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Amyloid-beta impacts nucleolar structure in hippocampal neurons

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, characterized by severe cognitive and behavioral deficits, including most notably memory loss. Over 5 million Americans currently suffer from AD, with an estimated 13.8 million cases projected by 2050. Amyloid-beta (Aβ), the main component of the senile plaques that pathologically define AD, has been extensively investigated for its impact on a range of cellular functions. However, little is known about how Aβ affects the nucleolus, the region of the nucleus responsible for the production of ribosomes. Post-mortem analyses suggest that nucleolar function is impaired in AD brains, which show hypermethylation of ribosomal gene promoters, reduced ribosomal RNA (rRNA) levels and decreased protein synthesis capacity. In addition, previous work in our lab has demonstrated a reduction in AD brains of nucleolar Poly(ADP-ribose) polymerase 1 (PARP-1), a chromatin remodeler necessary for rRNA synthesis induced by synaptic plasticity. Here we examine how inhibition of nucleolar activity affects PARP1 expression. We find that disruption of rRNA transcription by actinomycin D in HEK293T cells abolishes the nucleolar localization of PARP1. Further we examined how Aβ itself could impact nucleolar structure in hippocampal neurons and found that Aβ application reduced the expression of nucleolar markers fibrillarin and nucleostemin. These results demonstrate that nucleolar function and structure are sensitive to perturbations induced by Aβ and shed light onto novel cellular pathways affected by AD.