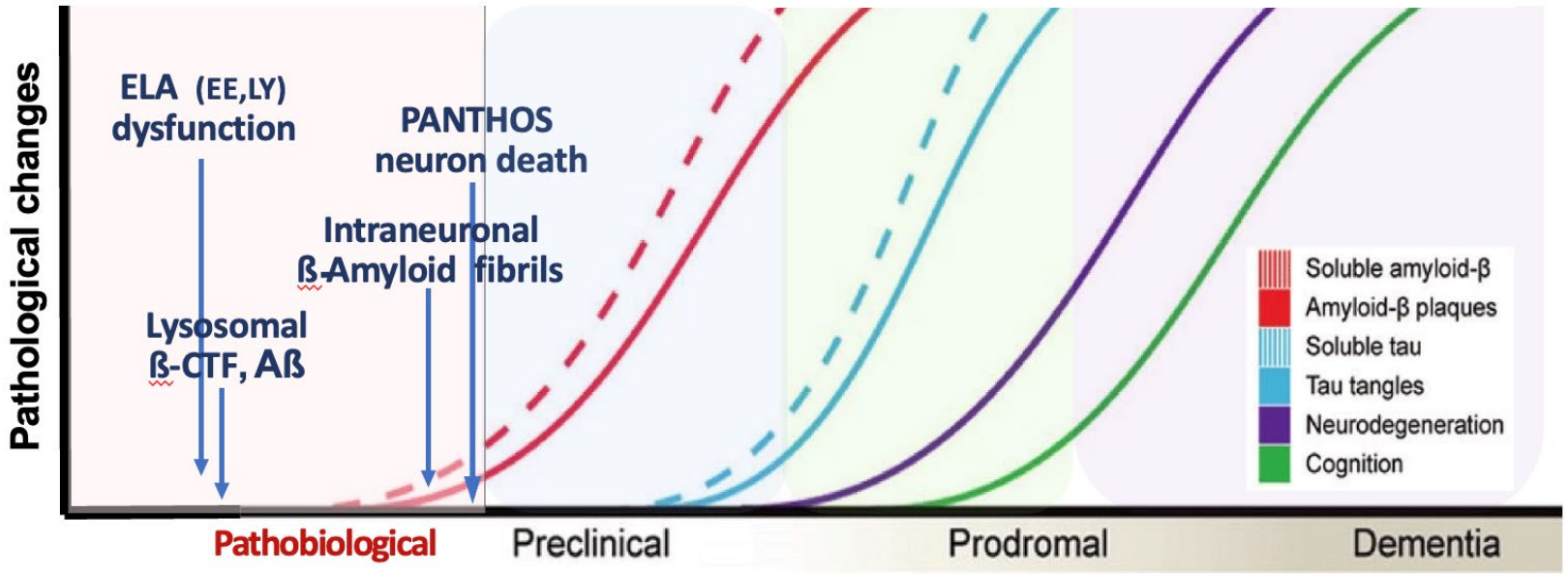
Endosomal- Lysosomal pathobiology: an integrative framework for understanding Alzheimer's and related dementias

