Energy Failure and Mitochondrial Cascades in Alzheimer's Disease

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Overview: Energy Metabolism in AD

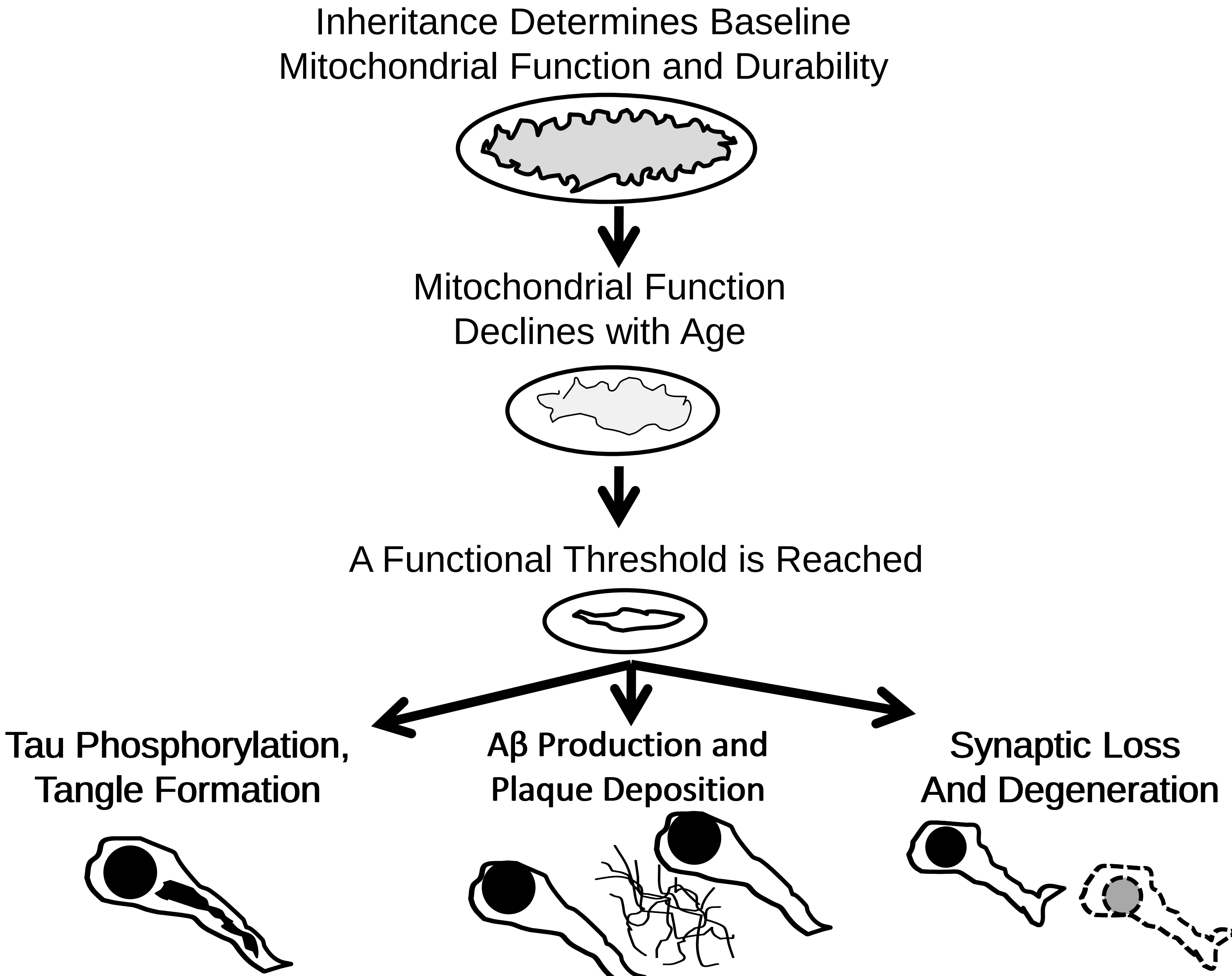
- AD is associated with alterations in
  - FDG PET
  - mitochondrial enzymes
  - mtDNA
  - mitochondrial mass and maintenance

Cause versus consequence?

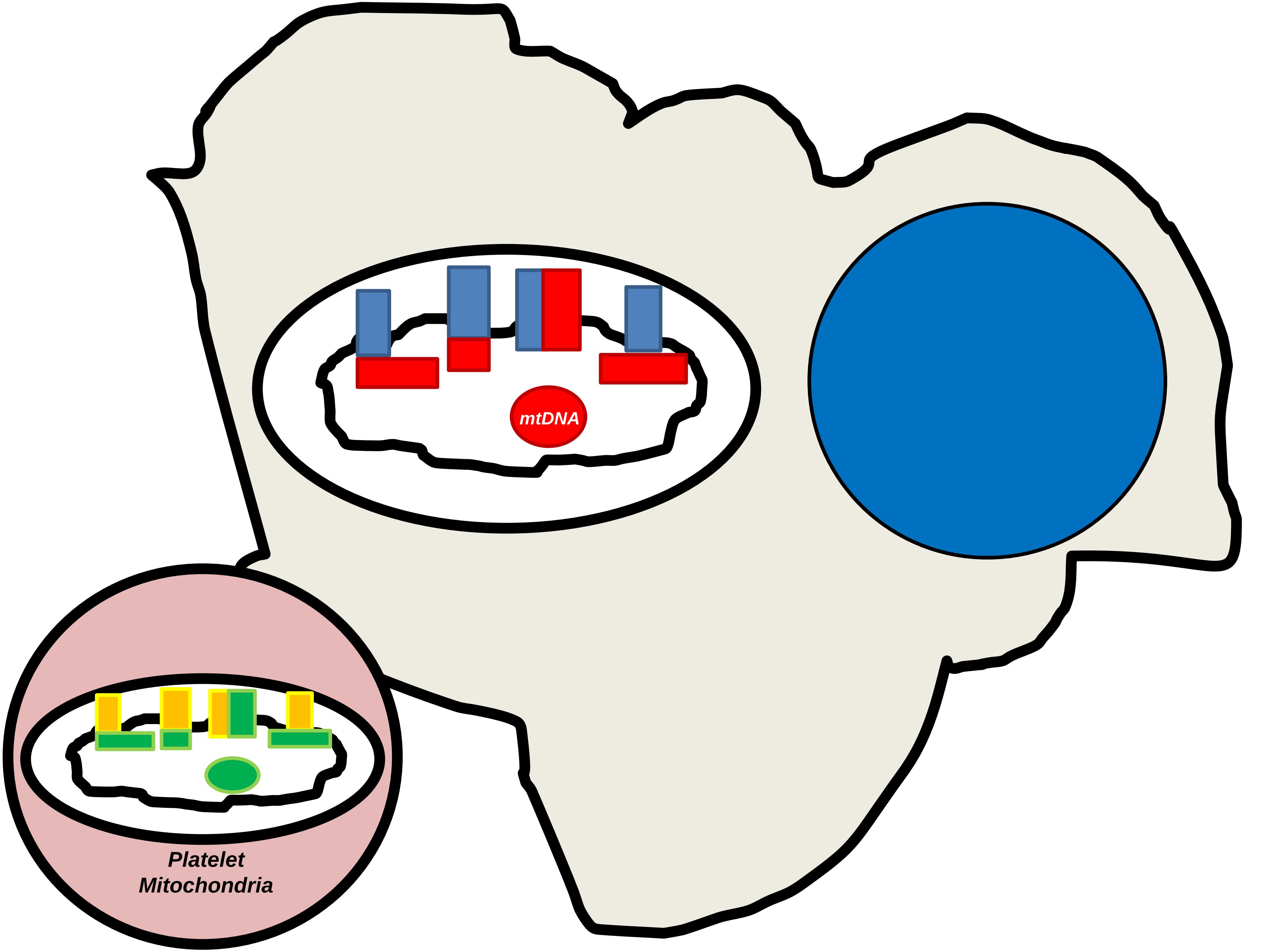
Possible Causal/Upstream Role?

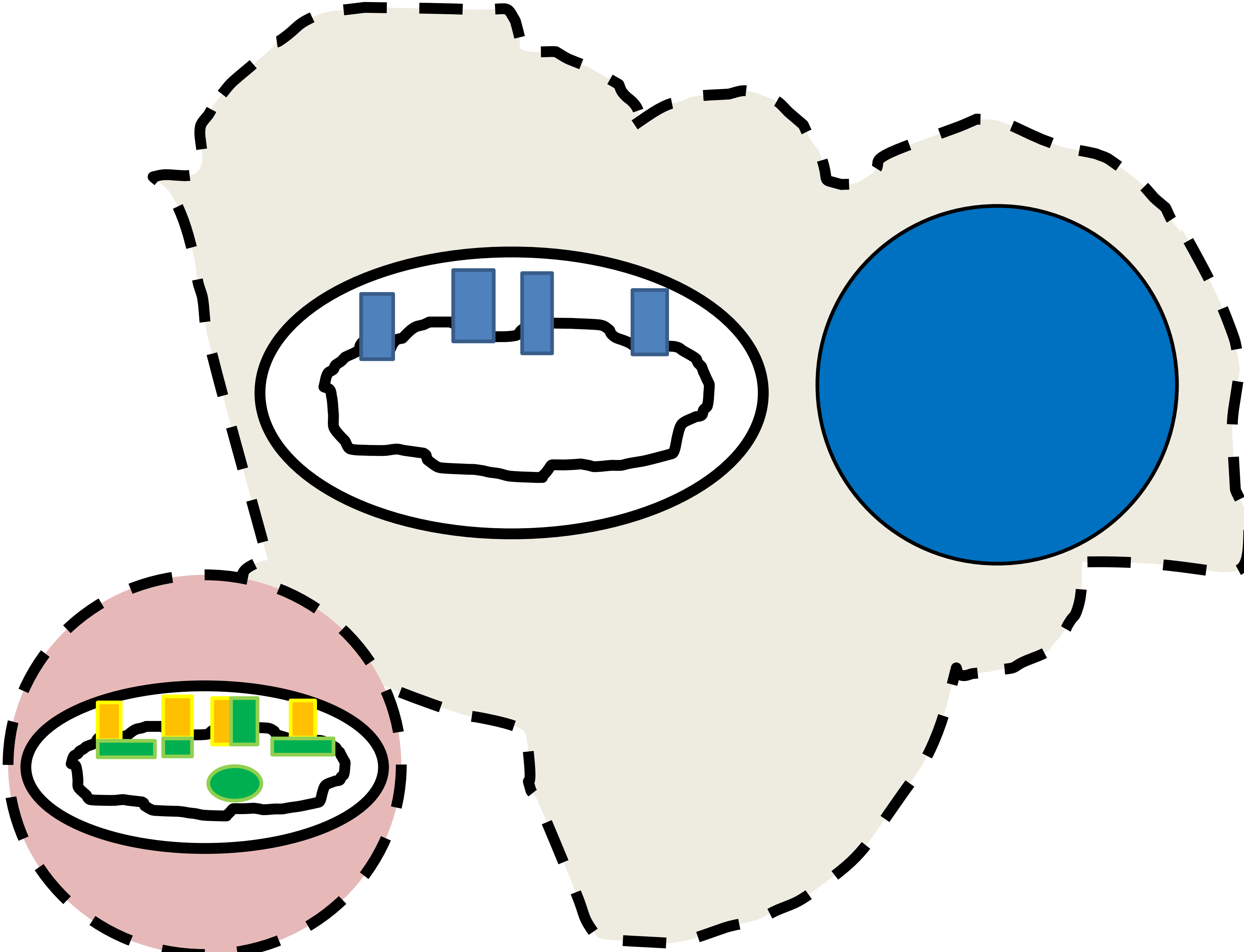
- Energy metabolism changes with *age*
- Inter/intra tissue *selective vulnerability*
- Endophenotypes suggest *early event*
- *Histopathology* associations
- Allow for *sporadic genetics* and *lifestyle* impact
- Changes present outside the brain

