Endolysosomal Ion Channels As Novel Therapeutic Targets In Alzheimer's Disease And Frontotemporal Dementia

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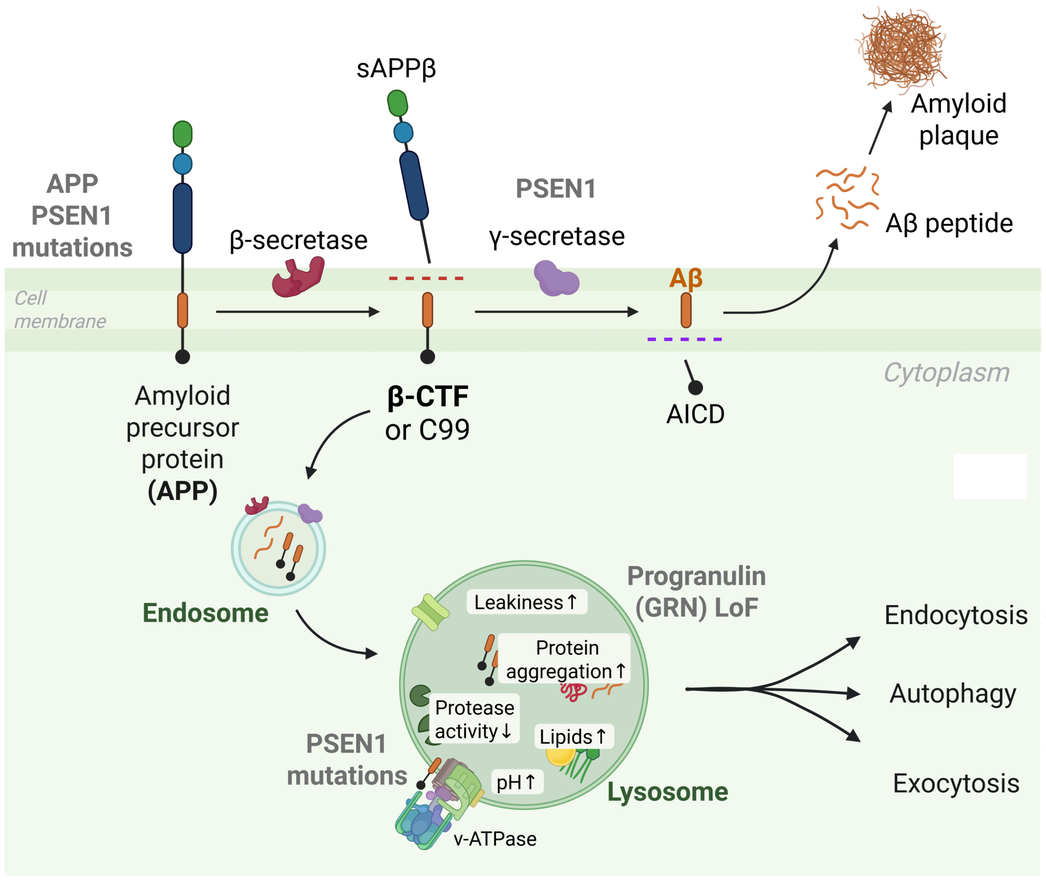
Dysregulation of the endo-lysosomal system in Alzheimer's Disease and Frontotemporal Dementia



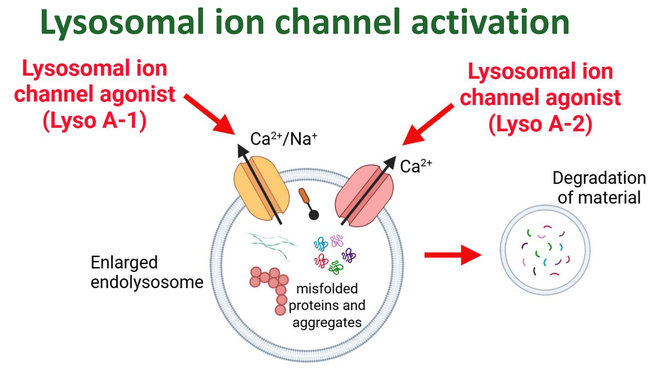
Familial Alzheimer's disease (fAD) results from mutations in the amyloid precursor protein (*APP*) and Presenilin-1 (*PSEN1*)

Under fAD state, APP is cleaved by β- and γ-secretases generating a **C-terminal fragment** (β-**CTF**) and Aβ peptides, which **accumulate** within enlarged **lysosomes** as well as in **early endosomes.** *PSEN1* (subunit of γ-secretase) mutations have been shown to reduce lysosomal acidification as well as alter lysosomal calcium storage and release.

