Role of ADAP-1/ Centaurin α1 In Alzheimer’s Disease

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Introduction and Objectives

Synaptic failure in Alzheimer’s disease (AD) is caused by accumulation of the toxic peptide beta-amyloid (Aβ42). Previous studies from our lab found that the brain-specific Ras-anchoring protein, ADAP-1/Centaurin α1 (CentA1) is involved in Aβ42-induced neuronal dysfunction. To evaluate the role of CentA1 in vivo, we created CentA1 knockout mice (CentA1 KO). To test the role of CentA1 in AD pathomechanism, we crossed the CentA1 KO mice with the J20-hAPP mouse model of AD (J20xCentA1 KO).

Methods

Immunofluorescence: NeuN staining of coronal brain sections to evaluate brain morphology
Biochemistry: Western blotting to validate CentA1 KO and APP overexpression in transgenic mice
Behavioral studies: Morris Water Maze (MWM) test to evaluate spatial memory

Golgi staining and spine density analysis in the SLM region of the hippocampus
Immunohistochemistry staining for amyloid plaque burden (6E10) and neuroinflammation (GFAP)

Transcriptome profiling using the NanoString nCounter mouse neuropathology panel

Results

Fig. 1. Generation and validation of hAPP-J20 mice on CentA1 KO background

Table 1. Significantly altered genes between genotypes

Table 1. List of genes significantly increased in the brain of transgenic mice compared to control (WT) mice; nCounter profiling identified the pro-apoptotic factor, Bid significantly reduced in the brain of AD mice on CentA1 KO background.

Conclusions

1. Lack of CentA1 ameliorates AD-like phenotypes (spine elimination, amyloid plaque burden and astrogliosis and spatial memory deficit) in the hAPP-J20 mouse model of disease.
2. Neuropathology gene expression profiling suggests that lack of CentA1 leads to reduced activation of pro-apoptotic signaling and upregulation of genes associated with neuronal survival.