INPP5D is associated with tau seeding and tau pathogenesis

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BACKGROUND

Background: Alzheimer’s disease (AD) is the most common type of dementia characterized by extracellular amyloid deposits and intracellular neurofibrillary tangles composed of hyperphosphorylated tau aggregates. GWAS studies have identified variants in several inflammatory genes as significant risk factors for AD, highlighting that neuroinflammation is a critical, underlying pathological component in AD. INPP5D, a family member of Src homology 2 domain containing inositol 5’ polyphosphatases (SHIPs), is an AD risk gene related to innate immunity in late-onset AD (LOAD). Inpp5d plays a role in regulating signal transduction initiated by immune cell surface receptors. INPP5D binds receptor ITIMs, competes with kinases, and converts PI(3,4,5)P3 to PI(3,4)P2, thereby limiting downstream signaling. We previously reported that Inpp5d expression is increased in LOAD and is positively correlated with amyloid burden. However, the relationship of Inpp5d in tau pathology remains unclear. We hypothesize that inhibiting INPP5D will release the break and increase microglial function.

METHODS

To assess the role of Inpp5d in tau pathology, we performed a fluorescence resonance energy transfer (FRET) assay on human-AD brains obtained from NCRAD. We also crossed a mouse model deficient in Inpp5d (Inpp5d+/-) with a PS19 model of tau pathology and measured tau phosphorylation and transcriptomics. Primary microglia were utilized to measure microglial internalization of Tau.

HYPOTHESIS

INPP5D expression is increased in LOAD subjects.

INPP5D is associated with tau pathology and measured tau phosphorylation and transcriptomics. Primary microglia were utilized to measure microglial internalization of Tau. INPP5D is associated with tau seeding and tau pathogenesis.

INPP5D expression is increased in LOAD subjects.

Inpp5d deficiency mitigates the motor deficits in PS19 mice.

Inpp5d haplodeficiency reduces tau deposition in PS19 mice.

CONCLUSIONS & FUTURE WORK

Our findings confirm that elevated Inpp5d expression in human-AD subjects is recapitulated in PS19 mice and correlated with increased tau pathology. In PS19 Inpp5d+/- mice we found alterations in immune related and cell migration related pathways suggesting that Inpp5d modulates the disease progression through these pathways. Furthermore, pathogenesis may be modulated through increased internalization of tau.

Inps5d haplodeficiency reduces tau, Trem2 and pAkt.

Differential gene expression analysis revealed distinct neuroinflammatory and cell migration pathways.

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