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Mini Review

Tau mRNA: A Brief History of its Localization

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Abstract

We describe how tau mRNA is localized to the axon hillock and along the neuronal axon. We also reveal how proteins binding the 3'UTR region were discovered and how it was determined the way these proteins interact with tau mRNA, forming a ribonucleoprotein complex, as well as how this complex is stabilized, anchored, localized and translated *in situ*. Tau's was the first mRNA molecule for which the mechanism of localization to the axon and its major function in maintenance of neuronal polarity were described.

Keywords: mRNA; Tau; Ribonucleoproteins; Subcellular localization

Introduction

An mRNA consists of three main regions: a 5'-untranslated region (5'UTR), a coding region and a 3'-Untranslated Region (3'UTR). The degradation of an mRNA highly depends on the size and sequence of the 3'UTR. The degradation process of an mRNA is tightly regulated and does not represent a random process [1]. When an mRNA leaves the nucleus, it is translated and degrades according to the particular degradation signals present in the 3'UTR. Sequences such as UUAUUUAUU [2] are sufficient for an mRNA to quickly degrade in the cytoplasm. It has also been determined that AU-regions in c/v-fos are sufficient to destabilize the mRNA molecule [3]. Expression of a number of proto-oncogenes, cytokines and lymphokines is regulated during degradation by a junction protein called HuR [4].

In neurons, an interesting event takes place, going from stabilization to the localization of several mRNAs [5,6]. Neuronal localization of messenger ribonucleic acids (mRNAs) was first studied through *in situ* hybridization experiments for vasopressine [7], proopiomelanocortin [8], preproenkephalin [9] and oxytocin [10], among others.

Axonal localization of tau mRNA

The study of subcellular mRNA localization began with Hirokawa's studies on tau mRNA during brain development in the rat, in 1991 [11].

Neurons typically consist of a cell body or soma, dendrites and an axon, and thus there was a need to identify those molecules involved in cell polarity. Previous observations had shown that at least two proteins participated in neuronal polarity: tau and MAP2 [12]. Immunohistochemical analyses revealed protein tau localized to axons and MAP2 was confined to dendrites [12]. Ginzburg's studies using *in situ* hybridization demonstrated the segregation of tau mRNA to the axon during neuronal development [13] and its association to microtubules [14]. Protein tau has the main function of stabilizing microtubules, thus contributing to the maintenance of neuronal polarity in the axonal region [15].

The essential question then was: how is the mRNA localized to the axon? There was the possibility that a signal sequence directed the cellular transport while preventing its degradation. Tau 3´UTR has a length of 3,865 bases. The mRNA is quite stable, with a half-life of 20h [16]. Using UV-crosslinking, it was demonstrated that two proteins of unknown nature, with molecular weights of 38 and 43 kDa, bind to a 91 nucleotide sequence in the 3'UTR of tau mRNA [17]. It was hypothesized that these proteins were necessary for the stabilization of tau mRNA during transition from neuroblasts to post-mitotic neurons [18]. Nevertheless, it had to be proved that these proteins bind naturally to this nucleotide sequence.

Previously, it had been demonstrated that MAP2 is localized to dendrites and that its mRNA possesses a signal sequence of 640 nucleotides in the 3'UTR [19]. Similarly, the Hu proteins, which are highly conserved in vertebrates [20] and have been associated with neurological disorders due to their important roles in development and neuronal maintenance [21], bind *in vitro* to an AU-rich sequence and regulate mRNA degradation [22]. Furthermore, a member of the Hu family, HuD, contains three copies of RNA recognition motifs (RRM) [23,24]. Our group investigated whether HuD had the ability to bind to the 3'UTR in tau mRNA, as this protein shows a molecular weight of 38-43 kDa which is consistent with the previous findings from the UV-crosslinking experiments. Using two different cell lines: the rat pheochromocytoma PC12 cells [25] and the mouse embryonic carcinoma P19 cells [26], we proved HuD interacts with tau mRNA and determined its localization (Figure 1).

In PC12 cells, we demonstrated HuD was localized to processes emanating when cells were treated with nerve growth factor (NGF) [27] and, through UV-crosslinking, its binding to an uracil-rich region in tau 3'UTR. In P19 cells differentiated with retinoic acid, we observed a phenotype characteristic of a neuronal cell with the capacity for neurotransmitter release [28]. Upon transfection of a tau uracil-rich sequence coupled to green fluorescent protein (GFP), fluorescence was observed along the axon.

After, we developed a method to immunoprecipitate (Figure 2) the complex formed by HuD and tau 3'UTR using anti-HuD antibodies, purified by Chung et al. [29], in PC12 cells in culture. We also amplified those regions near the binding site by RT-PCR.

