Title:

Lack of ADAP1/ Centaurin-α1 Rescues Cognitive and Synaptic Deficits in a Mouse Model of Alzheimer's Disease

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Abstract:

ADAP1/Centaurin-α1 (CentA1) is a brain-enriched and highly conserved, Arf6 GTPase-activating and Ras-anchoring protein. ADAP1 is involved in dendritic outgrowth and arborization, synaptogenesis and axonal polarization via regulating the dynamics of actin cytoskeleton. Increased level of ADAP1 and its association with amyloid plaques in the human Alzheimer's disease (AD) brain, suggest a role for this protein in AD progression. To further dissect the role of ADAP1/CentA1 in neurodegeneration, we crossed CentA1 KO mice with the hAPP-J20 mouse model of AD (J20 x CentA1 KO) followed by evaluation of behavioral and neuropathological hallmarks of the disease and gene expression profiling. Spatial memory evaluated by the Morris Water Maze test showed significant impairment in J20 mice, that was rescued by lack of CentA1. Neuropathological hallmarks of AD such as dendritic spine elimination, deposit of amyloid plaques and neuroinflammation were all significantly reduced in AD model mice on CentA1 KO background. To identify molecular mechanisms involved in AD phenotype rescue, we performed transcriptome profiling using Nanostring nCounter Neuropathology and Neuroinflammation panels (880 genes). We found significant upregulation of genes associated with apoptosis and gliosis in the brain of hAPP-J20 mice. CentA1 KO rescued this phenotype by reducing the level of the pro-apoptotic protein, Bid. In summary, our data indicate that CentA1 is required for progression of AD phenotypes and that targeting CentA1 signaling might have therapeutic potential for AD prevention or treatment.