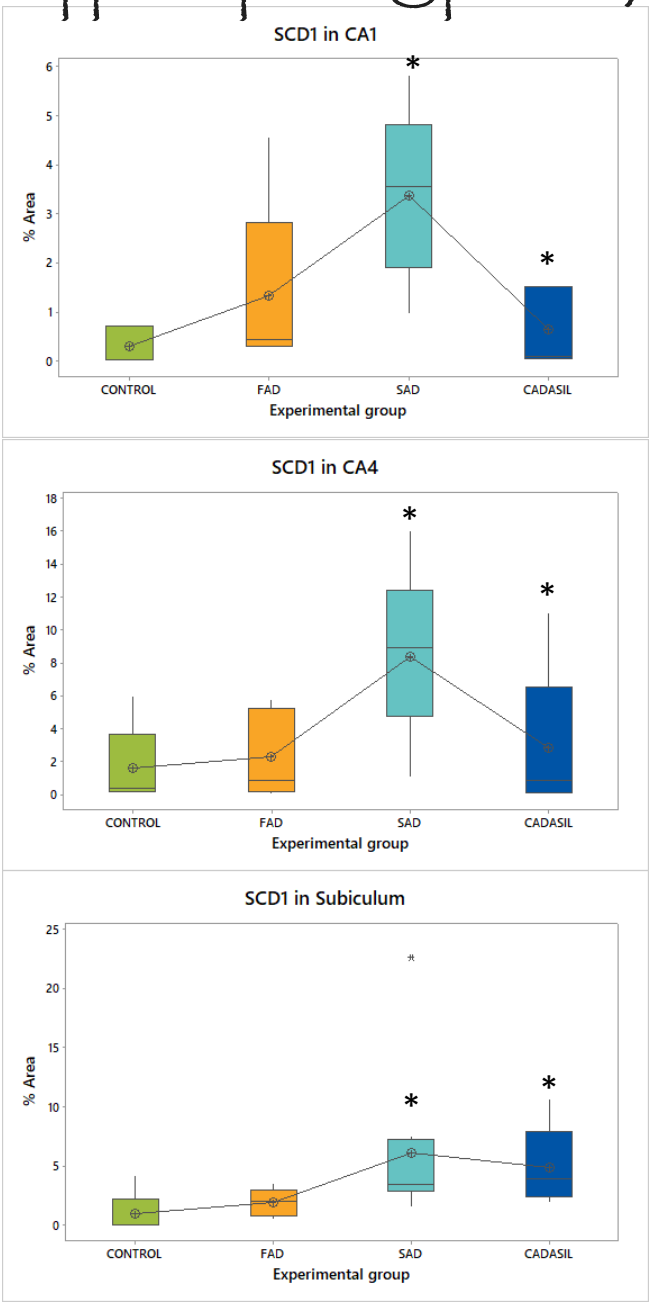
2A1



Pacheco M et. al. In preparation

SCD1 are mainly increased in the hippocampus of Sporadic AD





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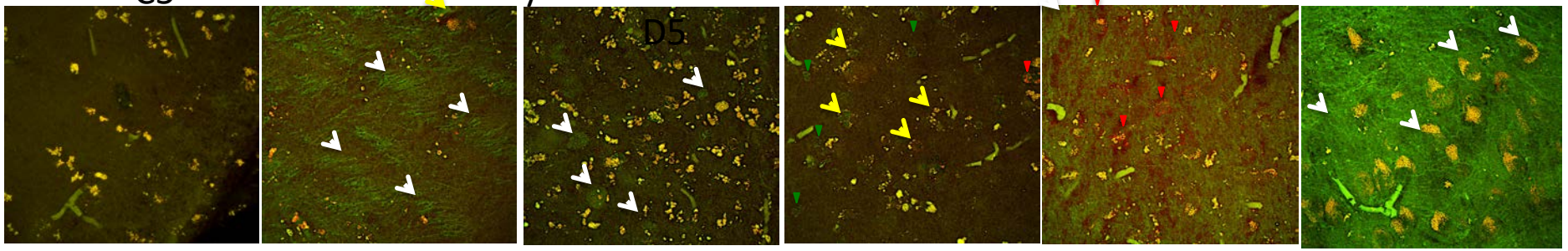
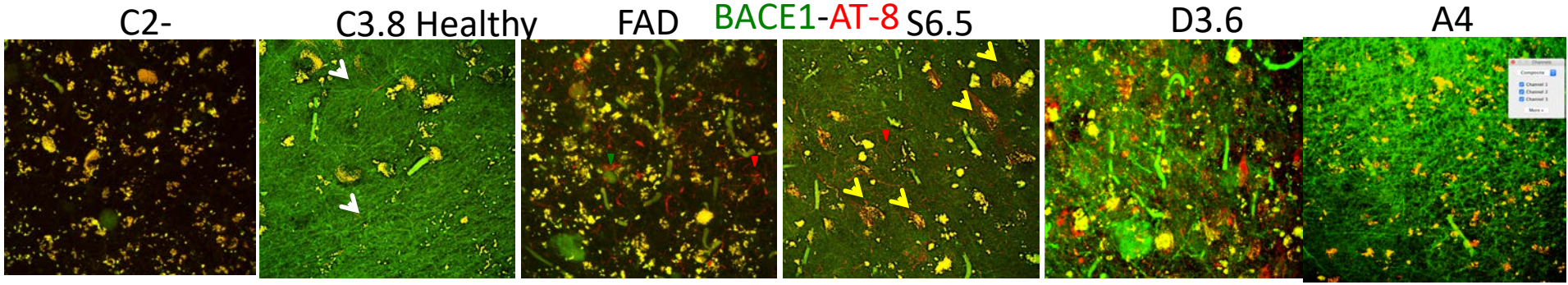
BACE1+SCD1+AT-8 are in the same cells of sporadic AD