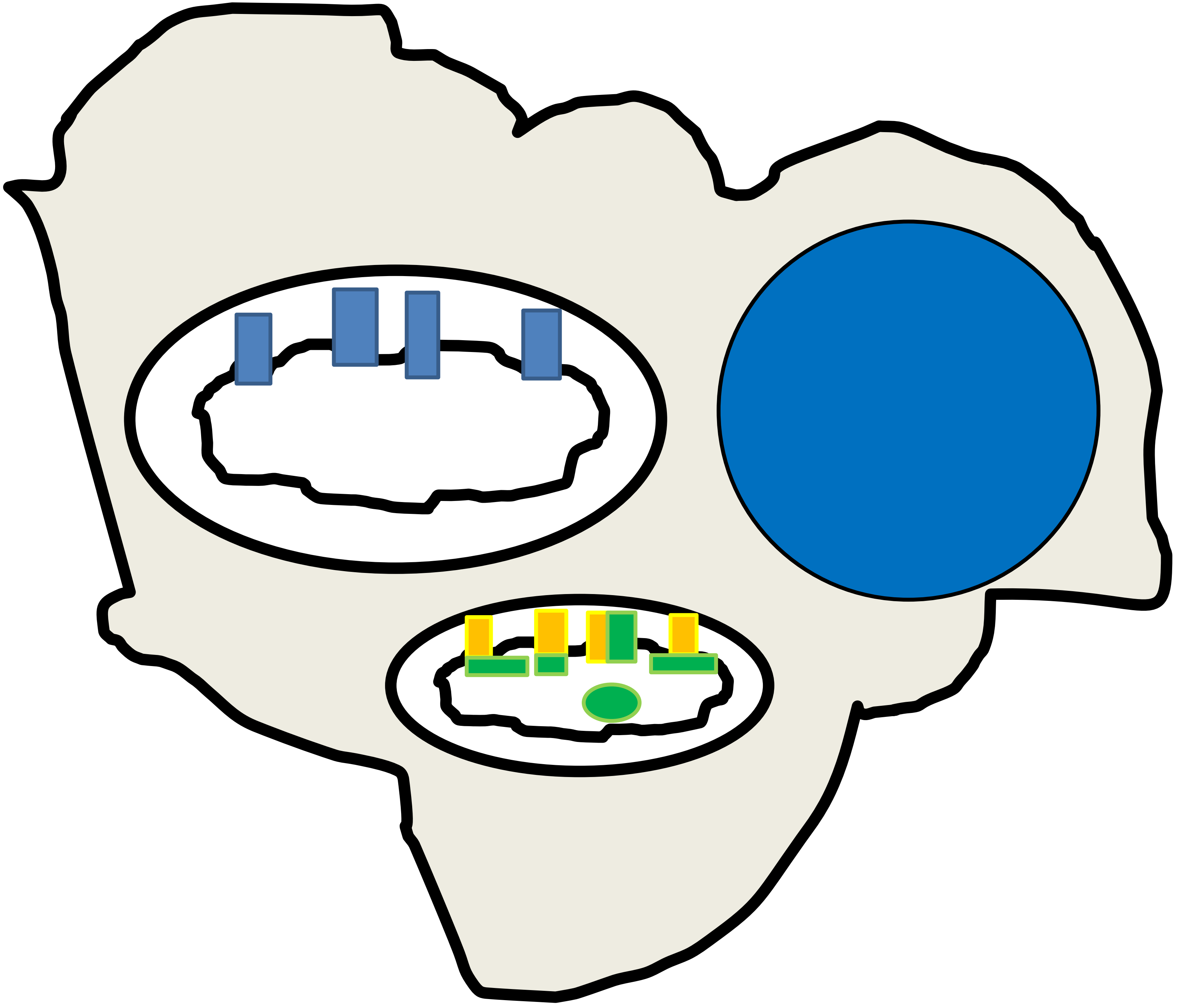
Mitochondrial Cascade Hypothesis

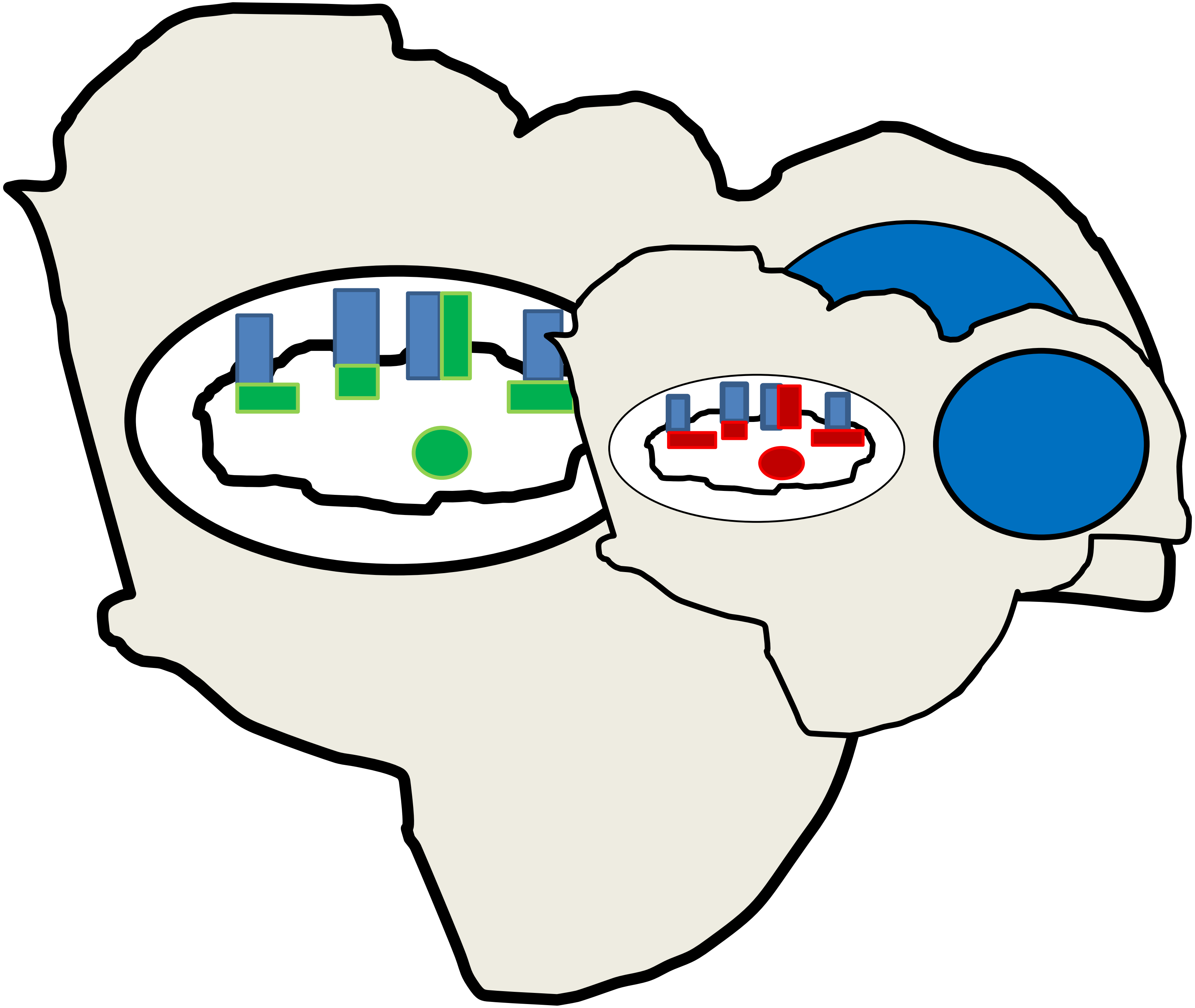


Swerdlow et al, BBA 1014;1842:1219-1231.


