Excitatory neuronal role of PLCG2 in Alzheimer's disease

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Abstract
Recent Genome-Wide Association Studies (GWAS) have identified novel rare coding variants (P522R, M28L variants) of the enzyme phospholipase-C-γ2 (PLCG2) in late-onset Alzheimer's Disease (LOAD). The role of PLCG2 and its variants in AD has been largely investigated in microglia and responses to Aβ pathology; however, little is known about the role of PLCG2 and its AD variants in other cell types or its role in tau pathology. To evaluate the immunoreactivity of PLCG2 and its relationship with tau pathology, we performed western blot and immunofluorescence staining on human AD post-mortem brains and PS19 tau mice. By stereotaxic injection of AAV8-CaMKIIa-cre and AD TBS-soluble tau seeds in PLCG2-floxed mice, we quantified tau spreading induced by PLCG2 knockdown. Furthermore, we generated human neural organoids derived from human iPSCs of a healthy donor and a CRISPR/Cas9-edited PLCG2 P522R knock-in (KI) cell line to investigate the autophagy-lysosomal pathway (ALP) dynamics induced by PLCG2 by using FUW-mCherry-GFP-LC3 reporter assay. We found higher global protein levels of PLCG2 in human AD cases and PS19 mice, but pathological tau-positive cells had a lower level of PLCG2 than neighboring pathological tau-negative cells. Knockdown of PLCG2 in excitatory neurons increased tau spreading in PLCG2-floxed mice. Autophagy flux increased in P522R KI organoids, even in the presence of Bafilomycin A1 (autophagy flux inhibitor), compared to wild-type organoids. Our results suggest that repression or dysfunction of PLCG2 may contribute to tau pathology in excitatory neurons of AD, probably via the regulation of the ALP.

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