Alzheimer

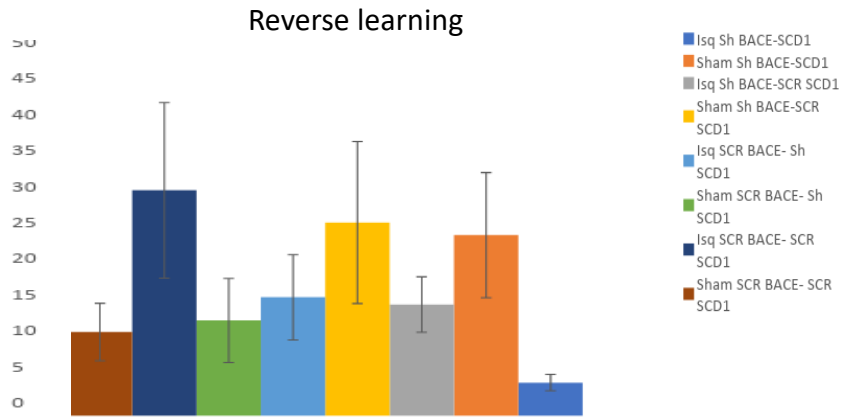
BACE1-SCD1



BACE1-AT-8



shBACE1+shSCD1 synergically prevent the cognitive impairment of ischemic rats