mtDNA
Platelet
Mitochondria



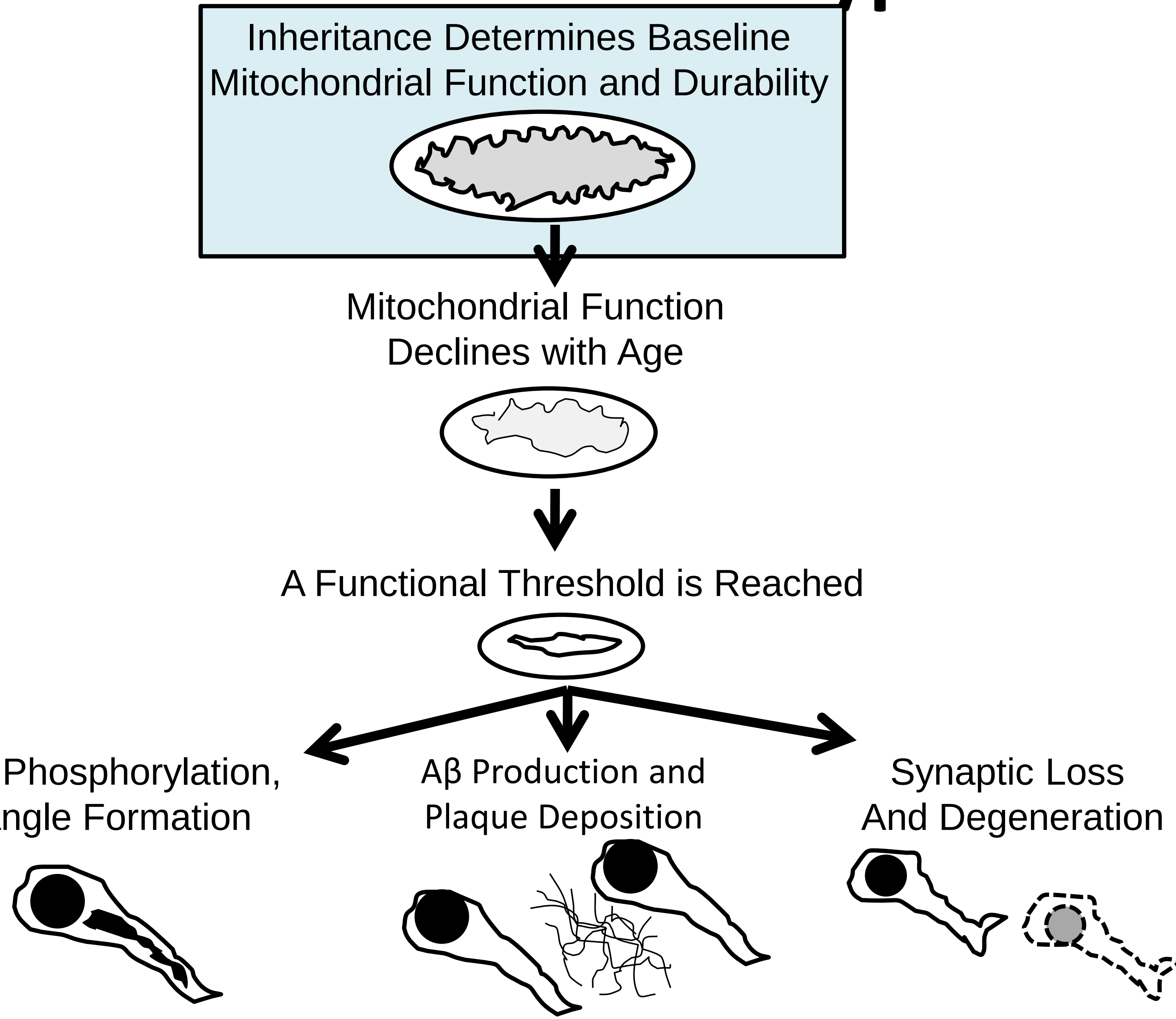




Differences in AD versus control brains also observed in AD versus control cybrid lines
Low cytochrome oxidase Vmax activity
Increased oxidative stress markers
Increased Aβ
Activated stress signaling pathways
Reduced PGC1α mRNA
Reduced HIF1α protein
Activated apoptotic signaling
NFκB activation
Overall increased COX2 protein
Reduced mTOR protein
Increased mitochondrial fission
Decreased SIRT1
Decreased O_2 consumption
Decreased glucose utilization

Swerdlow, Antioxid Redox Signal 2012;16:1434-1455.

Mitochondrial Cascade Hypothesis



Epidemiology Data

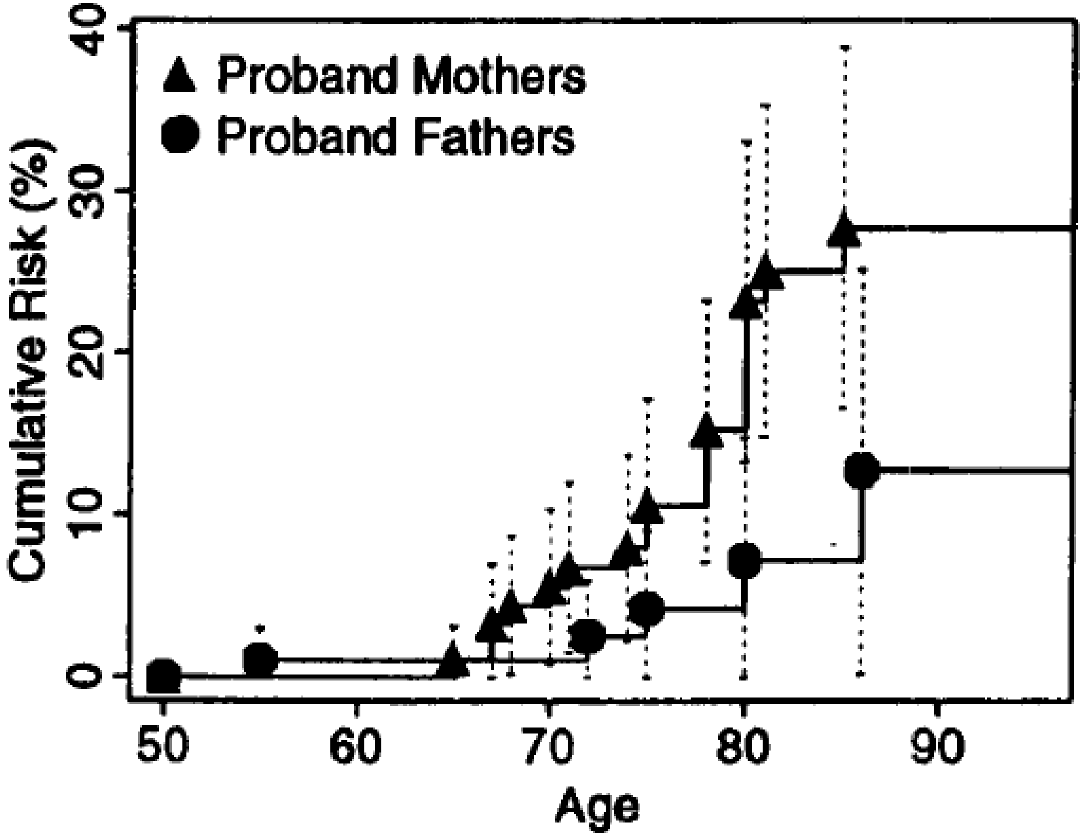


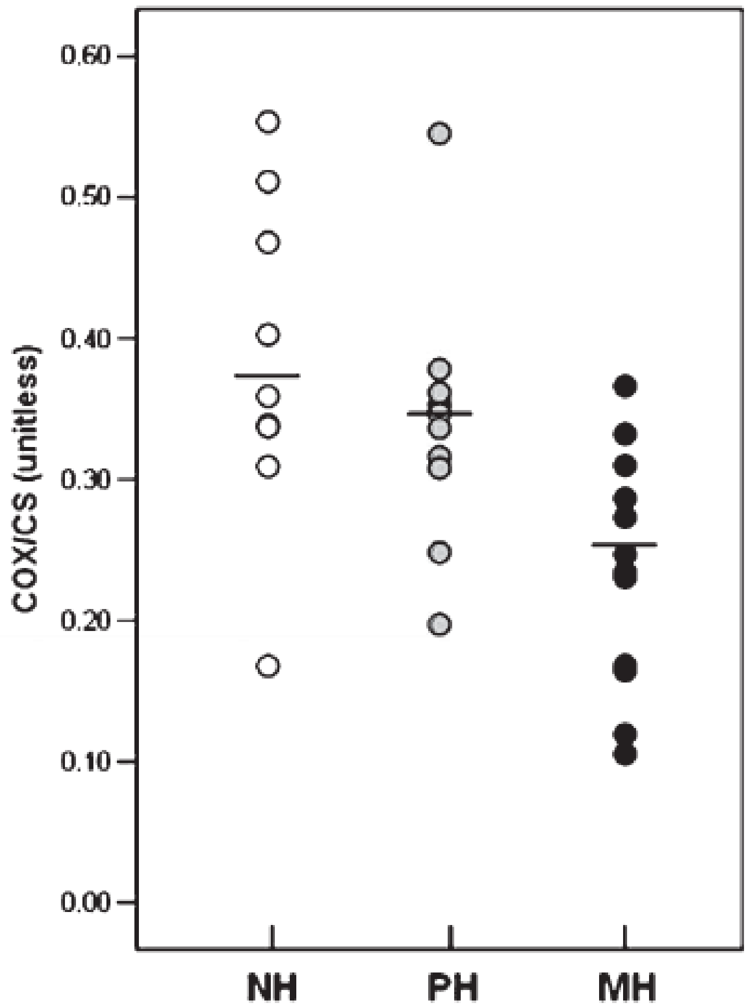
Figure. *Cumulative risk of primary progressive dementia (PPD) in mothers and fathers of AD probands. By age 90, the cumulative risk of PPD is estimated to be 27.7% for mothers and 12.7% for fathers.*

Edland et al, Neurology 1996;47:254-256.

Maternally-Inherited AD Endophenotypes

Endophenotype	References
FDG PET	Mosconi et al, 2007; Mosconi et al, 2009
Arterial Spin Labeling	Okonkwo et al, 2014
Amyloid Imaging	Mosconi et al, 2010; Honea et al 2012
CSF	Mosconi et al, 2010; Honea et al 2012; Liu et al, 2013
Volume/Atrophy Measurements	Honea et al, 2010; Honea et al 2011; Berti et al, 2011; Andrawis et al, 2012; Reiter et al, 2012
Cognition	Debette et al, 2009
Cytochrome Oxidase	Mosconi et al, 2011

Cytochrome Oxidase Endophenotype



Mosconi et al, JAD 2011;27:483-490.

Non-Synonymous mtDNA Changes in the KU ADC Cohort

Table 1. mtDNA sequencing of Clinical Cohort subjects (blood-derived mtDNA)			
Parameter	AD	CN	P Value
Times that a SNP/mutation was overrepresented in the AD or Control group	16 of 23 times	7 of 23 times	<0.05
Times that a non-synonymous SNP/mutation was overrepresented in the AD or Control group	4 of 4 times	0 of 4 times	
Subjects with a non-synonymous SNP/mutation	25/85 (29%)	15/170 (9%)	<0.0001
APOE4 with a non-synonymous SNP/mutation	20/55 (36%)	3/44 (7%)	0.0006

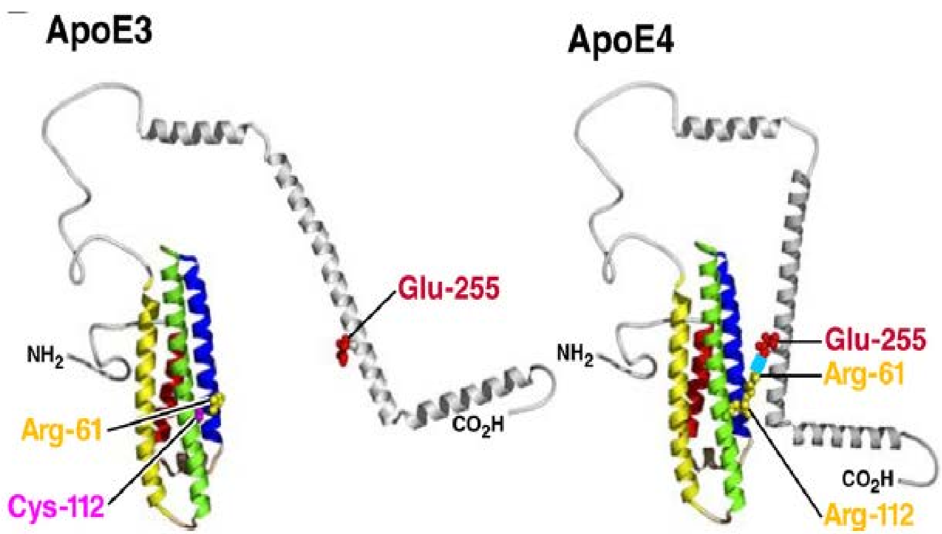
Double Hit?

