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*Regulation of Neuronal Clearance Pathways via Nuclear Calcium Signaling in Alzheimer's Disease*

Abstract:

Alzheimer’s disease (AD) is the most common and severe neurodegenerative disease of our time. With well-characterized general disease hallmarks, molecular mechanisms underlying AD pathogenesis remain elusive. Recently, inhibition of the lysosomal system has been described among the earliest changes in AD brains, likely preceding the well-known aggregation of amyloid and Tau tangles and having yet unknown consequences. We find that a decrease of nuclear calcium levels and consequently cAMP response element-binding protein (CREB)-mediated expression of its target genes associated with the autolysosomal pathway is the underlying mechanism for attenuated molecular clearance and decreased neuroprotection in PS and Tau mutants.

The overall goal of this proposal is 1) to understand the mechanisms leading to inhibition of molecular clearance in AD brains, and 2) to identify consequences of functional failure of neuronal clearance in aging and AD neurons to facilitate future development of interventions enhancing neuronal clearance and prevent neurodegeneration.