Current Issue - Neurodegeneration

Scientific Reports

A Small Compound Targeting Prohibitin with Potential Interest for Cognitive Deficit Rescue in Aging mice and Tau Pathology Treatment

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We analyzed the effects of a new purine derivative drug, PDD005, in attenuating mechanisms involved in the pathogenesis of neurodegenerative diseases, using both in vivo and in vitro models. We show that PDD005 is distributed to the brain and can rescue cognitive deficits associated with aging in mice. Treatment with PDD005 prevents impairment of neurogenesis by increasing sex-determining region Y-box 2, nestin, and also enhances synaptic function through upregulation of synaptophysin and postsynaptic density protein 95. PDD005 treatment also reduced neuro-inflammation by decreasing interleukin-1β expression, activation of astrocytes, and microglia. We identified prohibitin as a potential target in mediating the therapeutic effects of PDD005 for the treatment of cognitive deficit in aging mice. Additionally, in the current study, glycogen synthase kinase appears to attenuate tau pathology.

Cell Press - Neuron

Amyloid-Beta (Aβ) Plaques Promote Seeding and Spreading of Alpha-Synuclein and Tau in a Mouse Model of Lewy Body Disorders with Aβ Pathology

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Studies have shown an overlap of Ab plaques, tau tangles, and a-synuclein (a-syn) pathologies in the brains of Alzheimer's disease (AD) and Parkinson's disease (PD) with dementia (PDD) patients, with increased pathological burden correlating with severity of cognitive and motor symptoms. Despite the observed copathology and concomitance of motor and cognitive phenotypes, the consequences of the primary amyloidogenic protein on the secondary pathologies remain poorly understood. To better define the relationship between a-syn and Ab plaques, we injected a-syn preformed fibrils (a-syn mpffs) into mice with abundant Ab plaques. Ab deposits dramatically accelerated a-syn pathogenesis and spread throughout the brain. Remarkably, hyperphosphorylated tau (p-tau) was induced in a-syn mpff-injected 5xFAD mice.

Journal of Neuroscience

Loss of HIPK2 protects neurons frommitochondrial toxins by regulating Parkin protein turnover.

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In this study, we provide evidence that homeodomain interacting protein kinase 2 (HIPK2) and its kinase activity promote Parkin degradation via the proteasome-mediated pathway. The loss of HIPK2 increases cytosolic and mitochondrial Parkin protein levels under basal conditions and upon exposure to mitochondrial toxins, which protect mitochondria from toxin-induced damage. In addition, Hipk2−/− neurons and mouse embryonic fibroblasts also show increased expression of PGC-1α (peroxisome proliferator-activated receptor-γ coactivator 1), a Parkin downstream target that can provide additional benefits via transcriptional activation of mitochondrial genes. These results indicate that targeting HIPK2 and its kinase activity can have neuroprotective effects by elevating Parkin protein levels.

Nature Neuroscience

A single-cell atlas of entorhinal cortex from individuals with Alzheimer's disease reveals cell-type-specific gene expression regulation.

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Here we applied single-nucleus RNA sequencing to entorhinal cortex samples from control and Alzheimer's disease brains (n = 6 per group), yielding a total of 13,214 high-quality nuclei. We detail cell-type-specific gene expression patterns, unveiling how transcriptional changes in specific cell subpopulations are associated with Alzheimer's disease. We report that the Alzheimer's disease risk gene APOE is specifically repressed in Alzheimer's disease oligodendrocyte progenitor cells and astrocyte subpopulations and upregulated in an Alzheimer's disease-specific microglial subopulation. Integrating transcription factor regulatory modules with Alzheimer's disease risk loci revealed drivers of cell-type-specific state transitions towards Alzheimer's disease.