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Tau-microtubule-associated-protein: Regulation of expression and axonal localization in neuronal cells

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The primary determinants that govern neurite outgrowth and differentiation of neurites into axons and dendrites are yet unknown. A major question concerning neuronal differentiation relates to the cellular mechanisms responsible for the establishment of the cytoskeleton polarity, which distinguishes between axons and dendrites and involves the segregation of MAP2 and tau-MAP into the dendrites and axon respectively. Tau microtubule associated protein (MAP) is a neuronal-specific protein found primarily in axons and is developmentally regulated. The function of tau in stabilization of microtubules is important in establishing and maintaining neuronal polarity. The molecular mechanisms responsible for the segregation of proteins and organelles into the axons and dendrites is not yet fully understood, However, it is established that the cytoskeleton plays a key role in this function. Thus, in neurons the polarity of the microtubules and the segregation of tau- into the axon and MAP2 into the dendrites are involved in establishing neuronal polarity, which is crucial for its function. Tau is encoded by a single gene located on chromosome 17 and its regulation of expression lies in four levels: a) promoter activity; b) alternative splicing; c) subcellular localization and d) posttranslational modifications in particularly phosphorylations. Deregulation at any of the above-mentioned points, may cause dysfunction of the protein thus affecting axonal transport and culminating in cell death. We are interested in the molecular regulation of tau expression and localization in neuronal cells. during neuronal differentiation.

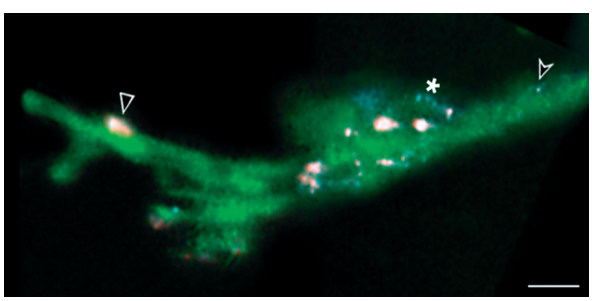

Fig. 1 *Tau RNP granules are present in growth cone and colocalize on MTs. Differentiated P19 cells expressing GFP-tau. Granules include tau mRNA (visualized by in situ hybridization-red), merged with HuD protein (cyan). Granules are colocalized with MTs (green).*

One mechanism that contributes to the generation and maintenance of neuronal polarity and contributes to neuronal plasticity, is the subcellular localization of specific mRNAs leading to their local translation. Subcellular localization of tau mRNA into the the axon is a multistep process which involves the interaction between cis-acting signals located in the 3' untranslated region of tau mRNA, and trans-acting protein factors. We have identified those signals and neuronal specific tau RNA binding proteins that control the stabilization of the message, which moves on the microtubule cytoskeletal system to its correct subcellular microdomain. Movement of the RNA is in the form of mRNP particles ,which includes the targeted RNA and motor protein (Fig. 1).

In addition, tau expression is regulated by its promoter that exhibits neuronal specificity. The isolation of the promoter of tau gene endows us with the ability to study the regulation of tau expression in the brain and its response to NGF and EGF growth factors. Recently we found that tau promter is responsive to estrogen treatment, which can be used for neuroprotective applications These studies will contribute to the understanding of the regulation of tau expression and localization during development and aging of neuronal cells, as well as in neurodegenerative disorders such as Alzheimer's disease.

Selected Publications

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neuronal cells and depends on axonal targeting signal. J. Neurosci. 21, 6577-6587.

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