Mechanisms of APP and APLP2 function at synapses

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USA

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NIH (NIA)

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1

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Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s Disease (AD) is the most common cause

of ageing-dependent dementia in the world and is associated with cerebral amyloid plaques, mostly composed of A? peptides. These peptides are produced by a double cleavage of the amyloid precursor protein (APP). BACE1 cleavage produces the C-terminal fragment, ?-CTF, which is then processed into several A? isoforms by ?-secretase. Genetic data suggest that regulation of APP processing contributes to AD. In addition, a polymorphism of APP that reduces processing of APP by BACE1 protects from sporadic AD and from normal aging-dependent cognitive decline. Thus, the human genetic evidence indicates that APP and APP processing are important for normal cognitive functions. To gain insights into the function of APP in the central nervous system, we have characterized the brain interactome of the APP intracellular domain. We isolated several proteins including proteins that regulate synaptic vesicles exocytosis (which we collectively refer to as the APP presynaptic interactome or Appresyome) and a multimolecular complex composing the E3 ligase CRL4CRBN. Interestingly, one of the components of CRL4CRBN, i.e. CRBN, is coded by a gene linked to intellectual disability. Our preliminary studies suggest that APP regulates the probability of release of glutamatergic synaptic vesicles and that this function is regulated by APP processing by BACE1. We also found that CRL4CRBN mediates ubiquitination of Snap25, Vamp2 and Stxbp1, three proteins that regulate synaptic vesicles exocytosis and that are also part of the Appresyome. Of note, CRL4CRBN and the Appresyome bind two distinct regions of the APP intracellular domain. Finally, we found that APLP2, a member of the APP protein family, shares many of these APP functions. In this study we will analyze the role of APP and APLP2 in synaptic transmission as well as the molecular mechanisms underlying it. We will also study how processing of APP (and APLP2) regulates synaptic transmission. Lastly, we will analyze the function of CRL4CRBN and of the CRL4CRBN/APP-CRL4CRBN/APLP2 complexes. Our studies will contribute to our understanding of the synaptic function of APP, BACE1 and CRBN and, perhaps, uncover signaling pathways that may be altered in AD. Thus, this study may shed light on the pathogenesis of AD, as well as unveil novel targets for disease-modifying AD drugs.

Lay Summary

PUBLIC HEALTH RELEVANCE: Mutations in genes that regulate the processing of APP cause Familial Dementias in humans. In spite of this pathological importance, no much is known about the physiological relevance of APP and APP processing. To investigate these issues, we have characterized the interactome of the intracellular region of APP. This interactome has given us clues concerning the function of APP in synaptic transmission. Our preliminary data show that APP regulates the release of synaptic vesicles containing the neurotransmitter glutamate. In addition, we have found a functional link between APP and CRBN, a protein coded by a gene linked to intellectual disability. These studies may unveil functions of APP that, if altered like n Alzheimer disease, may contribute to dementia.

Further information available at:

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