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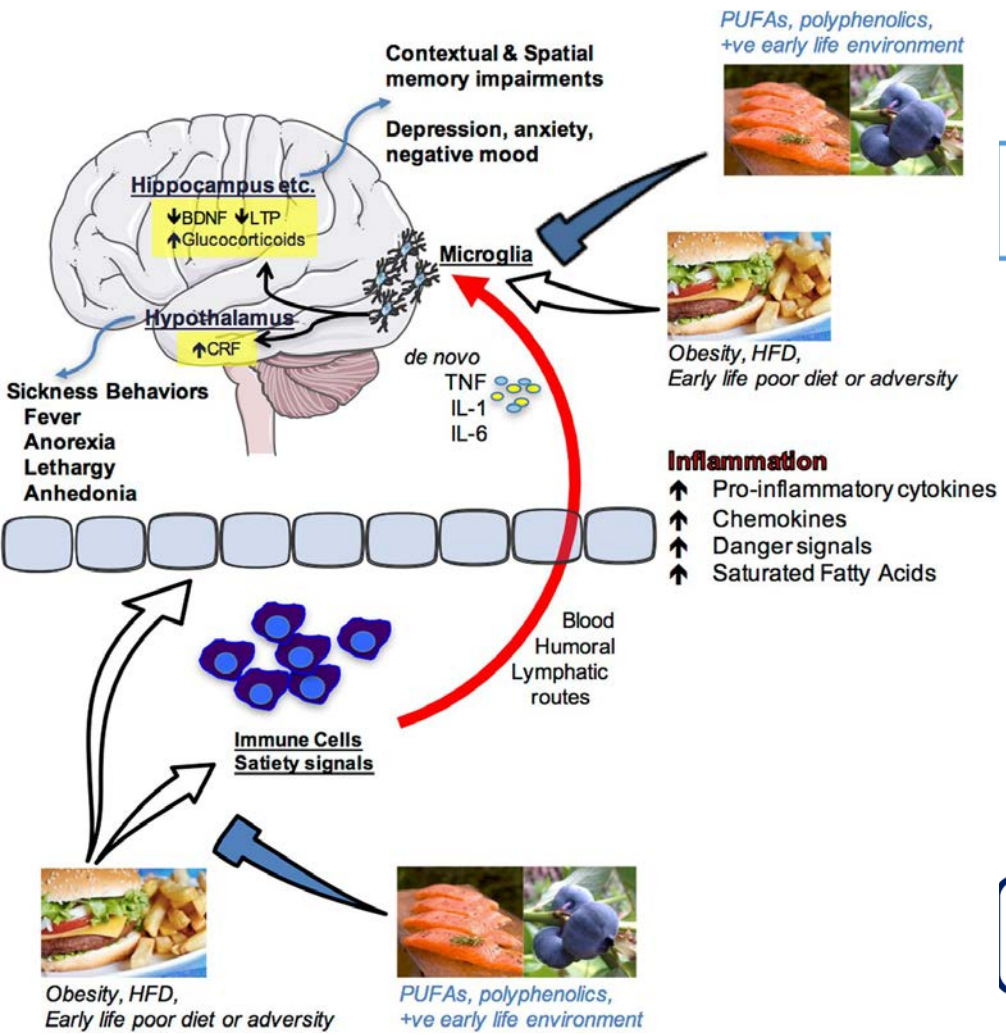
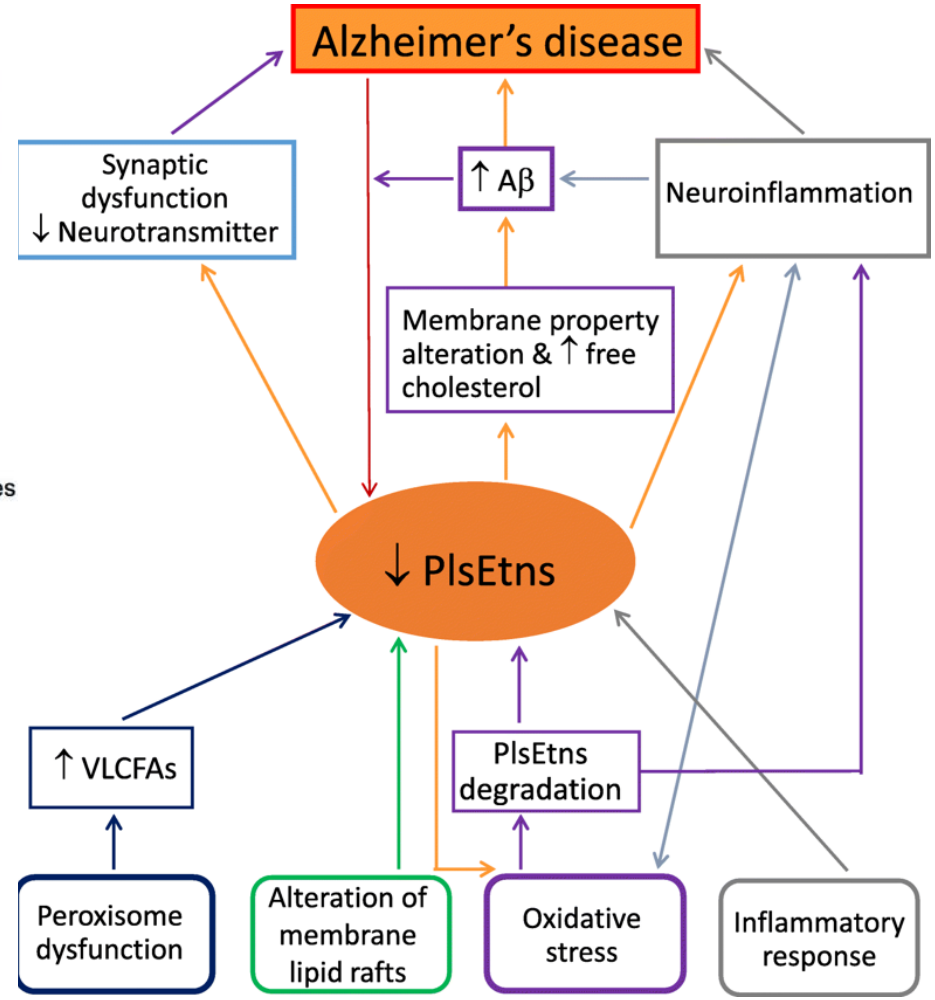
Pacheco M et. al. In preparation

