

Setting the Stage: Mitochondria, Bioenergetics, and the Road to AD

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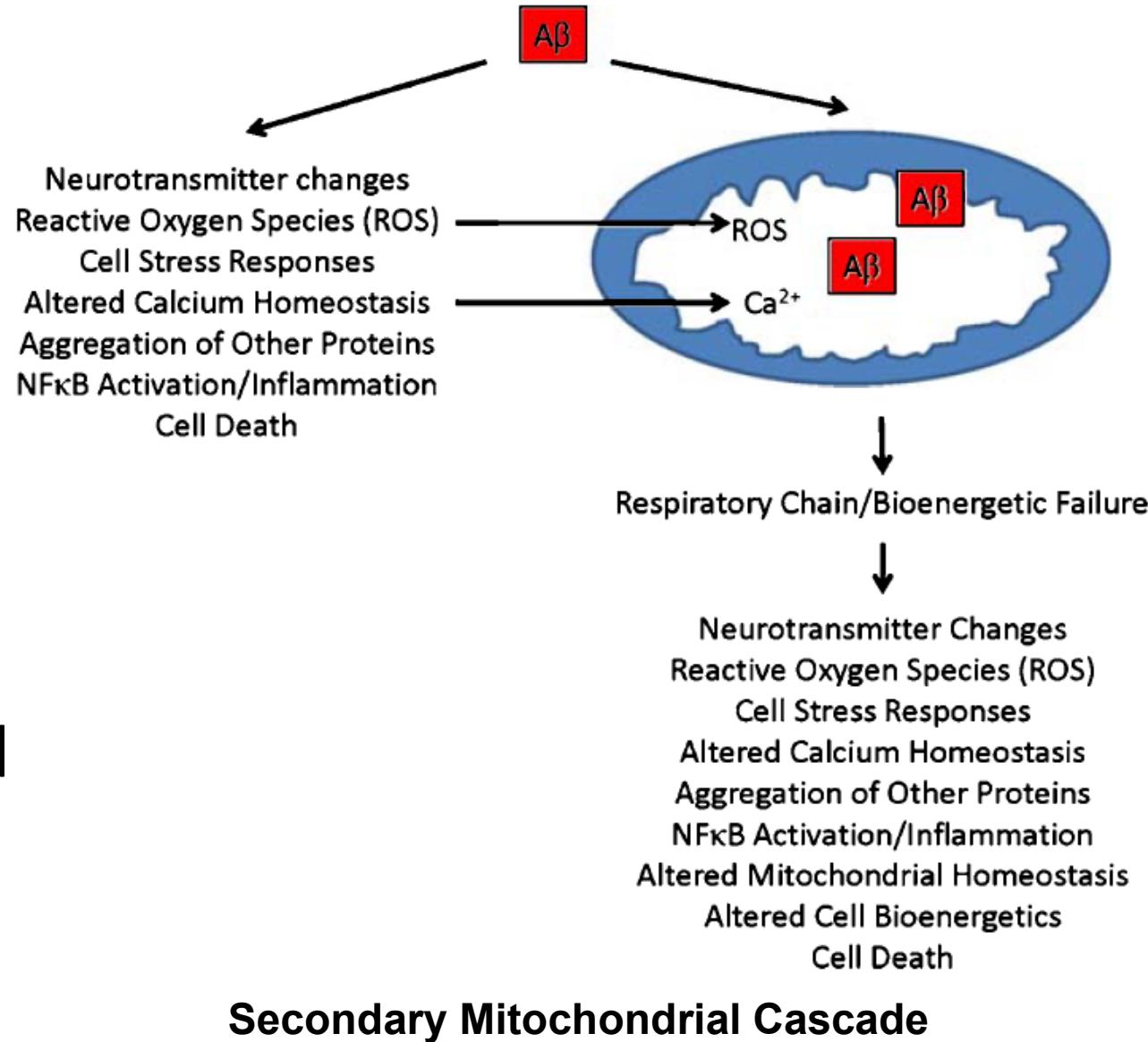
What Are Mitochondria?

- “Powerhouse of the Cell”
- Energy is important!
- They relate to other things:
 - Oxidative stress
 - Calcium homeostasis
 - Cell death
- They are dynamic
 - Fission, fusion
 - Increase or decrease in number
 - Travel around the cell (synapses)
- Contribute to aging