Table 4 Association of maternal vs paternal dementia and Alzheimer disease (AD) with baseline logical memory and visual reproduction scores, among *APOE* $\epsilon 4$ carriers

	Maternal dementia	p^*	Maternal AD	p^*	Paternal dementia	p^*	Paternal AD	p^*
No.	159		159		130		130	
LM-d[†]	-2.18 ± 0.64	$<0.001^‡$	-1.82 ± 0.70	$0.009^‡$	-0.44 ± 0.60	0.465	-0.98 ± 0.59	0.098
VR-d	-1.86 ± 0.57	$<0.001^‡$	-1.75 ± 0.63	$0.005^‡$	0.04 ± 0.56	0.947	-0.27 ± 0.57	0.628

Debette et al, Neurology 2009;73:2071-2078.

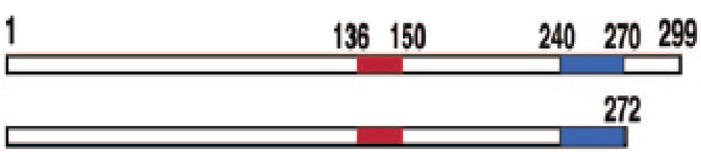
Apolipoprotein E



Mahley and Huang, J Med Chem 2012;55:8997-9008.

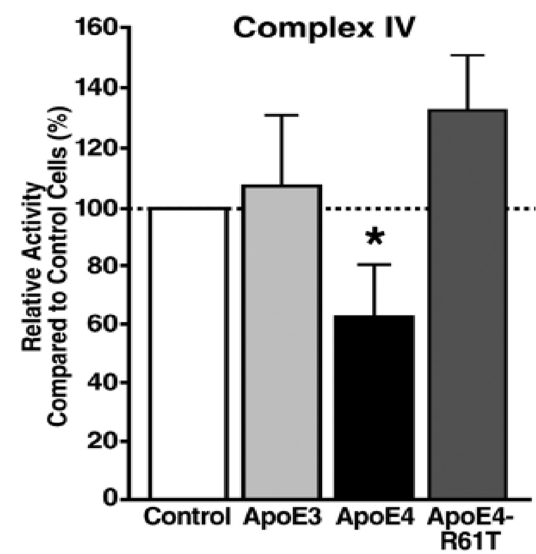
	Non-Carriers $n = 25$	Carriers[+] $n = 15$	
Amyloid ELISA (pg/mg total protein), mean ± stdev:			P
Soluble $A\beta_{1-40}$	6.0 ± 6.9	4.5 ± 3.7	0.36
Insoluble $A\beta_{1-40}$	3.5 ± 6.2	6.8 ± 10.3	0.29
Soluble $A\beta_{1-42}$	0.0 ± 0.0	0.0 ± 0.0	–
Insoluble $A\beta_{1-42}$	63.3 ± 89.6	71.8 ± 49.1	0.71
CO Activity (nmol cyt c/min/mg), mean ± stdev:			
Overall	361 ± 14	352 ± 15	0.036*
Superficial Layer I	360 ± 23	340 ± 14	0.011**
External Granular Layer II	364 ± 16	349 ± 10	0.004**

Valla et al, JAD 2010;22:307-313.



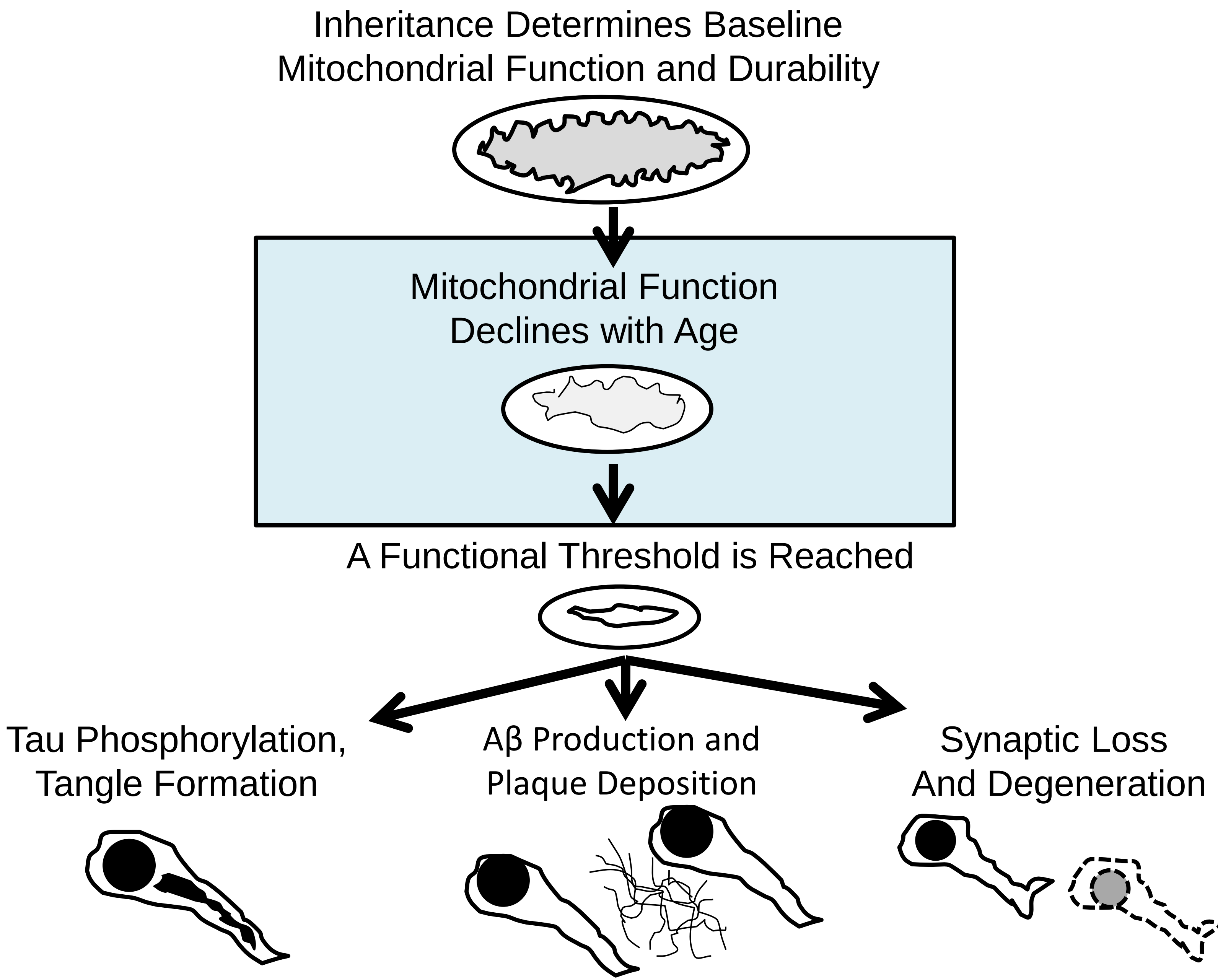
	Neuro-toxicity	Trans-location	Mitochondrial Localization
1–299	No	No	No
1–272	Yes	Yes	Yes

Mahley et al, PNAS 2006;103:5644-5651.

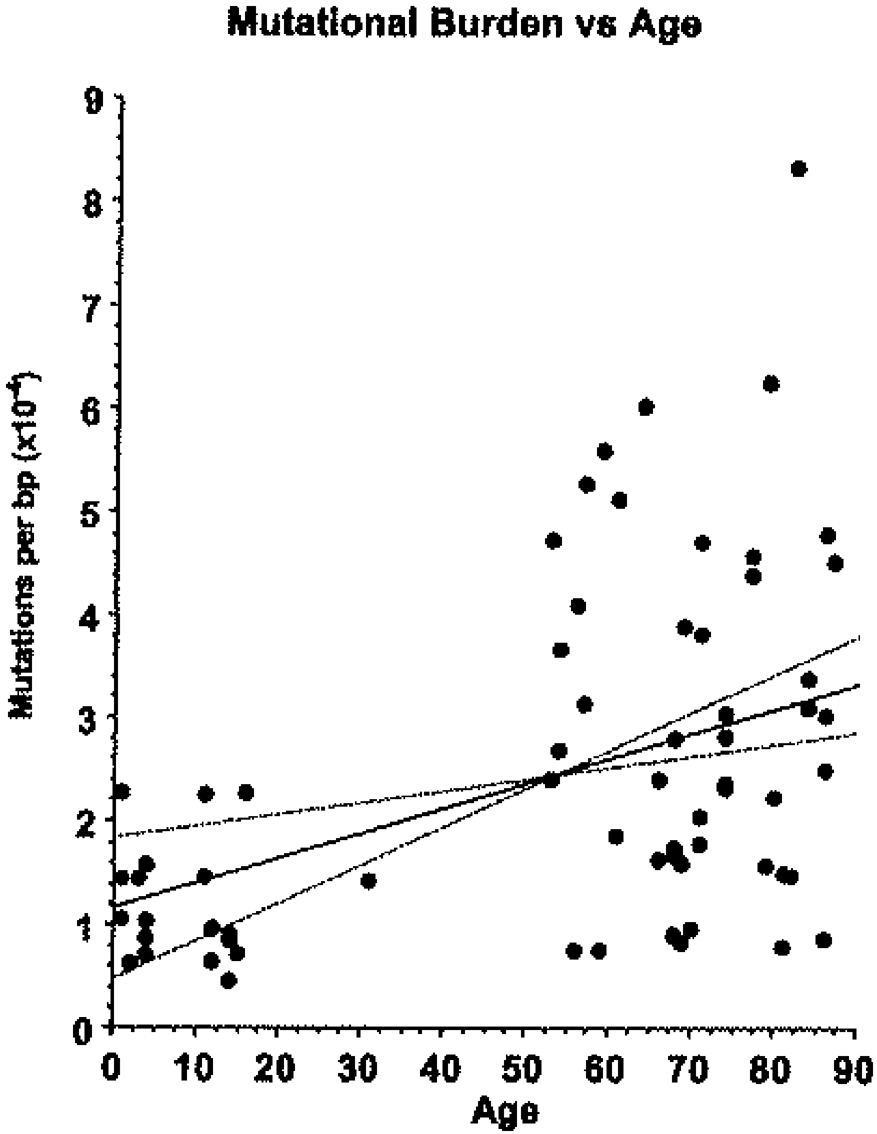


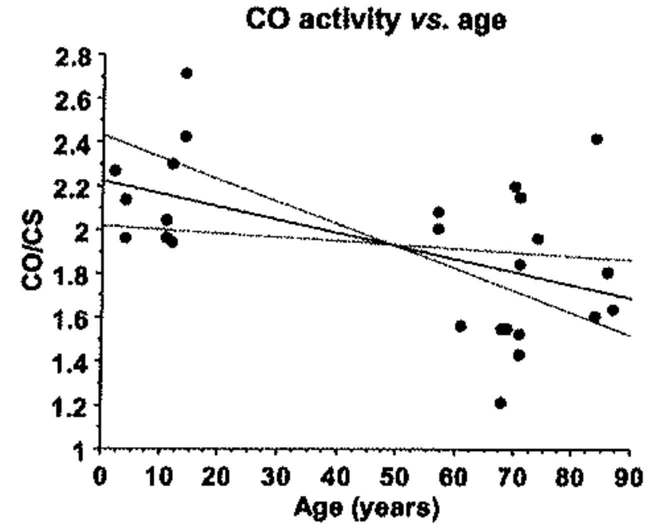
Chen et al, JBC 2011;286:5215-5221.

