INPP5D inhibition attenuates amyloid pathology through the regulation of microglial functions

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BACKGROUND

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by accumulated beta-amyloid (Aβ) deposits and robust microgliosis. Recent genome-wide association studies have identified genetic risk factors in late-onset AD (LOAD) which are largely microglial. Among the risk factors, Inositol polyphosphate-5-phosphatase D (INPP5D) confers an increased risk of developing AD. LOAD which are largely microglia. Among the risk factors, Inositol polyphosphate-5-phosphatase D (IP5D) confers an increased risk of developing AD and is associated with increased plaque deposition. As a microglia-specific lipid phosphatase, INPP5D negatively regulates signaling via several microglial cell surface receptors, including TREM2; however, the impact of INPP5D inhibition on AD pathology remains unclear.

METHODS

To determine the impact of Inpp5d on disease pathogenesis and microglial phenotypes, we utilized the 5xFAD model expressing Inpp5d haploinsufficiency.

HYPOTHESIS

INPP5D expression is increased in LOAD and is correlated with amyloid plaque density

Inpp5d deficiency mitigates the behavioral deficits in 5xFAD mice.

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CONCLUSIONS & FUTURE WORK

Distinct transcriptomic profiles altered by Inpp5d deficiency in 5xFAD mice.

INPP5D inhibition attenuates amyloid pathology increases the capacity of Aβ uptake and reduces Aβ induced cytotoxicity.

Differential gene expression analysis revealed distinct neuroinflammatory phenotypes

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