Why to follow the tauopathogenesis from phospholipic signature?

Public health ← Primary prevention → Early biomarkers



Spencer et al *npj Science of Food* **1**, 7 (2017)

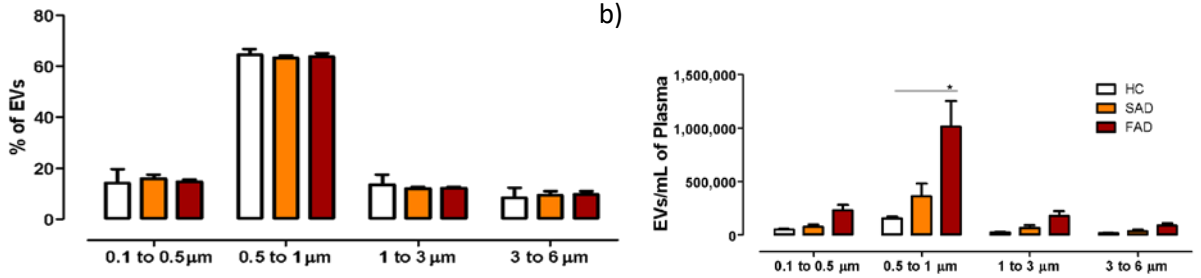


Su et al. Lipids in Health and Disease (2019)