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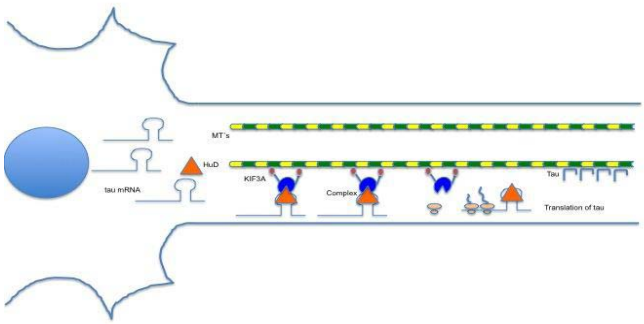

Figure 1: In the scheme shown as tau mRNA interacts with various molecules for transport to the axon. The HuD protein binds to a specific region of uracils in the 3'-UTR for this complex is subsequently anchored to the kinesin KIF3A and transported on the microtubules. Arriving at the right place, the complex disassembles the messenger of tau for translation.

Mutations to this site prevented immunoprecipitation of the complex and therefore the amplification of regions near the binding site. With these experiments, we demonstrated HuD binds naturally to this uracil-rich site concluding that HuD proteins were able to stabilize tau mRNA and keep it in the cytoplasm for about 20h.

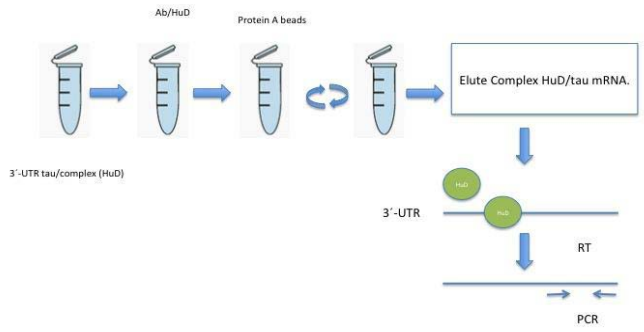

Figure 2: In this scheme briefly shows how complex formation HuD and tau messenger by immunoprecipitation and RT-PCR was determined.

Moreover, in P19 cells we showed the co-localization of tau mRNA and tau protein in the axon [30]. A group of proteins called kinesins had been identified in the squid's giant axon [31] and Hirokawa's studies on the motor patterns of kinesins along the microtubules [32,33] lead us to hypothesize that the HuD-tau mRNA complex was anchored to a kinesin. We proved this hypothesis using antibodies, showing that kinesin KIF3A anchors HuD and transports the HuD-tau mRNA complex to the axon [34]. When KIF3A expression was inhibited, the complex did not reach the axon. We had then completed the puzzle on how tau mRNA reaches the axon: tau mRNA is translated on the site of localization [34] and, in order to be translated *in situ*, tau mRNA has to be transported to the axon for which HuD protein binds to the uracil-rich 3'UTR in tau mRNA, serving as an anchor protein to kinesin and stabilizing the mRNA molecule so that translation can take place when required within the relatively long period of tau mRNA half-life.

We also investigated other messenger molecules that might localize to the axon. Using bioinformatics tools, we identified a number of mRNAs with uracil-rich 3'UTRs very similar to that in tau mRNA that could also be found in the axon [35,36].

Our findings on tau localization in the neuronal axon together with the protein complex involved in the *in situ* translation [34] made us the first to demonstrate mRNA axonal stabilization, transport, localization and *in situ* translation [37].

The implications of tau localization

Tau protein participates in the maintenance of neuronal polarity [13] and axonal transport by binding to microtubules, providing stability and shaping axonal morphology. When tau expression is inhibited, the axon retracts [27]. Efficient axonal transport of synaptic vesicles and organelles such as mitochondria allows the correct functioning of synaptic processes. It has also been shown that tau mRNA was co-localized in the distal part of the axon and growth cone, with the elongation factor 1a, which is a component of the translation machinery [38].

A number of studies have demonstrated that hyperphosphorylation of a truncated form of tau (pTau) prevents microtubule assembly [39] and localizes tau to the cell soma and degenerated neurites [40]. Upon tau hyperphosphorylation, the axon retracts and synapses are lost [41]. Mislocalization of pTau not only causes loss of synapses [42,43] but the accumulation of oligomers in dendritic spines which results in decreased long-term potentiation following internalization of AMPA receptors [42,44], thus affecting neuronal plasticity [45] (Table).

Table 1: Abnormal localization and hyperphosphorylation of tau, can lead to a spectrum of diseases known as tauopathies.

Tauopathies	Reference
Alzheimer Disease	[46]
Argyrophilic grain dementia	[47]
Corticobasal degeneration	[48]
Creutzfeldt-Jacob disease	[49]
Dementia pugilistica	[50]
Down´s syndrome	[51]
Frontotemporal dementia	[52]
Myotonic dystrophy	[53]
Niemann Pick disease, type C	[54]
Pick disease	[55]
Postencephalitic parkinsonism	[56]
Progressive supranuclear palsy	[57]

Conclusion

The demonstration of tau mRNA axonal localization broke with the myth that translation is a process exclusively taking place in the neuronal soma. Tau mRNA transport is essential for efficient neuronal function and maintenance of cell polarity. When tau mRNA is not properly localized to the axon, inefficient neurotransmission at the dendrites and axonal protrusion can be observed, leading to interruptions in transmission of the nerve impulses affecting pre-synaptic as well as post-synaptic neurons.

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