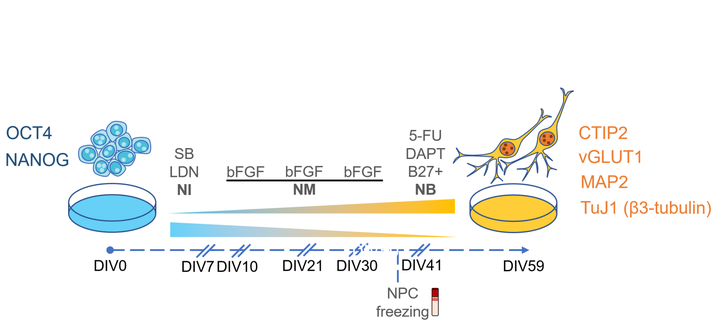
Loss of Progranulin (*PGRN*) leads to frontotemporal lobar degeneration (FTLD)

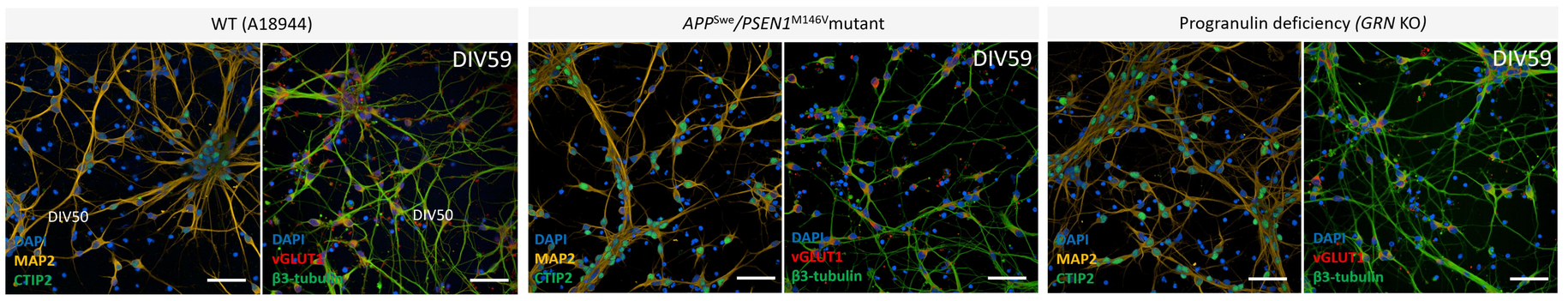
PGRN regulates multiple aspects of lysosomal function, including **lysosomal pH** and activities of multiple proteases, such as **cathepsin D** and **β-glucocerebrosidase** (GCase). ***GRN* knockout** leads to broad lysosomal dysfunction, contributing to **frontotemporal dementia** (FTD).

Lysosomal ion channel activation



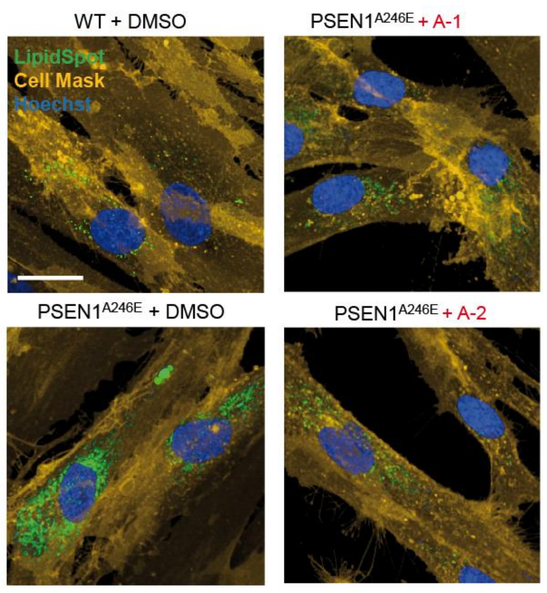
Human iPSC-derived cortical neurons

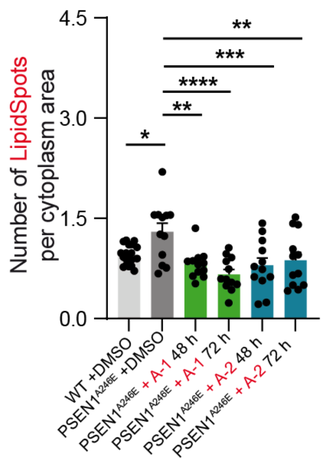




Mature cortical neurons express neuronal markers **β3-tubulin, MAP2** and the deep-layer cortical neuron transcription factor **CTIP2**. The biggest fraction of cortical neurons is **vGLUT1**-positive (glutamatergic).