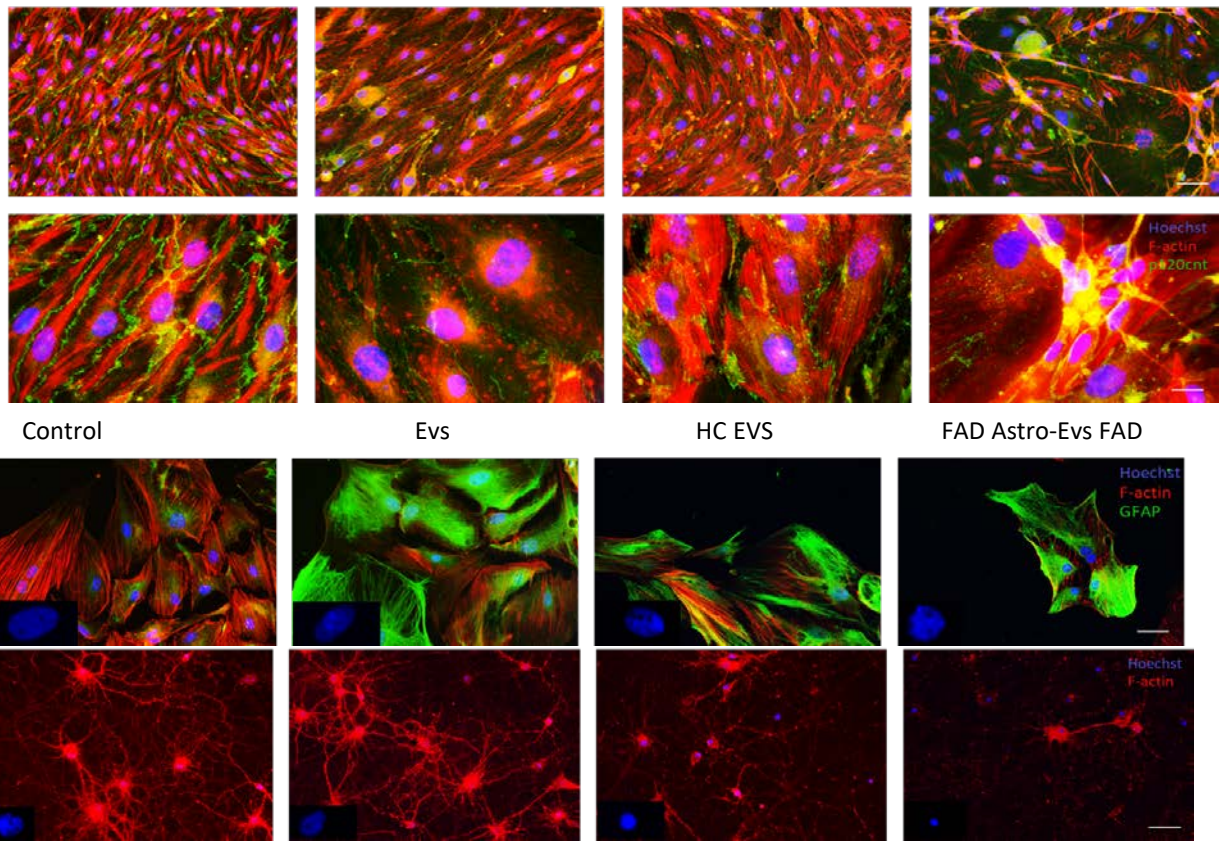
How tauopathogenesis might be found in the peripheral phospholipic signature?

a) **AD astrocytes and plasma microvesicles destroy neurovascular integrity**

b)



c)



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Villar JM et. al.
In preparation