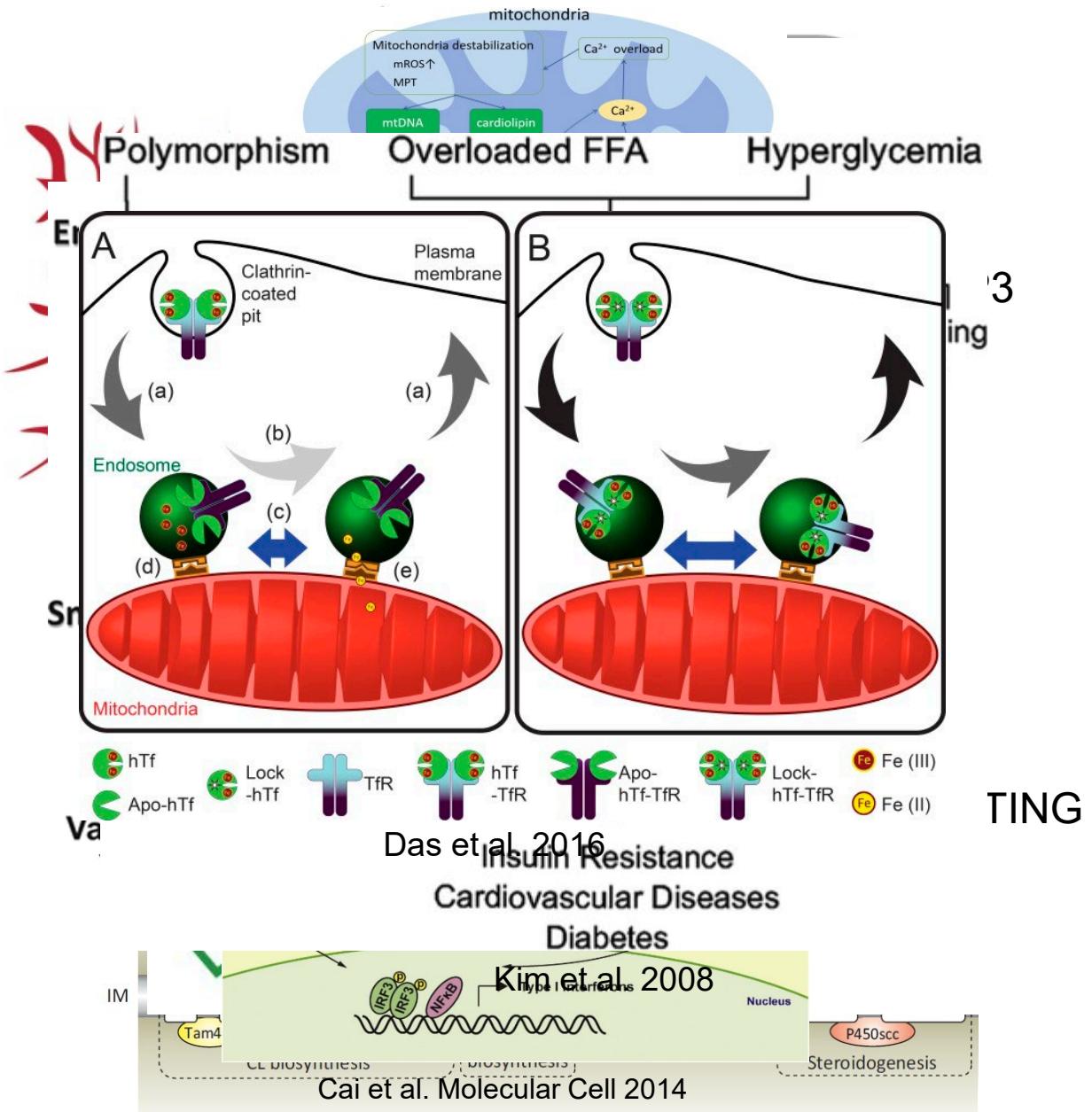
Mitochondria are Altered in AD

- Mitochondria in AD Brains
 - Look different
 - Smaller
 - Less turnover
 - Reduced enzyme activities
 - mtDNA changes
- Some Changes not Brain-Limited
 - Cause vs effect?