GENES
ENVIR. FACTORS
AGING

→ *PROXIMAL* PATHOBIOLOGY → HALLMARK NEUROPATHOLOGY → IMMUNE RESPONSE NEURODEGENERATION



Jack et al. 2013, Nordberg, McDade and Bateman

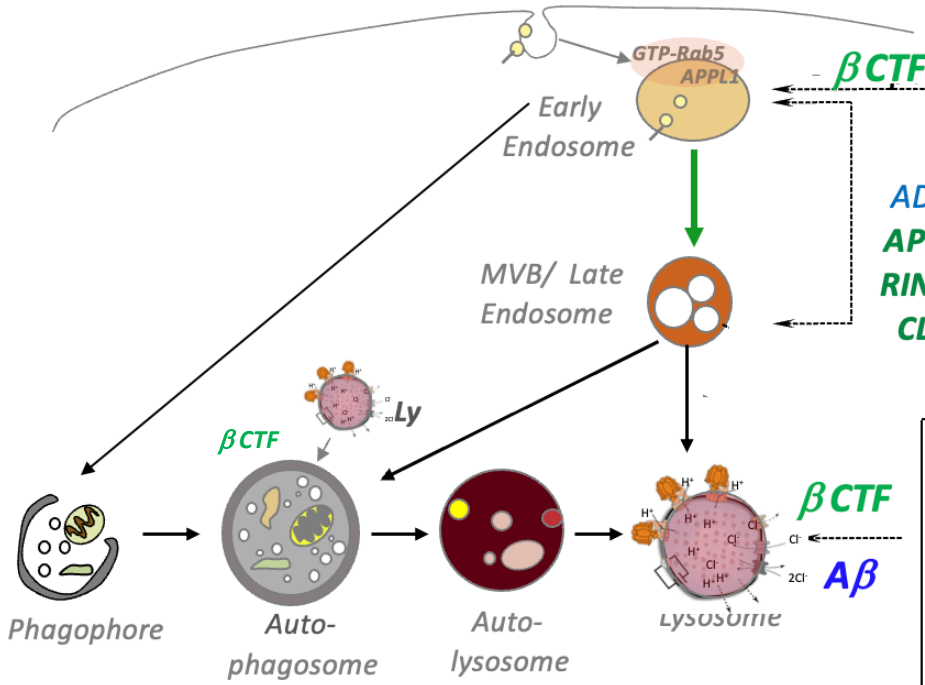
Primary E-L dysfunction

- In AD, ELA is essential partner with APP
- Genetics strongly implicate E-L a primary role in AD
- Intra-neuronal AD pathology precedes hallmark AD lesions
- E-L pathogenic mechanisms validated in AD models
- Relevant to other dementias

Revealed (and understudied) targets: ELA, endocytosis, APP biology esp. ßCTF, Cholinergic neurodegeneration, multiple lysosomal pathobiological pathways.

Nixon, FASEB J, 2017; Knopmann et al., Nature Rev, 2022
Nixon and Rubinsztein, Nature Rev. Cell Mol. Biol., 2024, In process

Endosomal-Lysosomal genes have a primary role in AD etiology



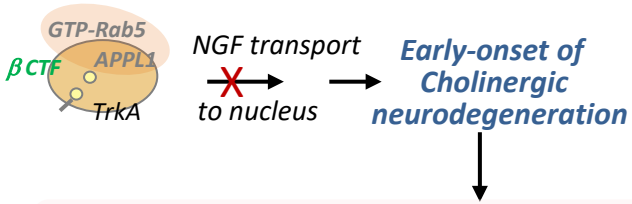
***APP* mutation**
***APP* gene duplication**
Trisomy 21 – 3n*APP*

AD risk genes impacting endocytosis:
APOE ε4 *CLU,* ***PICALM, BIN1,*** *EPHA1,* ***RIN3, RIN2,*** *MS4A4A/ MS4A6E, CD33,* ***CD2AP. SORL1****, SORCS1, ABCA7, LRP*

***APP* mutations**
***APP* gene duplication**
***PSEN1, PSEN2* mutations**

Other key factors:
Aging, *PLD3, APOE4, SORL1*
Cholesterol/high fat
Reactive oxygen species

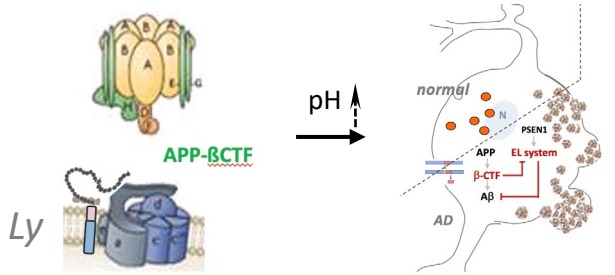
Signaling endosome, Rab5 over-activation



Positive outcomes Phase II clinical trial of NFMD reversal of rab5 over-activation in DLB - pivotal phase 2b underway

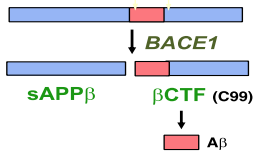
Jiang , Nat Comm. 2022;
Alam, Mol. Degen. 2023

***Early* lysosomal death of neurons**



vATPase PANTHOS

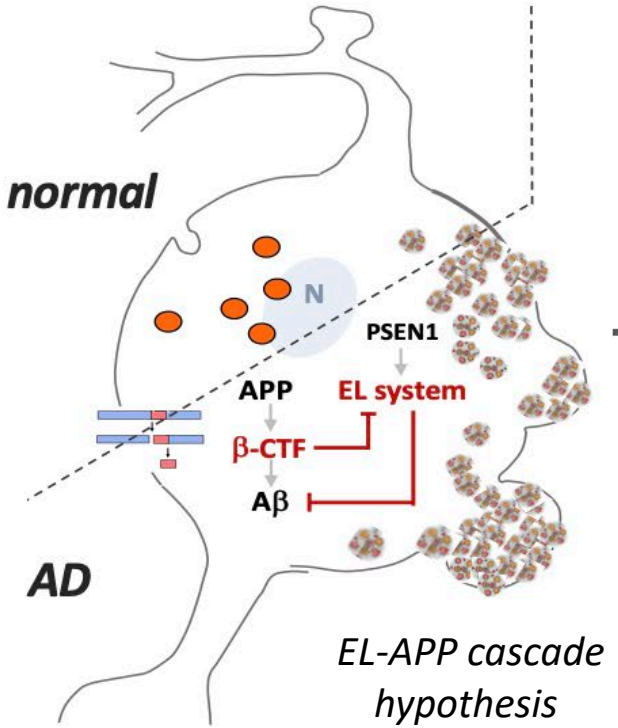
Early APP-dependent intraneuronal "inside-out" origin of ß-amyloid plaques



