P31

Macromolecular protein transport from synapse-to-nucleus regulates nucleolar function and facilitates protein synthesis in neurons

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Jacob is a protein messenger that encodes and transduces the synaptic and extrasynaptic origin of GluN2B-containing NMDA receptors (NMDAR) to the nucleus and couples NMDAR activity to CREB-dependent gene expression (Karpova et al., 2013). Nuclear import of Jacob following activation of extrasynaptic NMDAR leads to long-lasting dephosphorylation of CREB, loss of dendritic arborization and eventually cell death. Vice versa, nuclear import of Jacob following activation of synaptic NMDARs stimulation enhances plasticity related and CREB-dependent gene expression. However, apart from association with CREB still very little is known about the nuclear function of Jacob. Here we report that following nuclear import Jacob also localizes at nucleoli in hippocampal or cortical neurons. Nucleoli are sub-nuclear compartments where assembly of ribosomal RNA (rRNA) and pre-ribosomal subunits takes place. Nucleolar dysfunction contributes to the pathology of several rare human genetic disorders as well as neurodegenerative disorders (Montanaro et al., 2008; Hetman et al., 2012). Decreased rRNA synthesis and nucleolar disruption, known as nucleolar stress, are hallmarks of cellular stress associated with neurodegenerative diseases (Pietrzak et al., 2011; Lee et al., 2014). Alterations of nucleolar functions have been also associated with aging (Takada et al., 2015). Interestingly, it has been shown that nucleolar size in C. elegans is a highly predictive marker for longevity and this evidence arises the possibility that nucleolar size can also predict the life span of higher organisms (Tiku et al., 2017).
Here we demonstrate that Jacob associates with nucleoli and enhances rRNA synthesis. We show that Jacob can link between synaptic activity and control of de-novo protein synthesis machinery by regulating nucleolar functions.