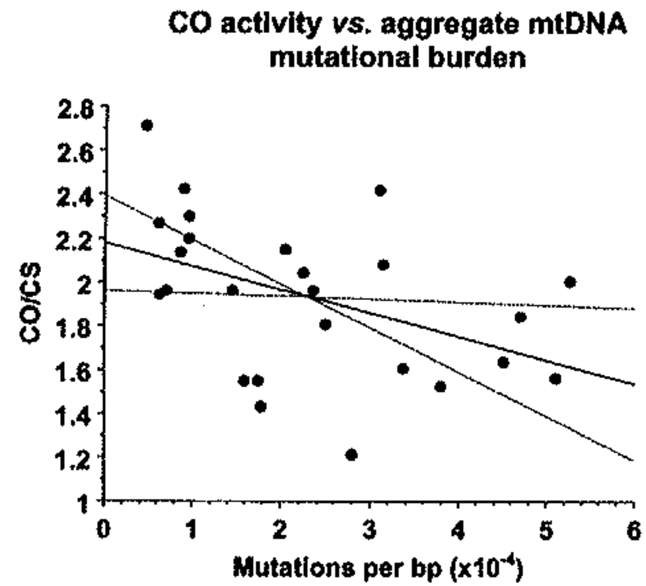
Mitochondrial Cascade Hypothesis



Aging and the Brain

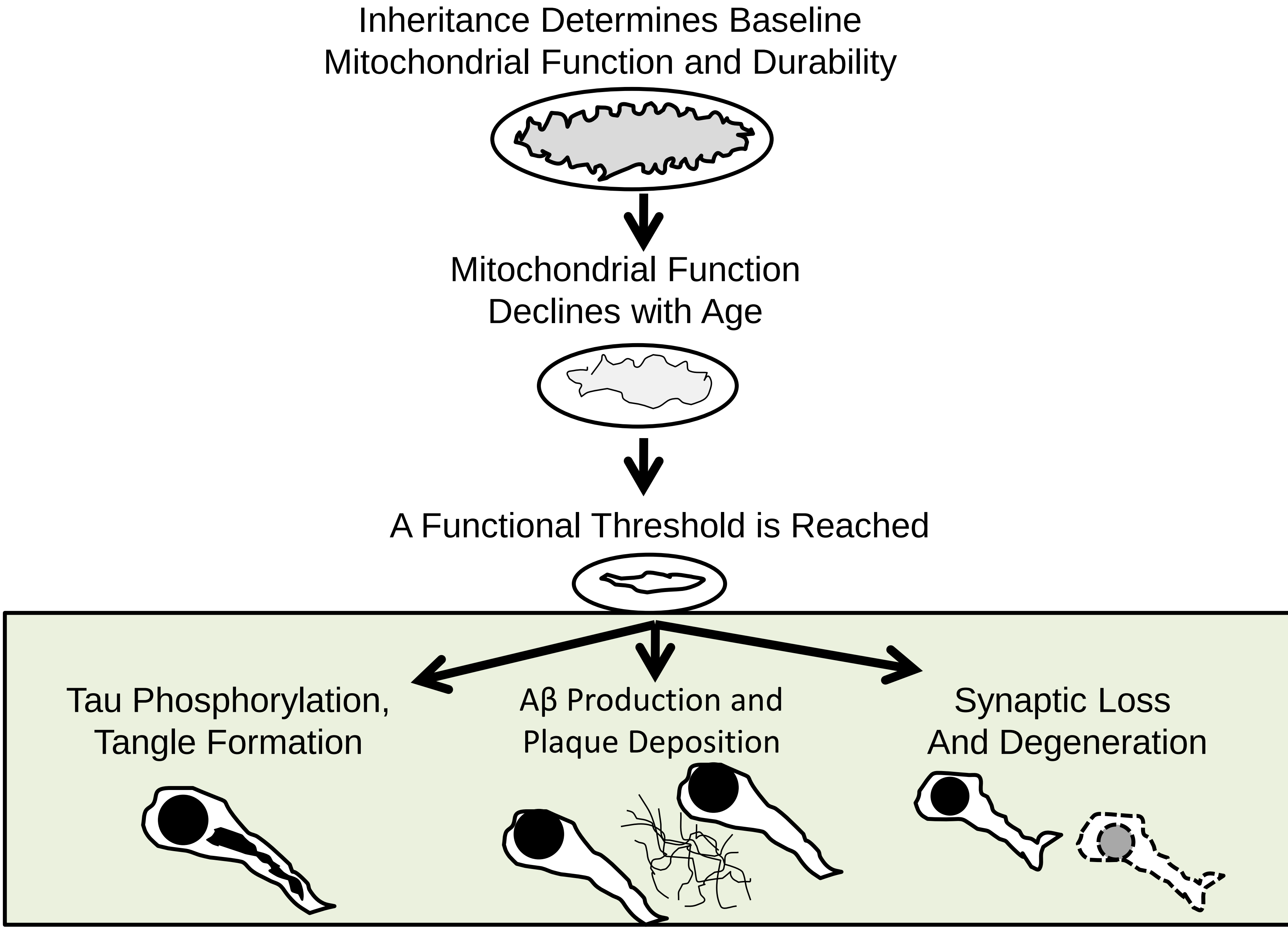




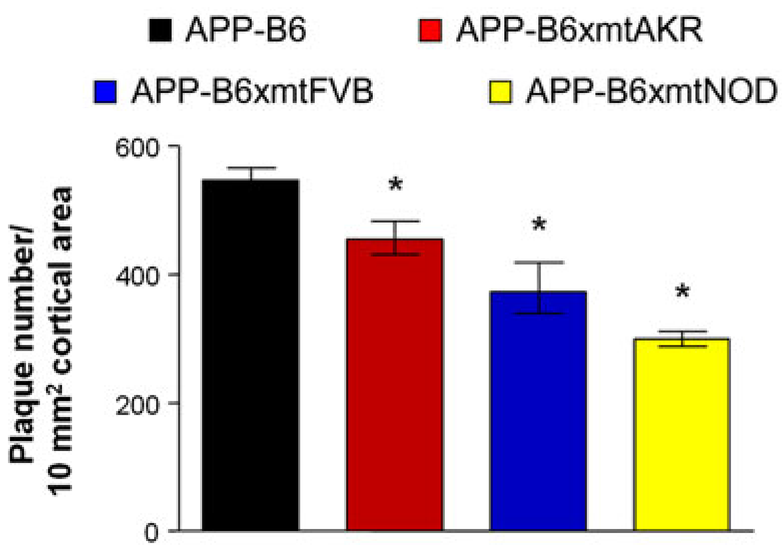


Lin et al, Hum Mol Genet 2002;11:133-145.

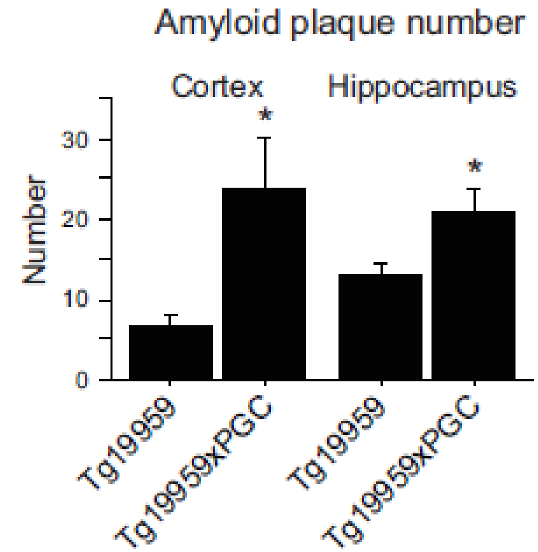
Mitochondrial Cascade Hypothesis



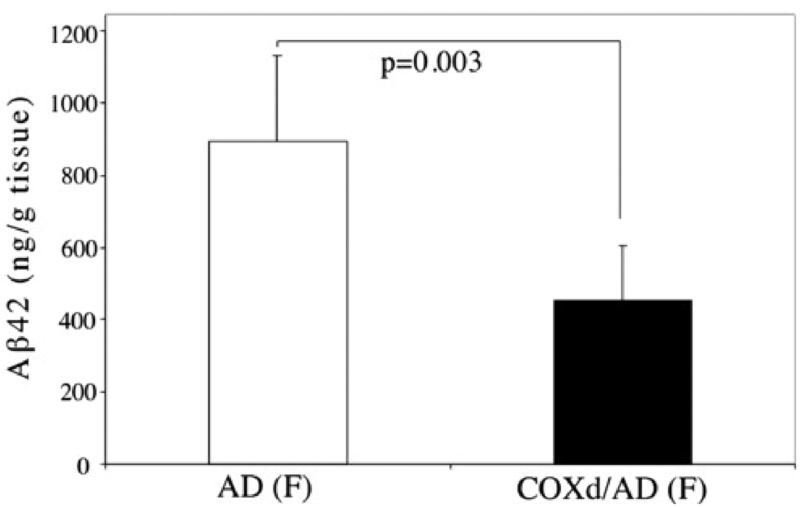
Mitochondria-Amyloid Relationships



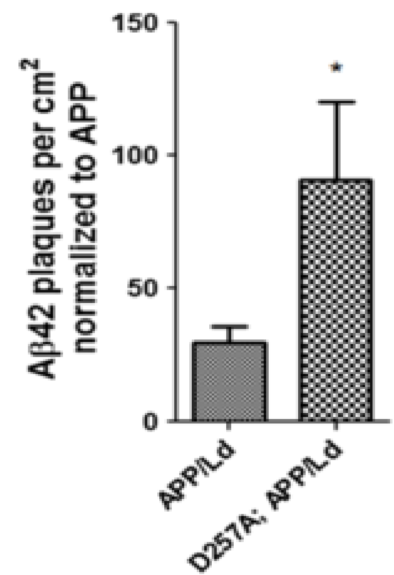
Scheffler et al. Acta Neuropathol 2012; 124:199-208