βCTF = β C-Terminal Fragment of APP

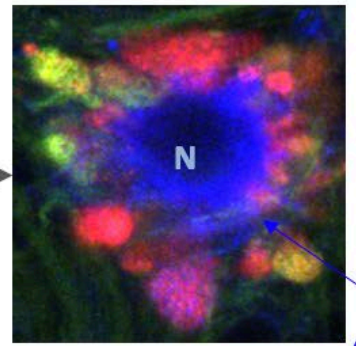
Im, Science Adv., 2023
Lee, Nature Neurosci, 2022;

PANTHOS neurodegeneration: ”Inside-out” origin of ß-amyloid plaques

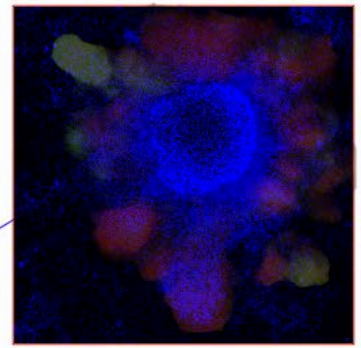


EL-APP cascade hypothesis

intact PANTHOS neuron



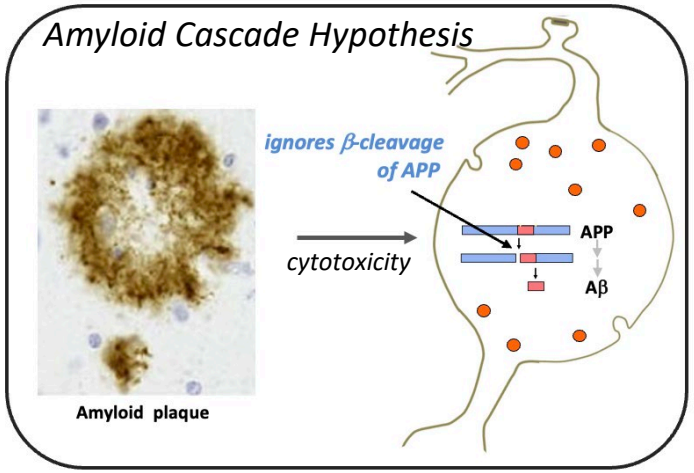
senile plaque (amyloid “ghost”)



β-amyloid

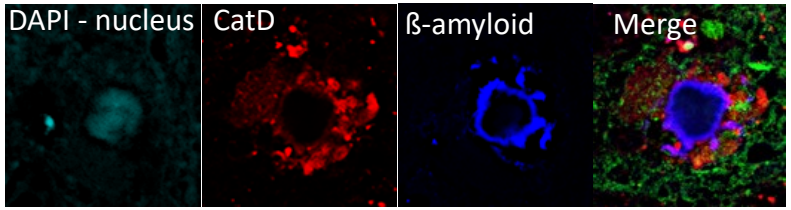
Glia / Inflammatory Phase

- **APP-ßCTF and additional factors impair vATPase and acidification as a primary event**
- **Failed ER-phagy induces fibrillar ß-amyloid accumulation within ER**
- ***Intraneuronal* amyloidogenesis yields senile plaque upon death of neuron**
- **Re-acidifying lysosomes *in vivo* attenuates autophagic stress, neuronal death, and plaques**



