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P3. UNRAVELING THE ROLE OF LOW-DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 8 IN ALZHEIMER'S DISEASE USING A NEW C. ELEGANS MODEL

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Alzheimer's disease (AD) is the most common neurodegenerative disorder. Familial AD is caused by mutations in APP, PSEN1 and PSEN2, while individuals carrying the ε4 allele of Apolipoprotein E (ApoE) are at increased risk of AD. One of the neuropathologic feature of AD is represented by the extracellular deposition of β-amyloid (Aβ), deriving from the proteolysis of the Amyloid Precursor Peptide (APP) by presenilins (encoded by PSEN1 and PSEN2), the catalytic core of the γ-secretase complex. Aβ accumulation seems to be responsible for the pathogenesis, although lately this hypothesis is debated. Recent data suggest the involvement of the ApoE receptor, the Low-Density Lipoprotein Receptor-Related Protein memory in AD genesis. LRP8 is involved in neuronal migration, cell proliferation and memory and, like APP, is cleaved by γ–secretase. We hypothesized that the expression levels and relative proteolytic processing of LRP8 may modulate and influence the AD phenotype, and the occurrence of neurodegeneration. To test our hypothesis, we used C.elegans to study in vivo the correlation among LRP8, PSEN and APP. We generated transgenics overexpressing in neurons human LRP8, as full-length or as fragmented proteins. These lines present a dose- dependent defect in development, locomotion and lifespan. Moreover, we showed PSEN involvement in LRP8 function, using a pharmacological and a genetic approach. The role of the different domains of hLRP8 in these phenotypes is under analysis and the impact on learning and APP proteolysis will be shown.