

RNF10 role in synaptic plasticity and Alzheimer Disease

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RNF10 is a protein with multiple cellular functions. It has been described as a E3-Ubiquitin ligase, with a key quality-control role during the initiation of translation in the early regulatory ribosome ubiquitylation (RQC). In addition, RNF10 plays in neurons a role as a synaptonuclear messenger, involved in the NMDA receptors (NMDAR) signaling cascade. RNF10 binds to the C-terminal region of the GluN2A subunit of the NMDAR and its translocation from the synapse to the nucleus translates synaptic NMDAR activation into gene expression changes. RNF10 is crucial in the physiology of the neurons, being involved in LTP-dependent modulation of dendritic spine morphology and in shaping of the dendrite's architecture in hippocampal neurons. Preliminary data show a potential involvement of RNF10 in Alzheimer's Disease (AD) pathogenesis. Amyloid beta oligomers, that are responsible for AD synaptic failure, promote RNF10 trafficking from the synapse to the nucleus, suggesting that RNF10 can be a mediator of Amyloid beta synaptotoxicity. To investigate the downstream effects of Amyloid beta-triggered RNF10 synapse-to-nucleus communication, we investigated RNF10 function as transcription factor and as regulator of ubiquitination in early translation. To this, we performed RNA-seq analysis using RNF10-silenced hippocampal neurons exposed to either Amyloid beta oligomers or to a synaptic stimulation protocol. Using the same experimental paradigm, we performed SUNSET experiments to evaluate the effect of RNF10 in early translation and specific assays to detect the levels of ubiquitination. The results provided a global picture of RNF10 function in physiological synaptic plasticity phenomena and in AD pathology.