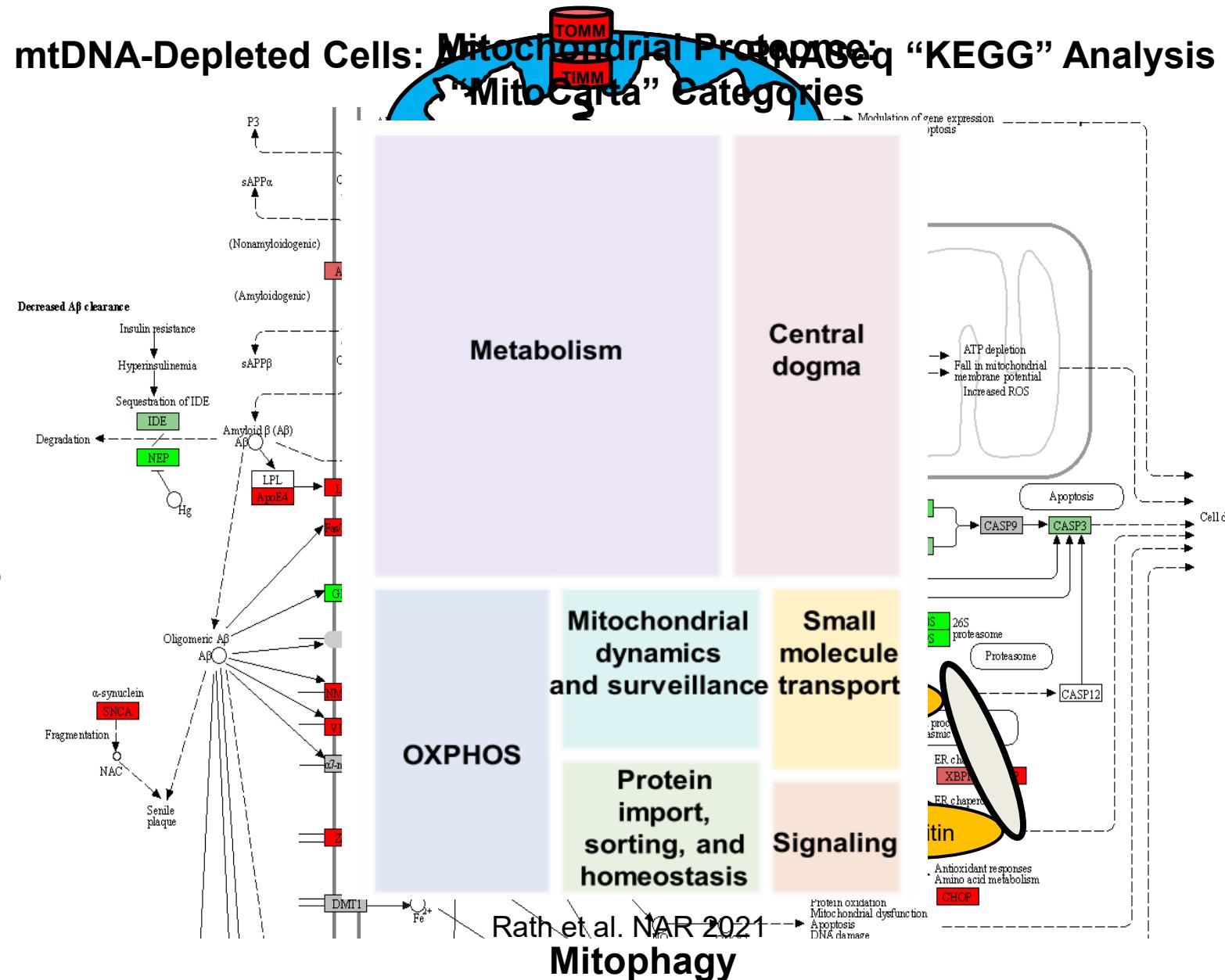
Mitochondria Influence AD Phenomena

- Cerebral blood flow
- White matter hyperintensities
- Insulin resistance
- Neuroinflammation
- Lipid biology
- Iron homeostasis