Dumont et al. Faseb J 2014;28:1745-1755

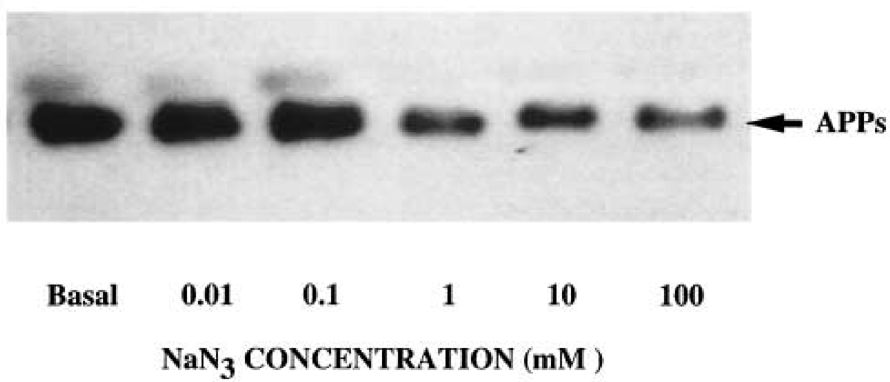


Fukui et al. PNAS 2007;104:14163-14168

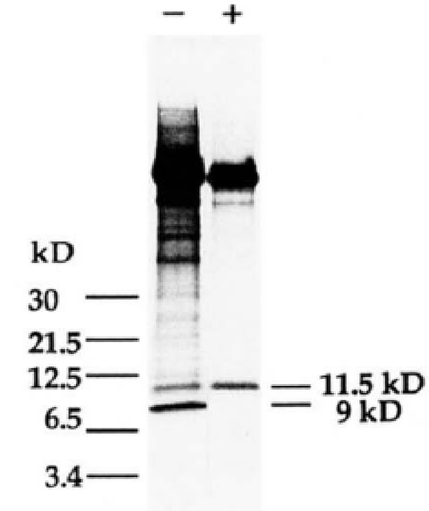


Kukreja et al. Mol Neurodegen 2014;9:16

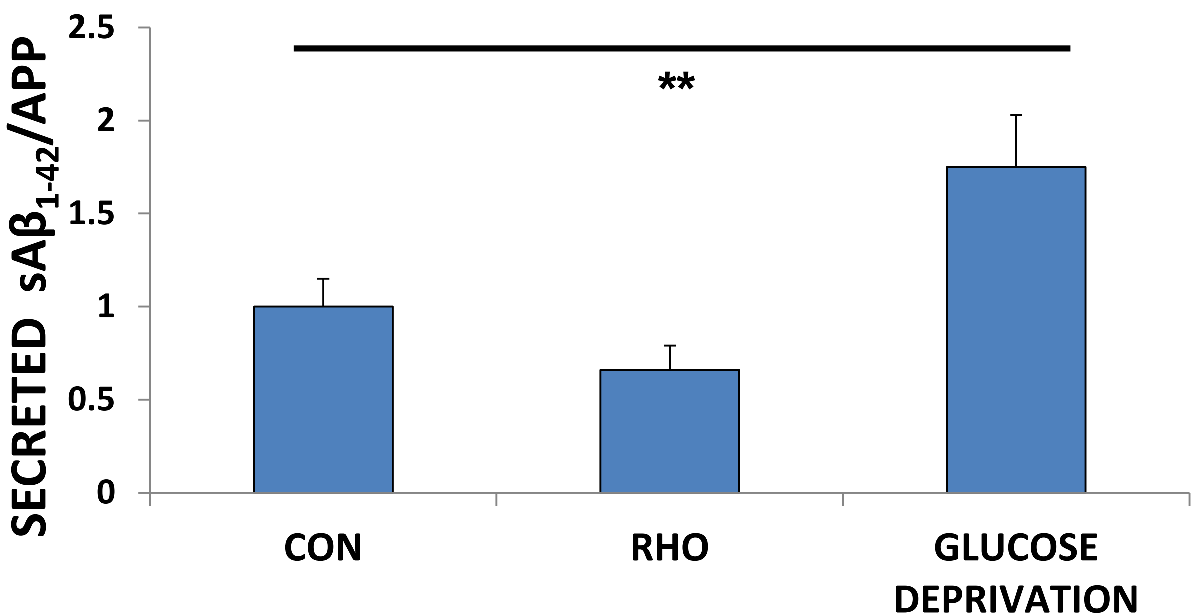
Respiratory Flux and APP Processing



Gasparini et al, Neurosci Lett 1997;231:113-117.



Gabuzda et al, JBC 1994;269:13623-13628.



Energy Metabolism-Aβ Nexus

<u>Aerobic Metabolism Challenged</u>
Limited Mitochondrial Defect
Increased Synaptic Activity
Awake

↓

Upregulate/Increase
Aerobic Metabolism

↓

More Aβ Production

<u>Aerobic Metabolism De-emphasized</u>
Profound Mitochondrial Defect
Decreased Synaptic Activity
Asleep

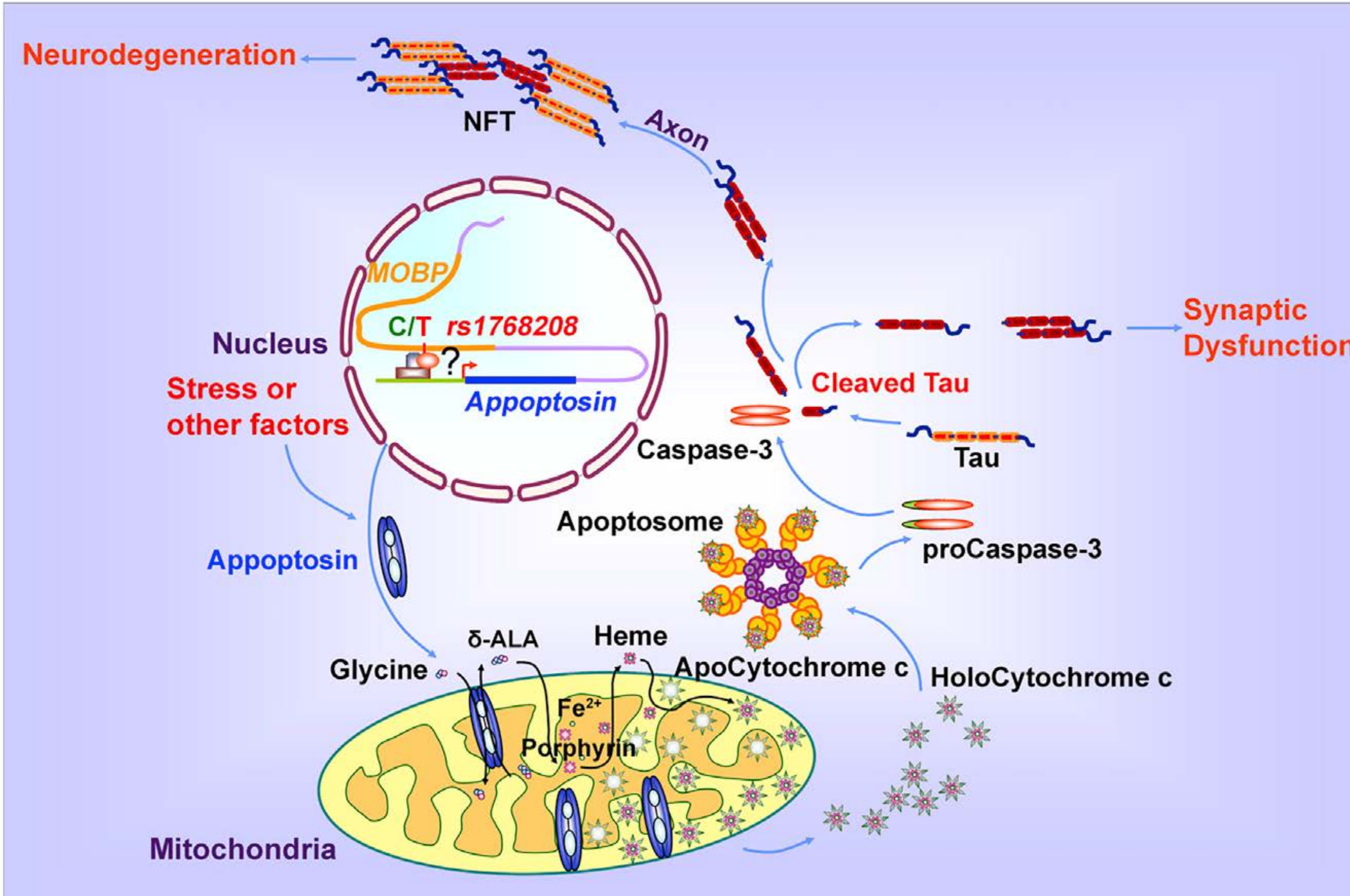
↓

Downregulate/Decrease
Aerobic Metabolism

↓

Less Aβ Production

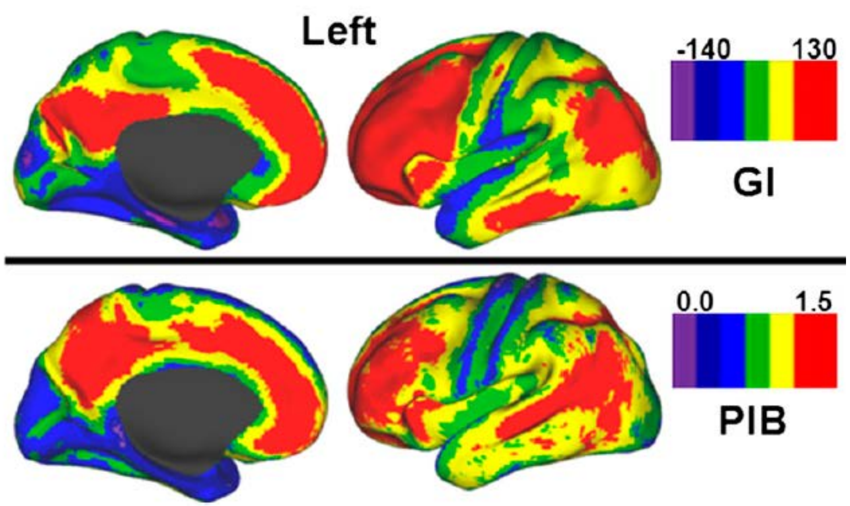
Example of Mito-Tau Interaction



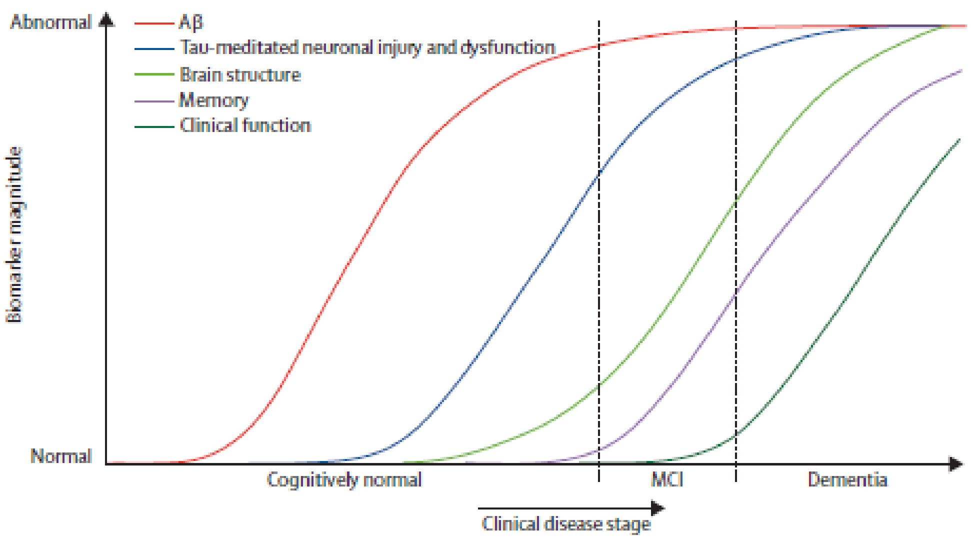
Zhao et al, Neuron 2015;87:963-975.

