Role of Plks in amyloidogenic APP processing

https://neurodegenerationresearch.eu/survey/role-of-plks-in-amyloidogenic-app-processing/

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Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common form of dementia. Currently, there are no treatments that can reverse the underlying disease progression, and thus new strategies and treatments are essential. Accumulation of amyloid beta (Abeta), a proteolytic cleavage product of amyloid precursor protein (APP), is considered the initiating step leading to cognitive impairment and neuronal cell death, but the signaling pathways that control proteolytic processing of APP are not well understood. Accumulating

evidence implicates synaptic activity as a key driver of APP amyloidogenic processing, and hyperexcitation is a characteristic feature of the AD brain during early stages. However, the molecular links between neuronal activity and Abeta production are unclear. Plk2 is a synaptic activity-inducible member of the polo-like kinase (Plk) family that plays an important role in homeostatic weakening of excitatory synapses in response to prolonged overexcitation. Our preliminary data demonstrate that Plk2 is upregulated in AD brain, directly phosphorylates APP and is required for neuronal activity-dependent APP amyloidogenic processing in vitro. Additionally, genetic inhibition of Plk2 reduced soluble Abeta levels and plaque deposition in AD model mice under basal conditions and eliminated the increase in Abeta formation in response to heightened synaptic activity. Finally, administration of a Plk inhibitor, BI-6727 (volasertib), o AD model mice also led to a marked reduction in soluble Abeta levels. In this proposal we will test the hypotheses that (1) BI-6727 (volasertib) reduces plaque deposition and ameliorates cognitive impairment and other pathological features in the 5xFAD mouse model of AD; and (2) Plk2 plays a selective role among Plk family members in APP processing, and functions in response to moderate and well as strong neuronal hyperactivity as evoked by graded optogenetic stimulation. This proposal is highly significant as it will help elucidate a novel mechanistic link between excitatory synaptic activity and APP processing. The identification of this regulatory pathway for APP processing presents Plk2 as an innovative and potentially attractive target for therapeutic interventions in AD.

Further information available at:

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