- Endosome trafficking

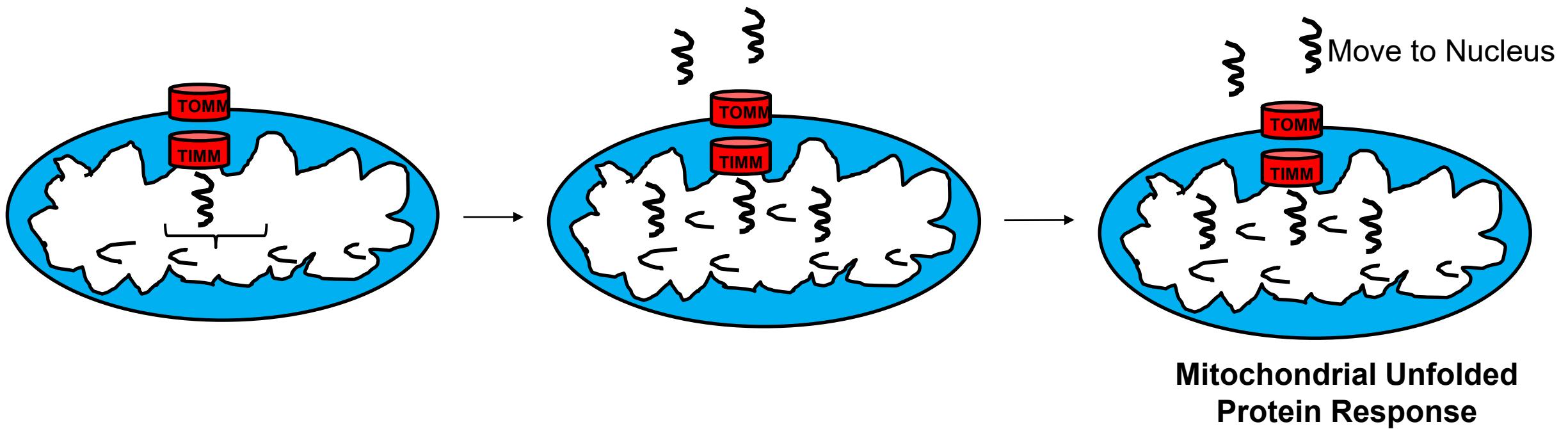


Mitochondria 101

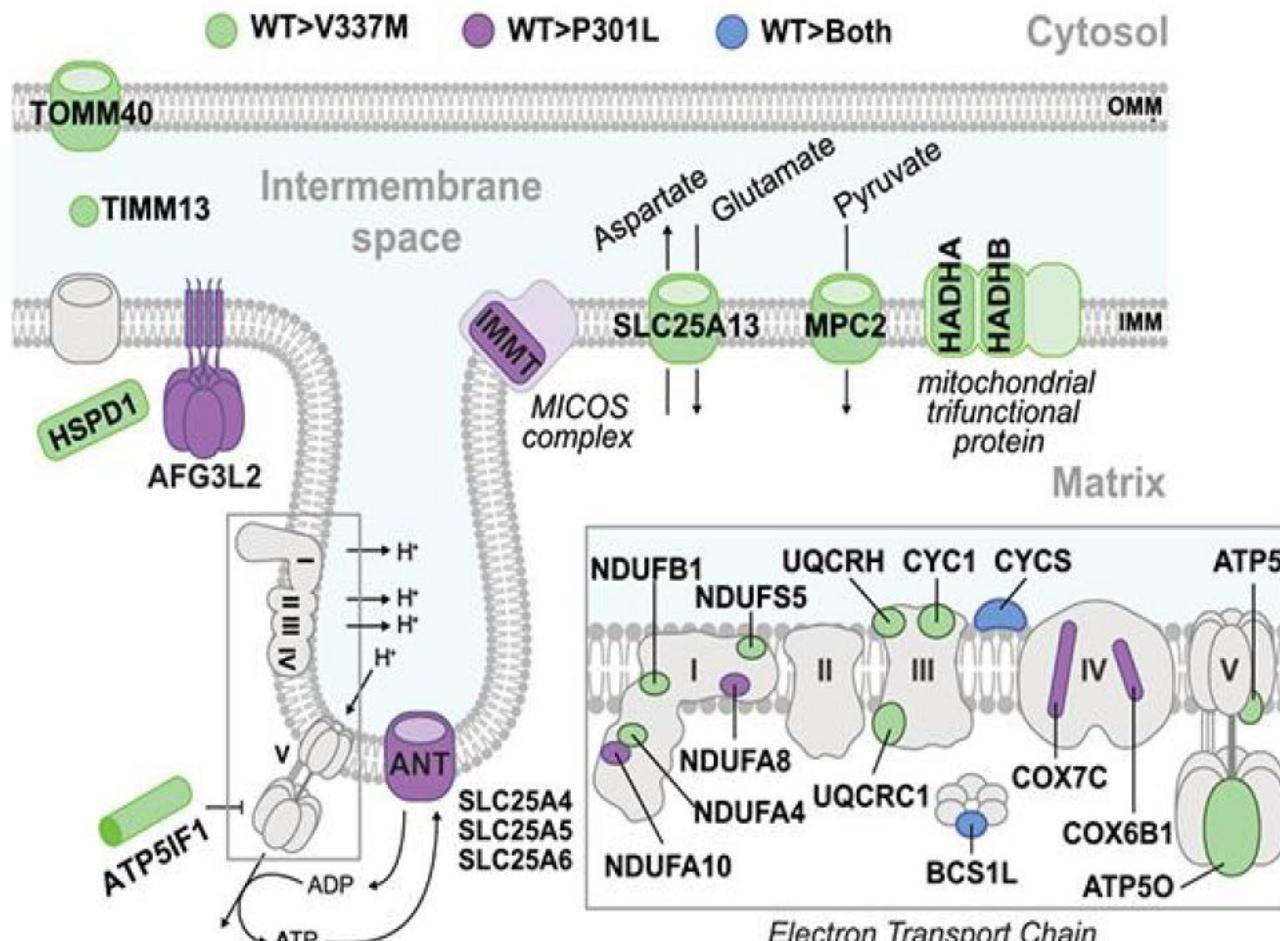
- Bioenergetics
- mtDNA
- Mito-Nuclear Cross Talk
- Mito Quality Control
- Mitochondrial Proteome