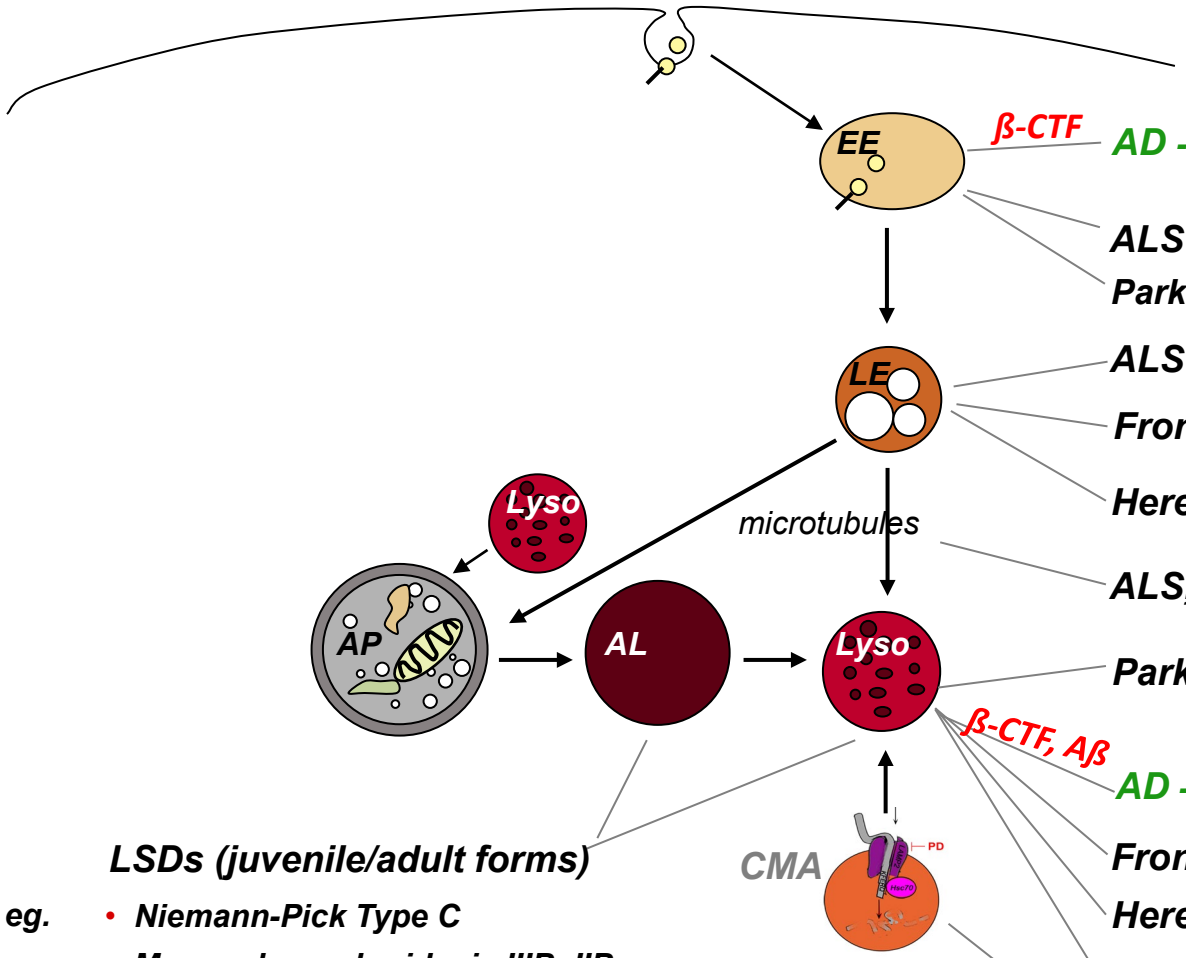
PANTHOS

Human PFC - AD
Braak III



Lee, Nature Neurosci, 2022; Im, Science Adv., 2023

The Endosomal-Lysosomal Network:
Genetic "Hotspot" in AD and other Neurodegenerative Diseases



ß-CTF

AD - *App mutation/triplication, ApoE ε4 (high risk)*

ALS – *Alsin, C9orf72,*

Parkinson's Disease – *LRRK2*

ALS – *CHMP2B*

Frontotemporal Dementia - *CHMP2B, p97/VCP*

Hereditary Spastic Paraplegia- *Spg4 , Spartin*

ALS, MND, CMT – *dynein, dynactin complex*

Parkinson's Disease - *ATPase 13A2, ATP6AP2 LRRK2 , α-synuclein, GBA, VPS35, TMEM175α-*

ß-CTF, Aß

AD - *Presenilins 1,2, APP, ApoE4 (high risk)*

Frontotemporal Dementia –*TMEM106B, PGRN, FUS, UBQLN2*

Hereditary Spastic Paraplegia- *Spg15, Spg11*

Wolfram Disease - *WFS1*

PD, FTD - *α-synuclein, UCH-L1, LRRK2*

LSDs (juvenile/adult forms)

eg.

- ***Niemann-Pick Type C***
- ***Mucopolysaccharidosis IIIB, IIB***
- ***Gaucher's (GBA) → Parkinson's (risk)***
- ***NCL → PD (ATPase13a2), ?FTD (GRN)***
- ***Chediak-Higashi (CHS/LYST) → ? PD/dementia***