Accumulation of lipids in PSEN1^{A246E} (AD) patient fibroblasts

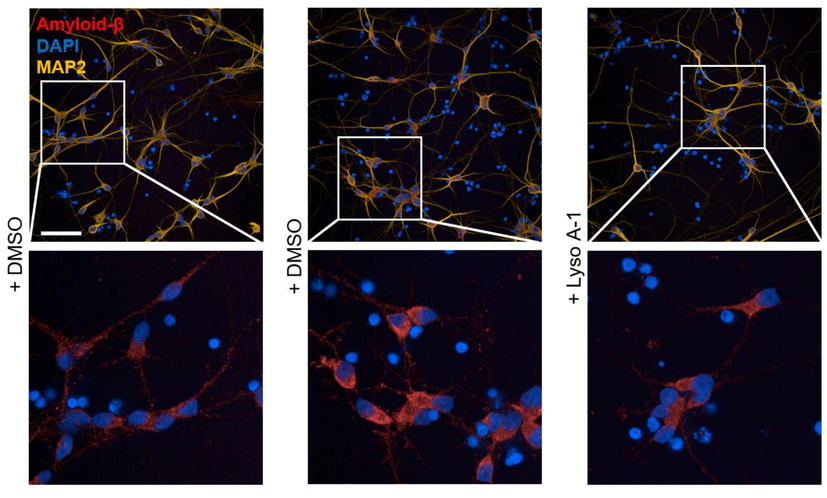


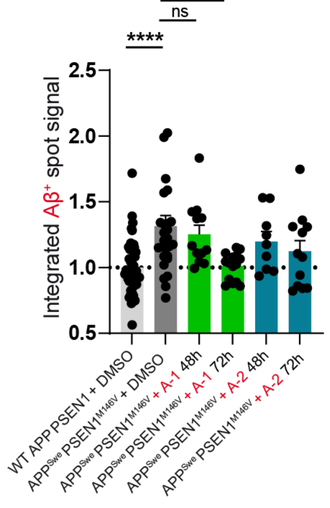


PSEN1^{A246E} human fibroblasts exhibit lipid droplet accumulation. This phenotype is **alleviated** following treatment with Lyso A-1 and Lyso A-2.

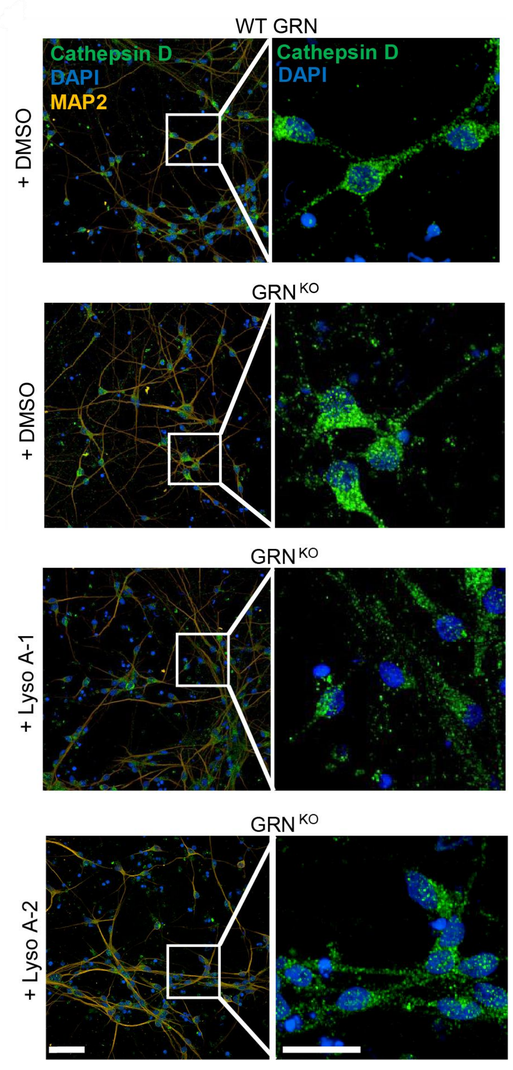
Elevated Amyloid-β load in APP^{Swe} PSEN^{M146V} (AD) cortical neurons

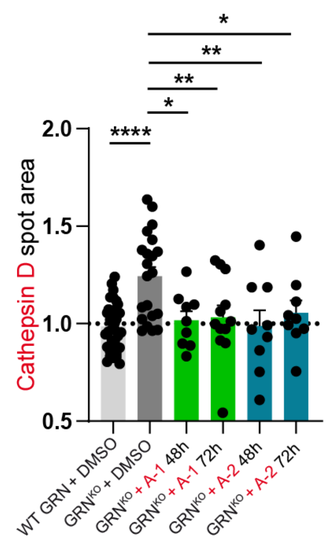
Amyloid-β levels are increased in APP^{Swe} PSEN1^{M146V} cortical neurons.
Treatment with **Lyso A-1**, but not with Lyso A-2, leads to **reduction of amyloid-β accumulation**.





Increased Cathepsin D in GRN^{KO} (FTD) cortical neurons





Expansion of the lysosomal protease **Cathepsin D** spot area in GRN^{KO} neurons reflects lysosomal enlargement and aggregation.
Treatment with **Lyso A-1** and **Lyso A-2** leads to **restoration** of **lysosomal homeostasis**.

Key Take-Aways & Outlook:

Phenotypic differences of endolysosomal morphology, aggregation and function were identified in human fibroblast and iPSC-derived AD/FTD neuronal models
Additional hallmarks include amyloid-β aggregation and lipid droplet accumulation
Preliminary data suggests that lysosomal ion channels could be potential therapeutic targets

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