It is a current challenge to find a peripheral prodromal signature of dementia

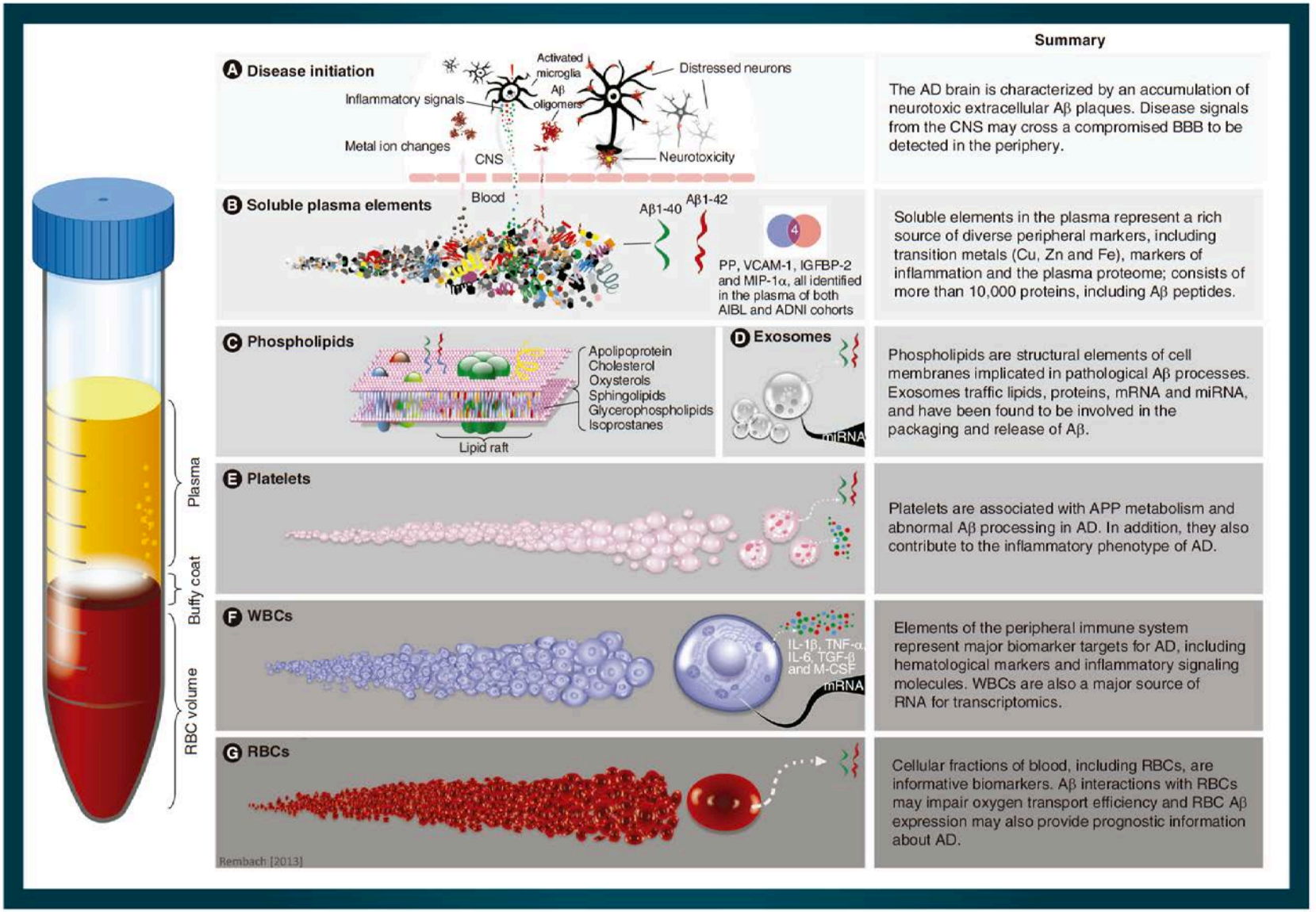


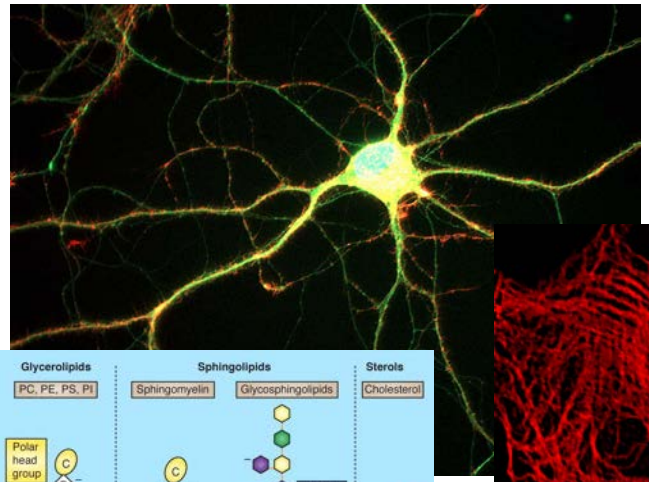
Figure 1. Various fractions of blood currently being investigated for putative peripheral biomarkers (continued on next page).

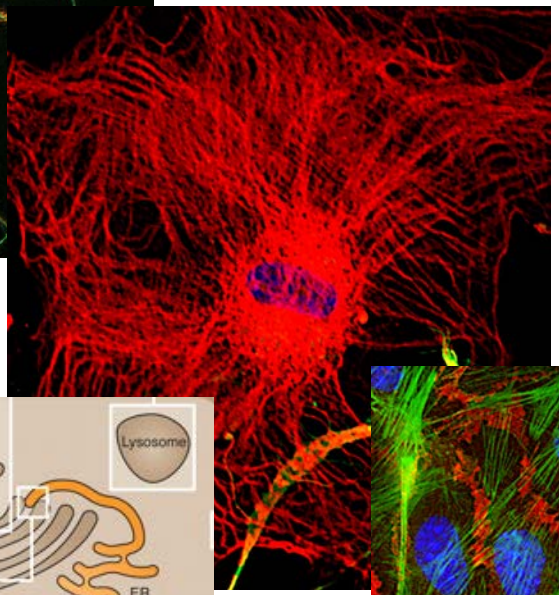
Rembach, Ryan, Roberts *et al.* ***Biomarkers Med.*** (2013) **7**(4), 641–662

