The Nucleolus in Memory and Alzheimer's Disease

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Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized clinically by memory loss and neuropathologically by the presence of ß-amyloid plaques in brain parenchyma and neurofibrillary tangles composed of hyper-phosphorylated tau within neurons. Although plaques and tangles are necessary for a neuropathologic diagnosis of AD, the neuropathology does not always correlate with clinical disease severity. The resilience of some individuals to AD neuropathology has been attributed to "cognitive reserve".

The nucleolus is a membrane-less organelle with a collection of DNA, RNA, and proteins that are instrumental in the construction of ribosomes. The neuronal nucleolus has been reported to be larger in size in individuals with AD neuropathology without dementia (Asymptomatic AD) and smaller in size in individuals with AD. We hypothesize that "cognitive reserve" may be related to neuronal nucleolar health, where nucleolar impairment leads to cognitive impairment and cell death; and nucleolar health recovery and nucleolar hyperactivation leads to amelioration, recovery, and enhancement of cognitive functions.

To start understanding the role of the nucleolus in memory and its role in AD, we have tested whether: a) PARP-1, a neuronal nucleolar protein associated with learning and memory, is altered in AD; b) transient inhibition of the nucleolus disrupts memory; c) nucleolar hyperactivation enhances memory. We find: a) PARP-1 shows distinct neuronal nucleolar staining in the hippocampus of older individuals without AD and decreased and diffuse staining in the hippocampus in AD; b) transient inhibition of nucleolar function by RNA Polymerase-I inhibitor CX-5461 impairs memory consolidation in mice; c) nucleolar hyperactivation by 3BDO, an mTOR activator, enhances memory in mice. Future experiments will look at whether 3BDO can also rescue memory when there is AD-associated memory impairment.