Predictions

- Bioenergetic changes promote Aβ in run-up to clinical AD
- Age-related pattern of up (compensated) then down (uncompensated) aerobic metabolism
- Aging to AD transition=Compensated to Uncompensated
- Translation: Enhance brain energy metabolism?
- Compensation initiates histology changes
- Biomarkers reflect brain bioenergetics/aging



Vlassenko et al, PNAS 2010;107:17763-17767.



Jack et al, Lancet Neurol 2010;9:119-128.

Acknowledgments

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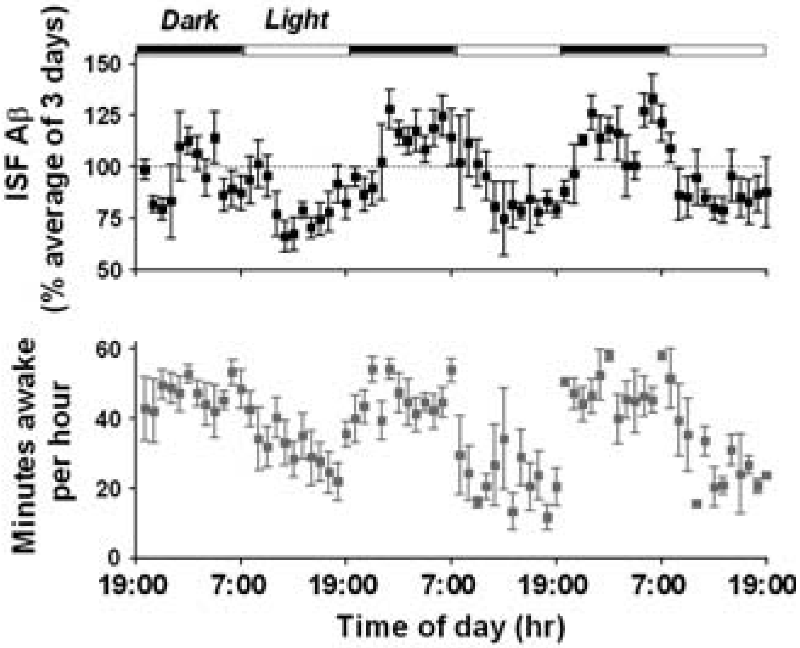
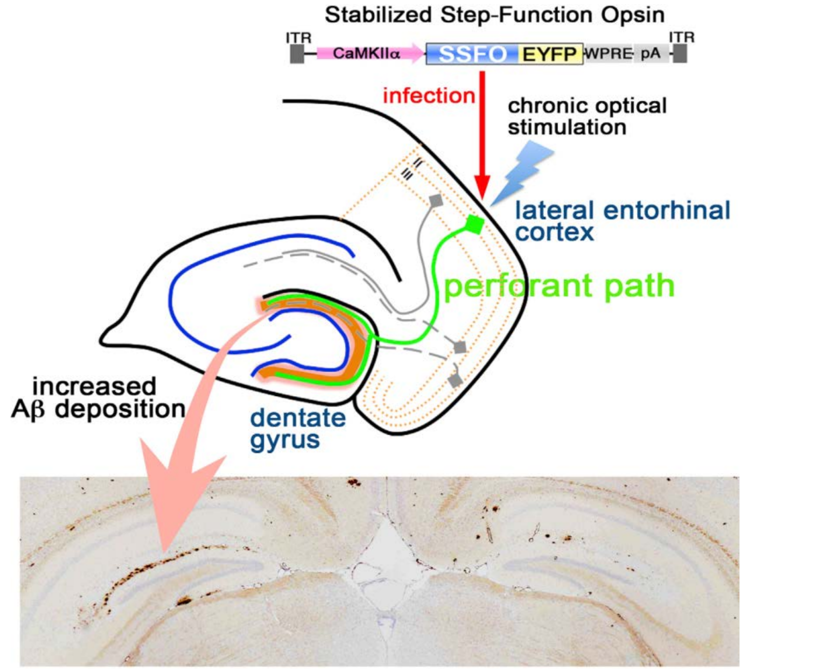
Cited investigators/Investigations

NATIONAL INSTITUTES OF HEALTH

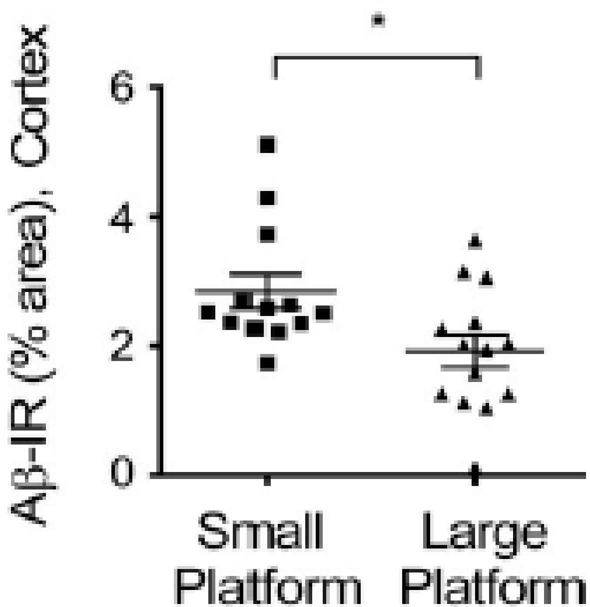
National Institute on Aging



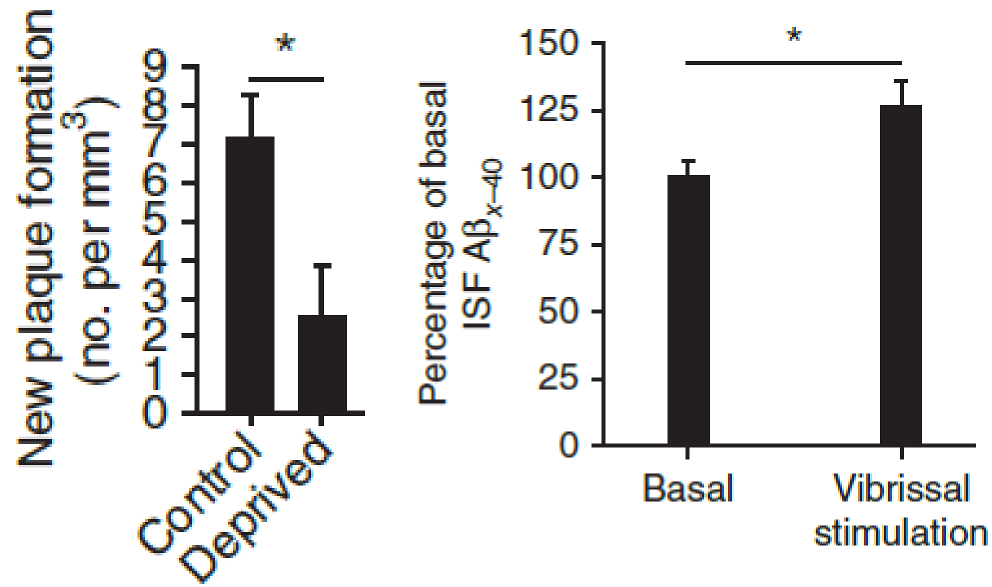
Kang et al, Science 2009;326:1005-1007.



Yamamoto et al, Cell Reports 2015;11:859-865

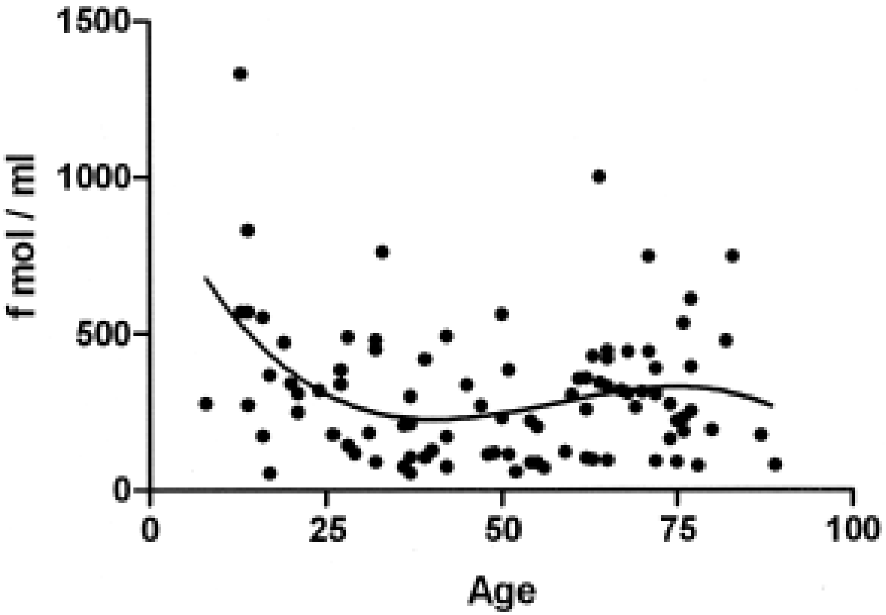


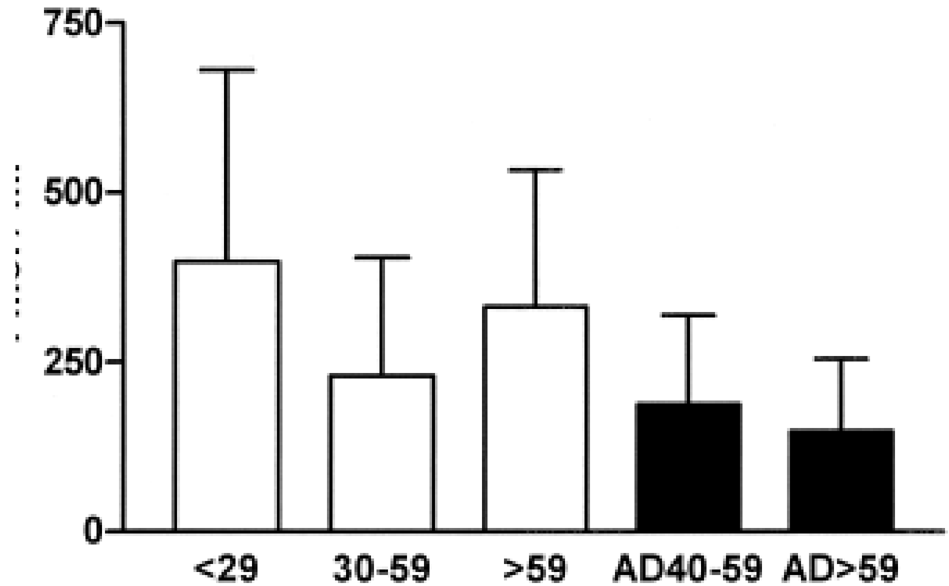
Roh et al, J Exp Med 2014:211:2487-2496.