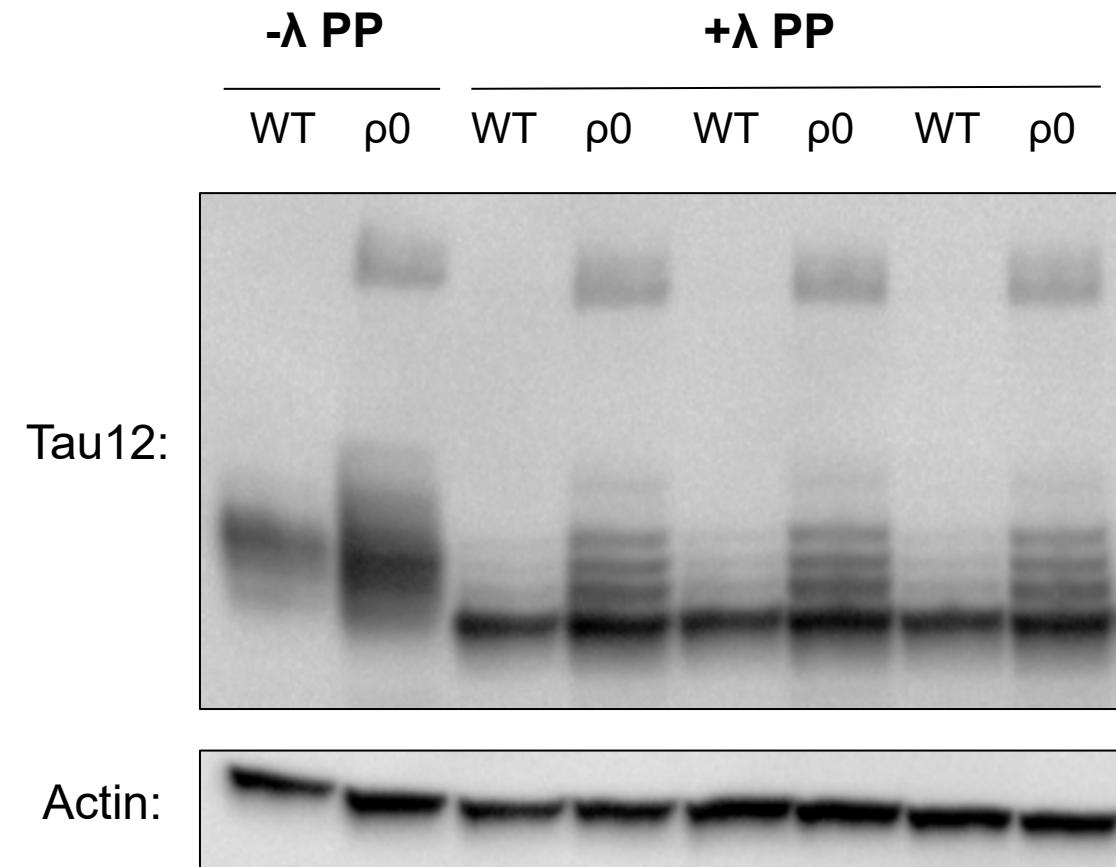
Mitochondria Handle Proteins



Tau Affects Mitochondria, Mitochondria Affect Tau

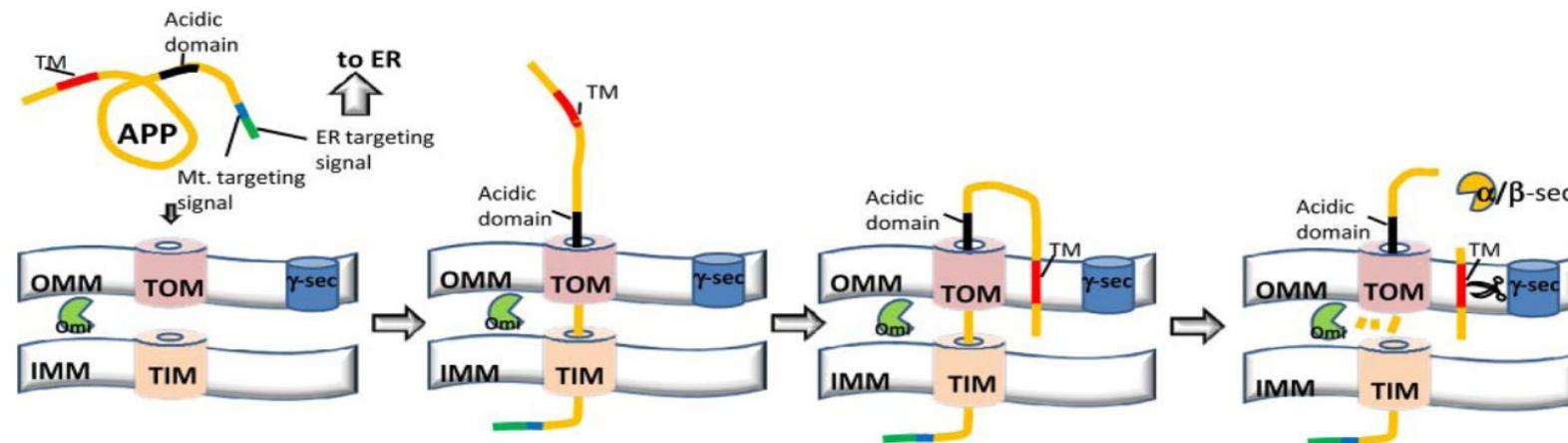


Tracy et al. Cell 2022

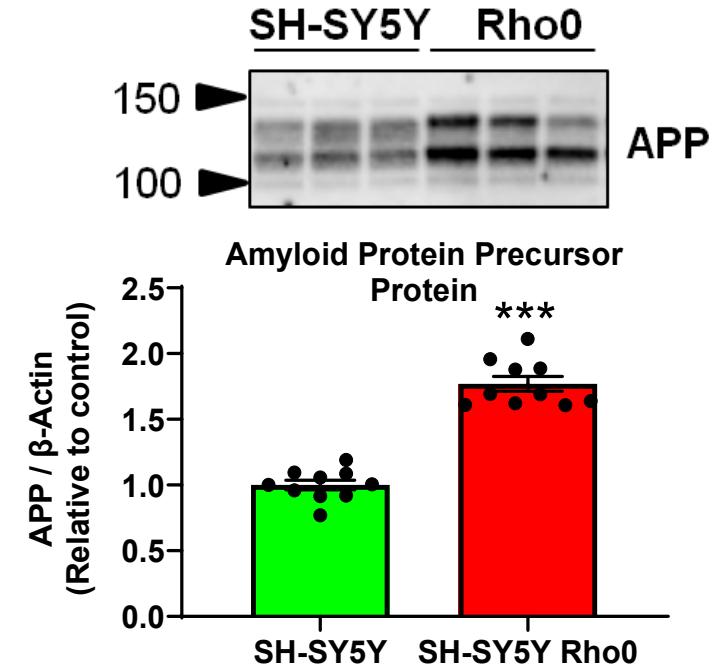
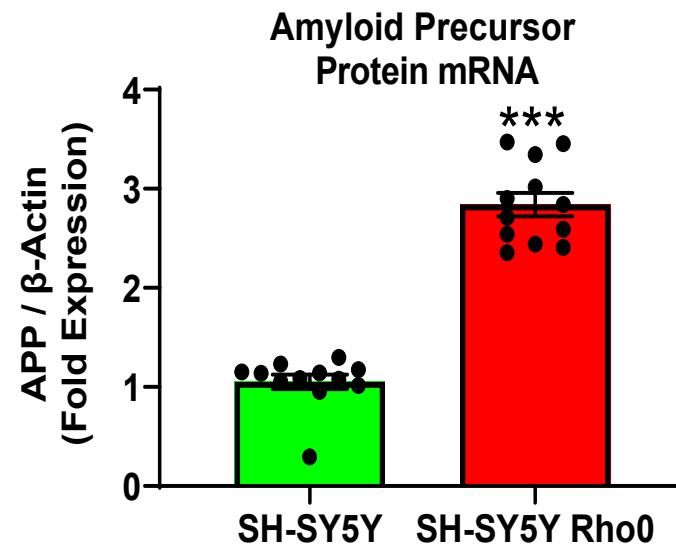


