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Systemic and network functions of the microtubule-associated protein tau: Implications for tau-based therapies

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ABSTRACT

Tau is a microtubule-associated neuronal protein, whose primary role was long thought to regulate axonal microtubule assembly. Tau is subject to many posttranslational modifications and can aggregate into neurofibrillary tangles, which are considered to be a hallmark of several neurodegenerative diseases collectively called "tauopathies". The most common tauopathy is Alzheimer's disease, where tau pathology correlates with sites of neurodegeneration. Tau belongs to the class of intrinsically disordered proteins, which are known to interact with many partners and are considered to be involved in various signaling, regulation and recognition processes. Thus more recent evidence indicates that tau functionally interacts with many proteins and different cellular structures, which may have an important physiological role and may be involved in neurodegenerative processes. Furthermore, tau can be released from neurons and exert functional effects on other cells. This review article weighs the evidence that tau has subtle but important systemic effects on neuronal network function by maintaining physiological neuronal transmission and synaptic plasticity, which are possibly independent from tau's microtubule modulating activities. Implications for tau-based therapeutic approaches are discussed.

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Contents

1. Neurons, networks and the cytoskeleton

Interactions between nerve cells constitute functional networks that produce behavior. These networks are subject to neuronal plasticity as already put forward by the Spanish neuroanatomist Ramon y Cajal >100 years ago, although the use of the term "plasticity" remained ambiguous (DeFelipe, 2002; Stahnisch and Nitsch, 2002). Nowadays the term "neuronal plasticity" refers to the brain's ability to reorganize itself throughout life by forming new connections through mechanisms such as axonal sprouting, or by modifying the strength of existing synapses, *e.g.*, during learning and memory (Kandel, 2000).

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; AMPAR, AMPA-type glutamate receptor; CNS, central nervous system; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; GFP, green fluorescent protein; GSK-3β, glycogen synthase kinase-3β; IDP, intrinsically disordered protein; KO, knockout; LTD, long term depression; LTP, long term potentiation; MAPs, microtubule-associated proteins; MBR, microtubule binding region; MT, microtubule; NFTs, neurofibrillary tangles; NMDAR, NMDA-type glutamate receptor; PNS, peripheral nervous system; PTM, posttranslational modification; TH, tyrosine hydroxylase.

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The neuronal cytoskeleton is the major intracellular structure that determines the morphology of neurons and is thought to have a critical role in the development of the nervous system, neuronal plasticity, and neurodegenerative diseases. In particular, changes in microtubule (MT) dynamics are associated with axon formation and axonal sprouting, but are also involved in mediating structural and functional changes of dendritic spines, which represent the major site of excitatory postsynaptic input (Penazzi et al., 2016a).

MT dynamics are regulated by several factors, which affect the assembly state of this polymer. MT-associated proteins (MAPs) play an important role in regulating neuronal MT assembly since they promote MT nucleation and elongation in a compartment-specific manner and are also subject to regulation by posttranslational modification (PTM) (Penazzi et al., 2016a). Of particular importance is the MAP tau, which becomes enriched in the axonal compartment during neuronal development and redistributes to the somatodendritic compartment in a state of increased phosphorylation ("hyperphosphorylation") during neurodegenerative conditions such as Alzheimer's disease (AD) and other tauopathies (Arendt et al., 2016). Surprisingly, acute or chronic knockdown of tau does not appear to affect MT stability and organization or the overall structure of a neuron to a major extent (Harada et al., 1994; Tint et al., 1998). While this may be in part due to compensatory effects of other neuronal MAPs, it also poses the question whether tau has activities beyond a direct role in regulating axonal MT polymerization, which are disturbed during AD and other tauopathies. In fact, tau belongs to the class of intrinsically disordered proteins (IDPs), which interact with many partners and show a remarkable structural plasticity allowing them to react quickly in response to changes in their environment by altered PTMs (Uversky, 2015). Thus tau may affect various signaling and regulatory processes dependent on its modification, thereby regulating the function and plasticity of neurons during learning, memory and degenerative processes.

2. Tau, a promiscuous binder involved in signaling and regulation

Originally, tau was identified as a factor that becomes enriched during repeated cycles of MT assembly and disassembly from brain homogenates classifying it as a MT protein (Cleveland et al., 1977). Later it was shown that tau is the product of a single gene, which is localized in humans on chromosome 17q21 and consists of 16 exons (Andreadis et al., 1992) (Fig. 1A). In the CNS, tau is expressed in six alternatively spliced isoforms, of which the shortest isoform (0N3R) is the only one present in the fetal brain. In the PNS, three additional exons are expressed. Mis-splicing of tau in CNS, in particular an increase in the expression of longer tau isoforms at the expense of shorter ones, can contribute to the development of tauopathies (Goedert et al., 1998).