Bero et al, Nat Neurosci 2011;14:750-756.

CSF Aβ42 Levels Vary With Age





Shoji et al, Neurobiol Aging 2001;209-215.

APOE4 Attenuates Age-Related CSF Aβ Increase

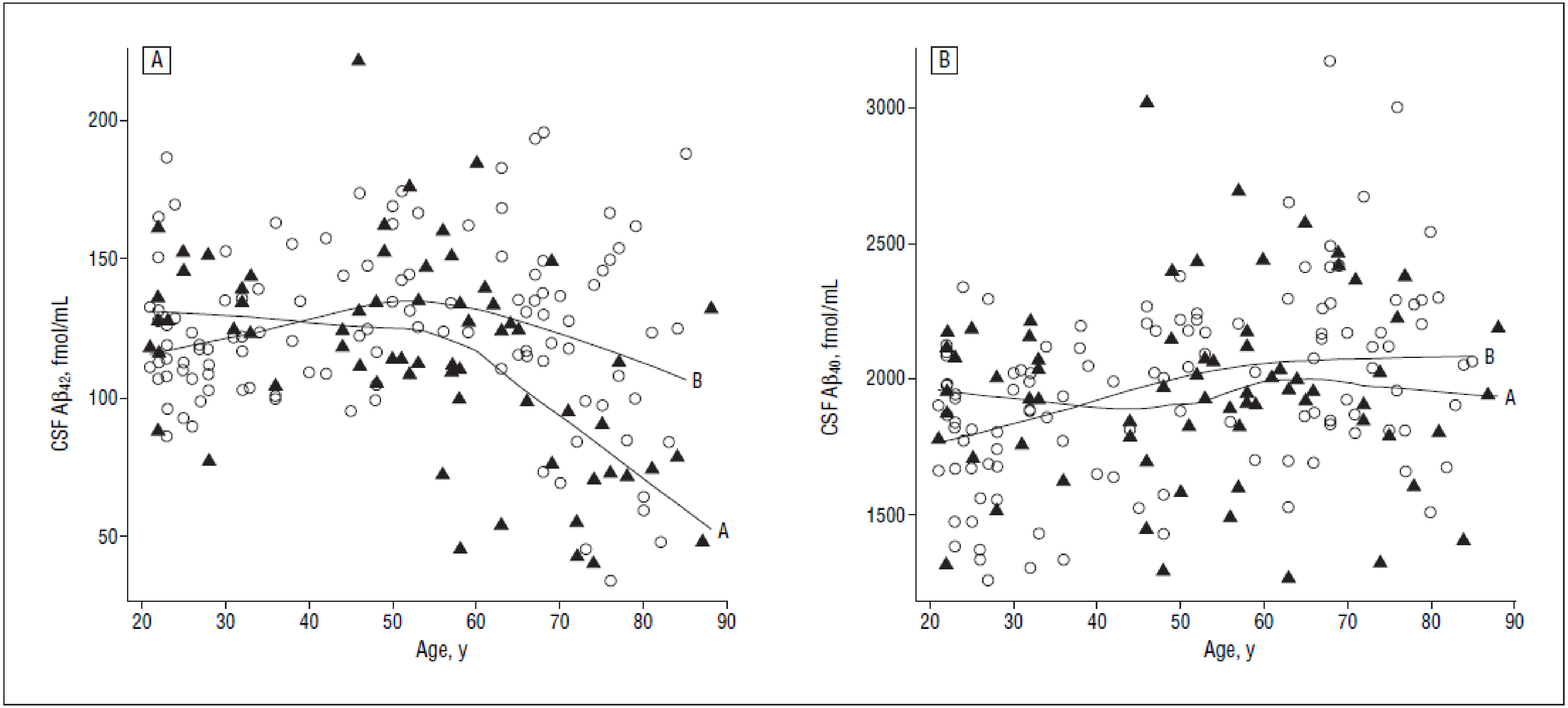
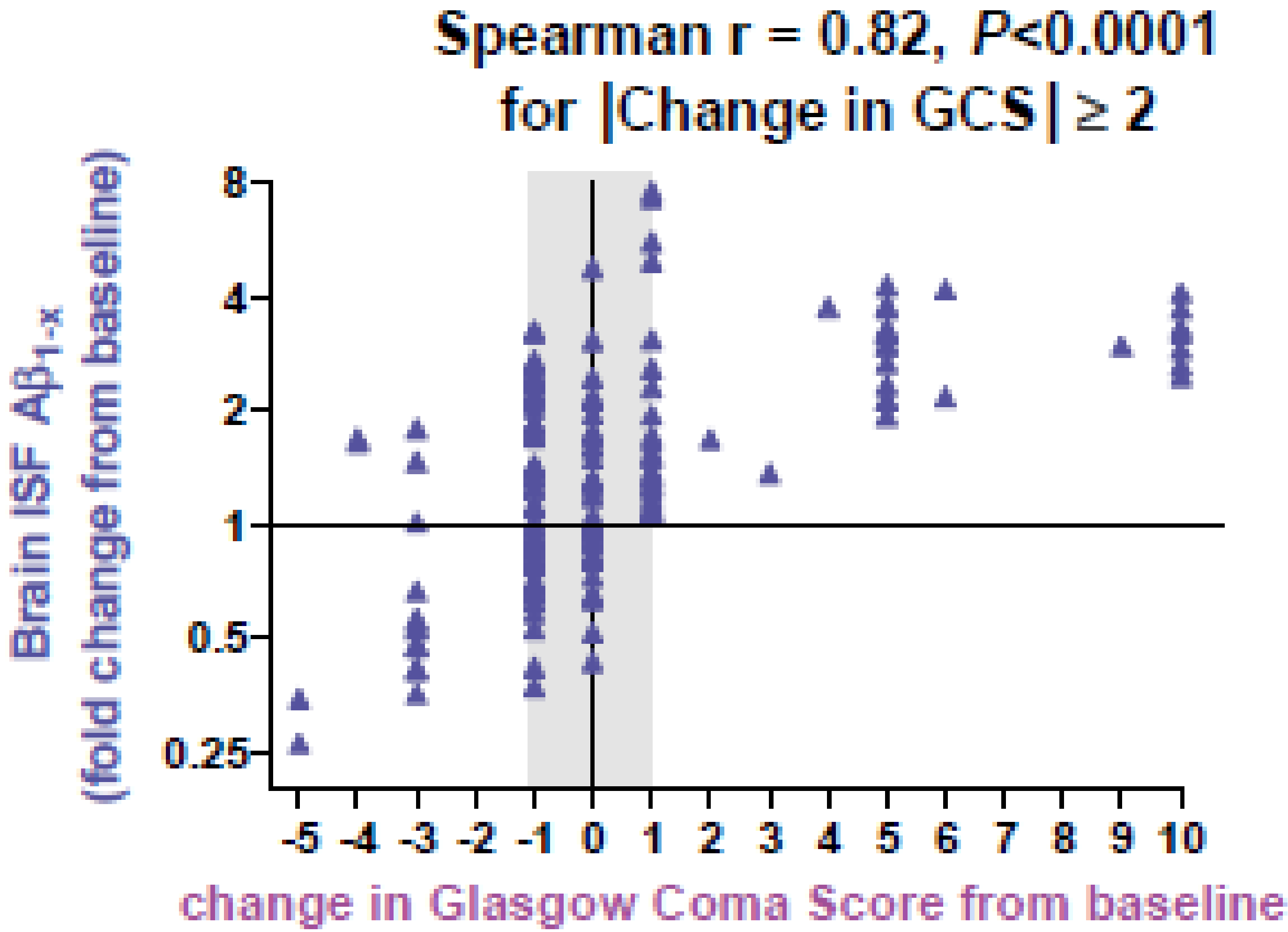


Figure. Cerebrospinal fluid (CSF) β-amyloid 42 ($A\beta_{42}$) (A) and $A\beta_{40}$ (B) concentrations by age and apolipoprotein E (*APOE*4*) allele status in 184 normal adults aged 21 to 88 years. Closed triangles represent *APOE*4*-positive subjects; A = Loess-fitted line for *APOE*4*-positive subjects. Open circles represent *APOE*4*-negative subjects; B = Loess-fitted line for *APOE*4*-negative subjects.

Peskind et al, Arch Neurol 2006;63:936-939.

ISF Aβ Correlates with Coma and Recovery



Brody et al, Science 2008;321:1221-1224.

Aβ: Part of a Synapse Negative Feedback Loop?

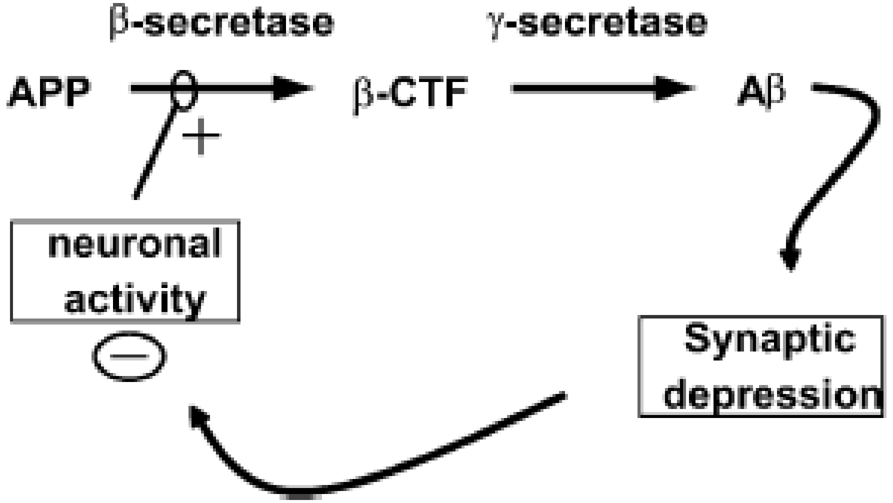


Figure 7. Negative Feedback Model Indicating Proposed Interaction between Neural Activity and APP Processing

Neural activity regulates β-secretase actions on APP. Formation of Aβ depresses synaptic transmission. Synaptic depression decreases neural activity.

Kamenetz et al, Neuron 2003;37:925-937.