Weidling et al. JAD 2020

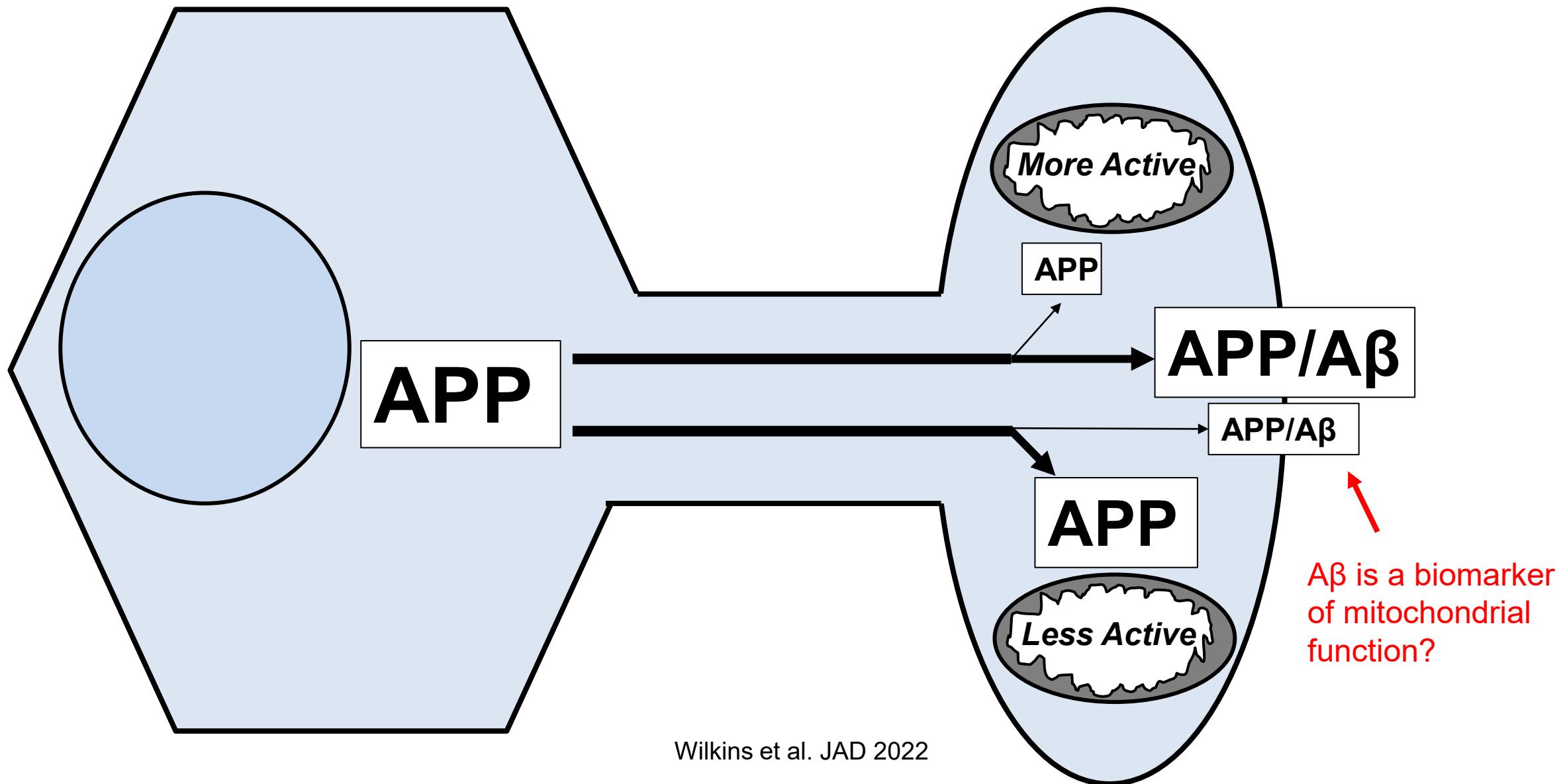
APP Affects Mitochondria, Mitochondria Affect APP