The interaction of tau with MTs occurs through the MT-binding region (MBR) (Fig. 1, indicated in yellow color). The MBR binds to MTs *via* small groups of evolutionarily conserved residues (Butner and Kirschner, 1991; Goode and Feinstein, 1994; Kadavath et al., 2015; Lee et al., 1989; Sundermann et al., 2016). In axon-like processes, binding is strongly increased by a pseudorepeat region, which flanks tau's MBR at its C-terminus (Niewidok et al., 2016). The majority of tau is associated with MTs under physiological conditions (Konzack et al., 2007; Samsonov et al., 2004; Weissmann et al., 2009). However, the interaction of tau with MTs is highly dynamic and it has recently been shown using single molecule tracking experiments that tau rapidly interconverts between free and MT-bound states with a dwell time being only ~40 ms on a single binding site (Igaev et al., 2014; Janning et al., 2014). It is noteworthy that such a "kiss and hop" mechanism, as it has been termed, is also compatible with non-MT related functions and multiple interactions of tau in the cell.

Tau possesses IDP regions, which may play diverse roles in the modulation and control of the functions of many different binding partners. IDP regions are generally of >30 amino acids in length and are featured

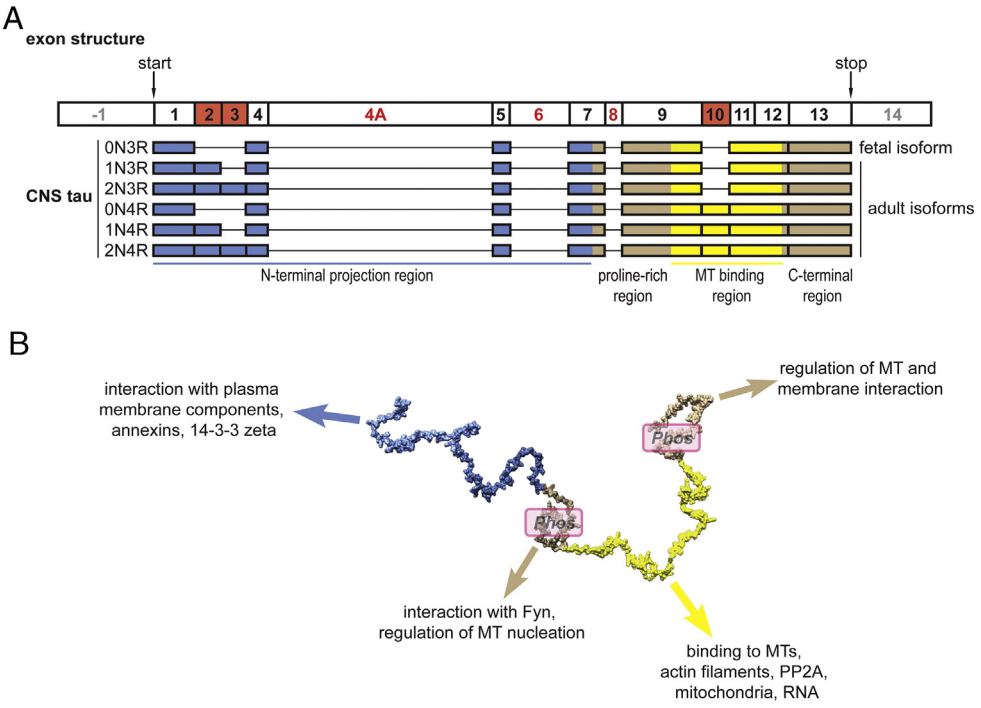

Fig. 1. Exon structure, CNS isoforms and functional organization of the MT-associated protein tau. (A) Exon structure and CNS isoforms of tau. The exon structure of tau with the conventional numbering according to Andreadis et al. (1992) is shown on top. Exons that are expressed only in the PNS are indicated by red numbers. Alternatively spliced exons in the CNS are shown as red boxes. The exon structure of the 6 splice variants, which are expressed in the CNS, is shown below. The nomenclature indicating the number of repeats (3R or 4R) and the presence or absence of inserts in the tau's N-terminus (0N, 1N, 2N) is shown on the left. The N-terminal projection region is indicated in blue and the MT binding region in yellow. (B) Functional organization of tau. A representative 3D structure of tau (2N4R isoform) generated by the Random Coil Generator (RCG) software is shown (Jha et al., 2005). The domain organization was mapped onto the 3D structure. Visualization and structure rendering was performed using the Visual Molecular Dynamics (VMD) package as surface representation (Humphrey et al., 1996). Interaction partners, whose interactions have been mapped to specific tau regions, are indicated.

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