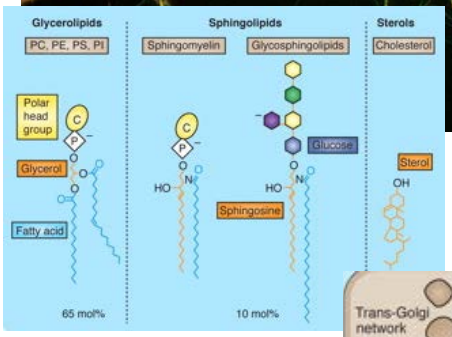
CONCLUSIONS

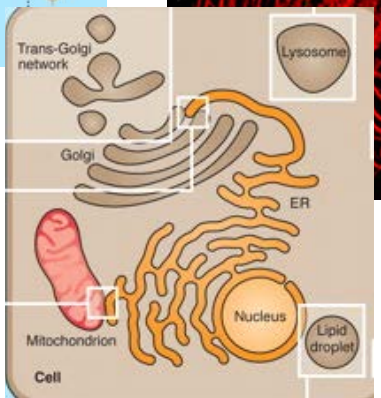
- In general, chronic inflammation, failure in the degradation rate and lipid environment are critical in the pathophysiology of Dementia (type AD).

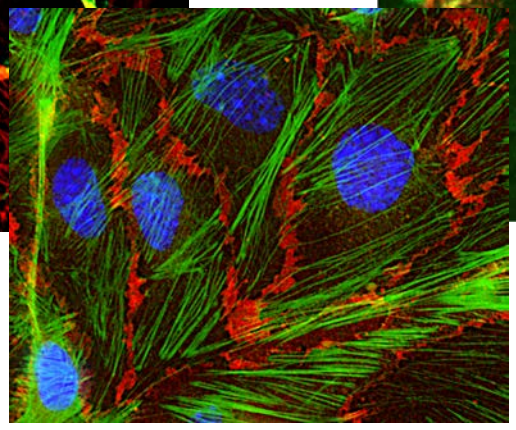
- Phospholipid composition with pro-inflammatory fatty acid, such as Phospholipids 16:1, 18:0, 20:4, 22:6 are involved in cognitive impairment and dementia; and it has potentail as early biomarker of tauopathogenesis

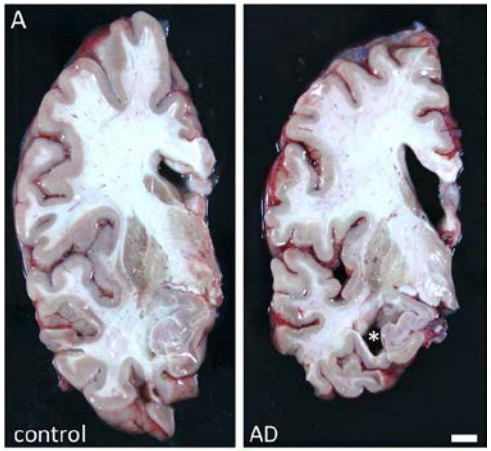


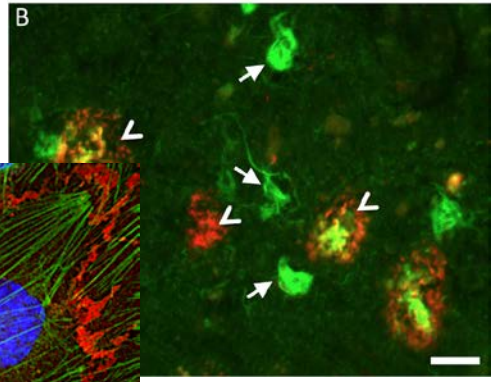












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