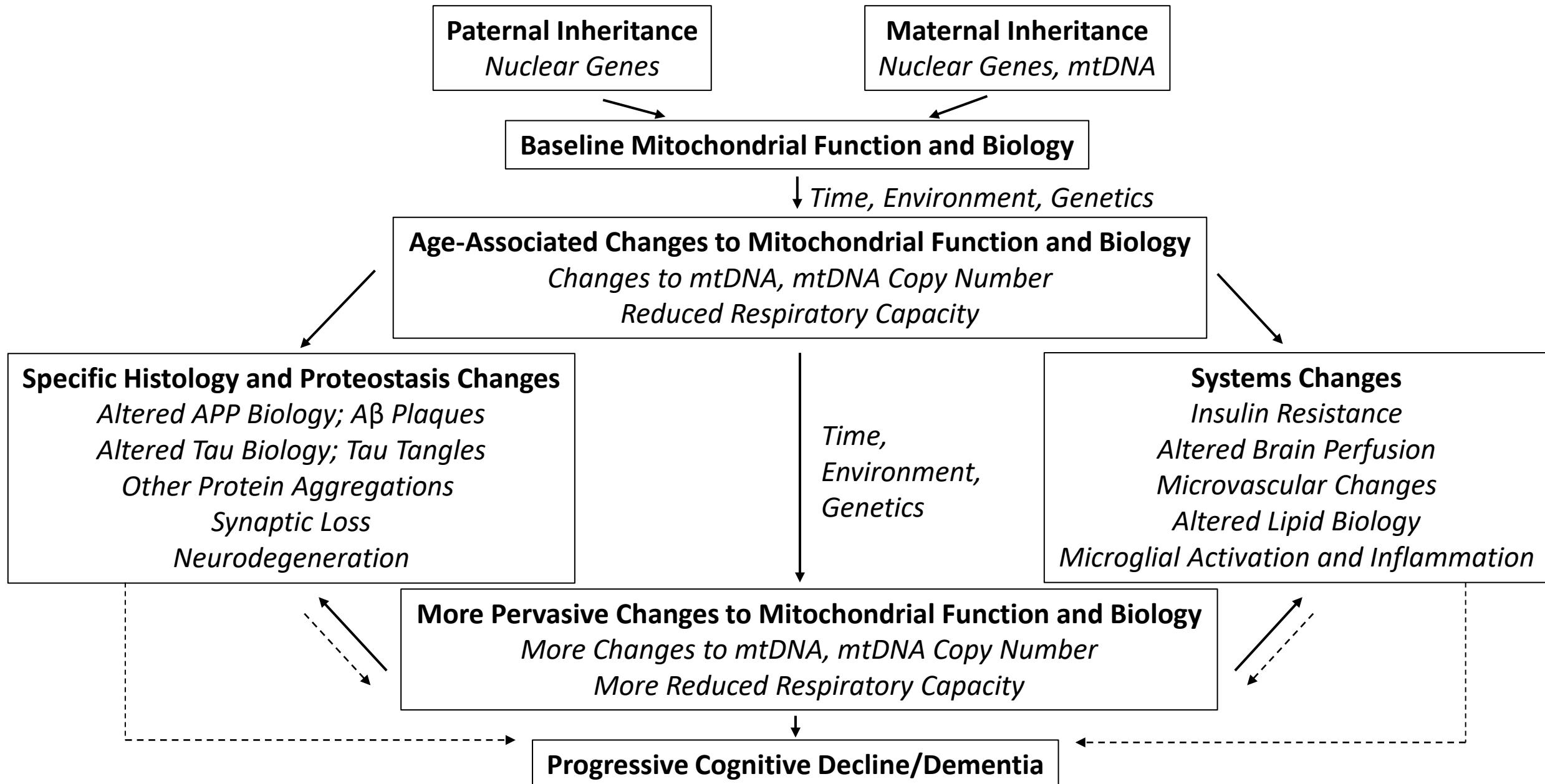
Pavlov et al. Faseb J 2011



Mitochondria Affect APP Trafficking and A β Release

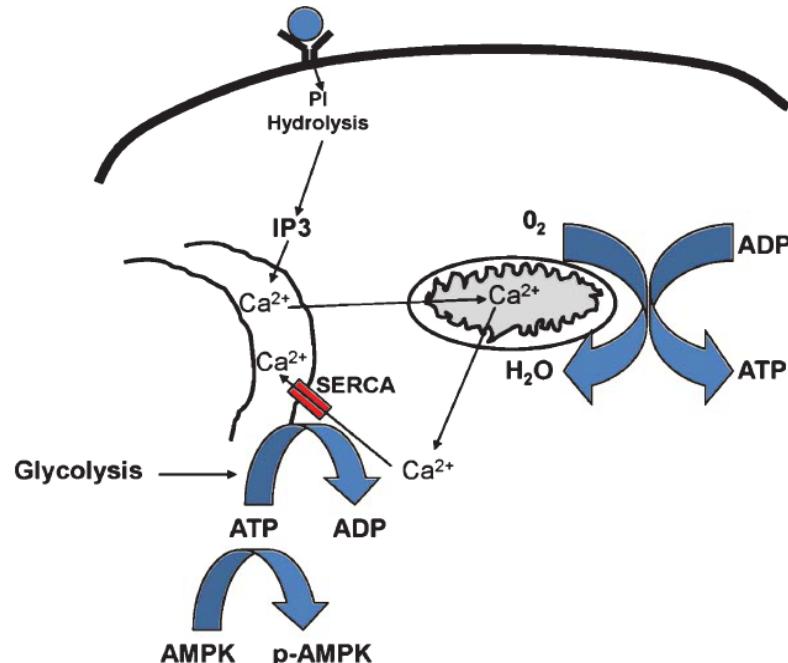


Mitochondrial Cascade Hypothesis (Swerdlow et al, JAD, 2018)

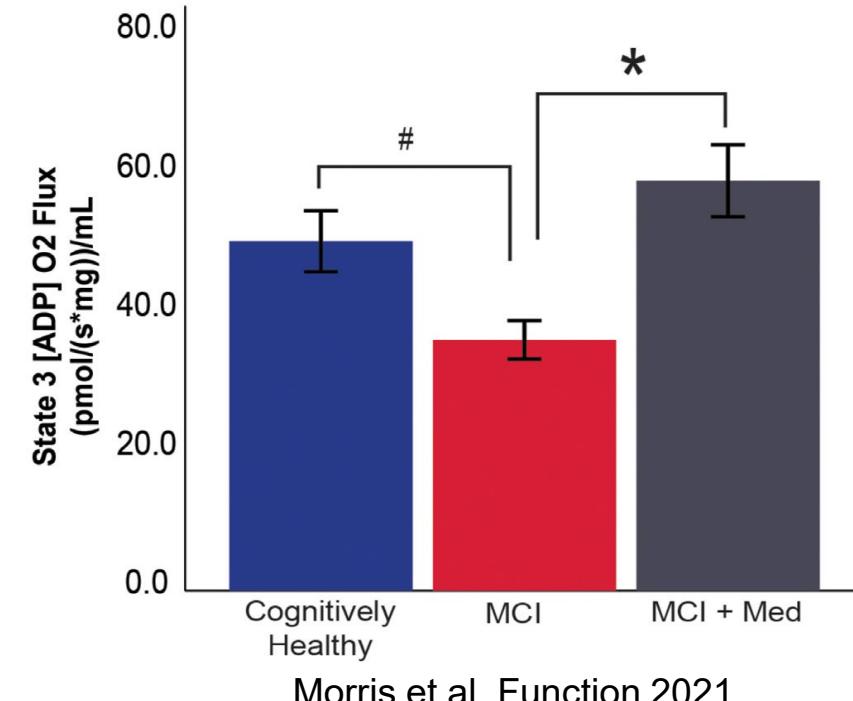


Targeting Mitochondria

- Neurotransmitter manipulation (cholinesterase inhibitors)
- Promote mitophagy
- Protect (from oxidative stress, abeta, ApoE)
- Promote bioenergetic fluxes



Lu et al. JAD 2013.



