

The Regulation of Tau neuronal Protein Expression, Localization, and Phosphorylation in Neuronal Cells

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Localization and local translation of mRNAs are posttranscriptional regulatory steps, involved in establishment of neuronal polarity, which is important for neuronal function. We have previously shown that the axonal localization of tau protein in the axon, is the result of tau mRNA localization and its local translation. Tau mRNA localization occurs in the form of ribonucleoprotein granule (RNP).


Using P19 stem cells, we have demonstrated that tau mRNA granules include HuD, insulin-like growth factor mRNA binding-protein (IMP1), and Ras-GAP SH3 binding protein (G3BP1), to form the tau mRNP complex. Tau mRNP granules were isolated from P19 embryonic carcinoma neurons. The RNPs include IMP1, HuD RNA binding proteins, ribosomes and a variety of mRNA molecules but not the initiation factor of protein synthesis eIF4E. These large RNA granules were found to be structurally resistant to various translation inhibitors, but sensitive to EDTA treatment. The granules change their composition with neuronal differentiation and in response to various stimuli. During the onset of P19 neuronal differentiation, there is an increase in the ribosomal proteins content of the granules together with a significant reduction of IMP1 protein. The HuD and IMP1 proteins function in mRNA stabilization and control of mRNA translation. Furthermore, KCl depolarization and treatment with zinc disrupted the granule structure, as well as the colocalization of RNA granules with IMP1 protein.


Taken together, our results suggest that RNA granules are dynamic structures, which include RNA binding proteins, various mRNAs and clusters of ribosomes. We suggest that the mRNAs in the granule are kept in a translationally repressed state both during their movement and in situ, while waiting to start translation. Upon stimulation or during various physiological conditions, the granule structure is disrupted and the mRNA is released and available for local translation. The dynamic changes in the composition of the RNA granules along development and differentiation of neuronal cells, can contribute to a rapid local translation of different mRNA molecules, followed by vast changes of the cell proteome.

Following the translation of tau mRNA to tau protein, the protein is phosphorylated at various specific epitopes. Hyperphosphorylation, and intracellular fibrillar formation of the modified protein, are the pathological hallmark found in Alzheimer Diseased brains, and in a variety of neurodegenerative disorders referred to as "tauopathies". We tested how Brain Derived Neurotrophic Factor (BDNF), an extracellular factor, which is down regulated in Alzheimer Disease brains, affects tau phosphorylation. BDNF stimulation of neuronally differentiated P19 cells, resulted in a rapid, 60% decrease in tau phosphorylation, at a phospho-tau epitope recognized by the AT8, Tau1, and p262 antibodies. K252a, a Tyrosine Receptor Kinase (Trk) inhibitor, attenuated this dephosphorylation event, suggesting that BDNF activation of TrkB is responsible for the tau dephosphorylation. In addition, BDNF had no affect on tau phosphorylation in the presence of Wortmannin, a PI-3Kinase inhibitor, or lithium, a GSK3 β inhibitor, suggesting that these two kinases are part of the signaling transduction cascade leading from TrkB receptor activation to tau dephosphorylation. These results suggest a link between a correlate of Alzheimer disease, decrease in BDNF levels and an Alzheimer disease pathology, tau hyperphosphorylation, which may suggest a therapeutical approach that may alleviate the symptoms of the disease.

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