Morris et al. Function 2021

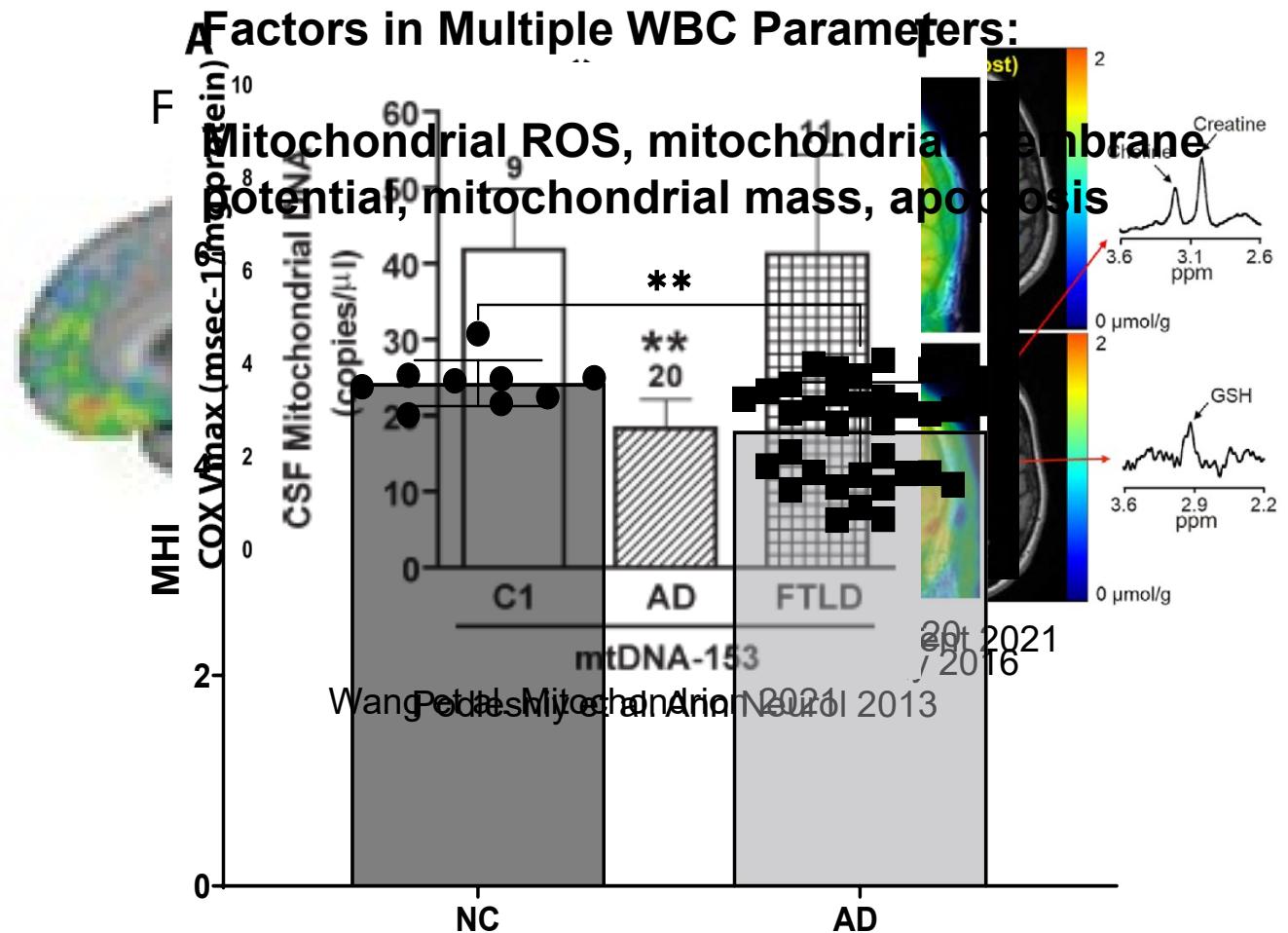
Ketogenic Diet Brain Changes: Unbiased KEGG Pathway Analysis

Activated by KD in Neurons	q-value	Pathways Activated in Neurons by KD	q-value
Alzheimer's disease	0.000655132	Protein processing in endoplasmic reticulum	0.000655132
Parkinson's disease	0.001667042	Insulin signaling pathway	0.001221279
Huntington's disease	0.002016036	Oxidative phosphorylation	0.001221279
Renal cell carcinoma	0.002158549	Adrenergic signaling in cardiomyocytes	0.001221279
Non-alcoholic fatty liver disease (NAFLD)	0.002715537	Dopaminergic synapse	0.001221279
Proteoglycans in cancer	0.00405118	cAMP signaling pathway	0.001221279
Alcoholism	0.004716036	Autophagy - animal	0.001221279
Morphine addiction	0.006020527	MAPK signaling pathway	0.001221279
Amphetamine addiction	0.009695652	ErbB signaling pathway	0.001221279
Bacterial invasion of epithelial cells	0.010793315	Oocyte meiosis	0.001246883
Fluid shear stress and atherosclerosis	0.011455177	Ras signaling pathway	0.001559926
Prostate cancer	0.011447938	Ribosome	0.001667042
Endometrial cancer	0.016090616	Long-term potentiation	0.001686365
Colorectal cancer	0.017046446	Retrograde endocannabinoid signaling	0.001745341
Type II diabetes mellitus	0.017063526	Oxytocin signaling pathway	0.001839688
Choline metabolism in cancer	0.020426807	Glutamatergic synapse	0.001948751
MicroRNAs in cancer	0.021320745	GABAergic synapse	0.001948751
Glioma	0.024955821	Endocytosis	0.002273079
Insulin resistance	0.024973282	Neurotrophin signaling pathway	0.002273079

Mitochondrial Biomarkers

Mitochondrial Health Index

- Neuroimaging
 - Direct assays
 - CSF
 - Exosomes
 - A β ?



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