Review

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Lost after translation: missorting of Tau protein and consequences for Alzheimer disease

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Tau is a microtubule-associated-protein that is sorted into neuronal axons in physiological conditions. In Alzheimer disease (AD) and other tauopathies, Tau sorting mechanisms fail and Tau becomes missorted into the somatodendritic compartment. In AD, aberrant amyloid-β (Aβ) production might trigger Tau missorting. The physiological axonal sorting of Tau depends on the developmental stage of the neuron, the phosphorylation state of Tau and the microtubule cytoskeleton. Disease-associated missorting of Tau is connected to increased phosphorylation and aggregation of Tau, and impaired microtubule interactions. Disease-causing mechanisms involve impaired transport, aberrant kinase activation, non-physiological interactions of Tau, and prion-like spreading. In this review we focus on the physiological and pathological (mis)sorting of Tau, the underlying mechanisms, and effects in disease.

Tau involvement in neurodegeneration

AD is a neurological disorder which inflicts a high burden on the caretakers and the society. Neuropathologically, brains of AD patients contain extracellular amyloid plaques composed primarily of Aβ, and intracellular neurofibrillary tangles (NFTs) composed mainly of pathologically aggregated and post-translationally modified Tau (reviewed in [1]). NFTs are located mainly in the somatodendritic compartment of neuronal cells, and abnormally phosphorylated Tau is detectable even before NFTs in the soma and dendrites. However, in physiological conditions of adult neurons, Tau is mainly an axonal protein but becomes mislocalized ('missorted') into the somatodendritic compartment at early stages of pathology. Because tangle load correlates well with cognitive decline and synapse loss in AD [2], missorting of Tau likely plays a key role in Tau pathology. Recent evidence of beneficial effects of Tau reduction in animal models [3,4], and detrimental effects of dendritic Tau, led to a reappreciation of the importance of proper sorting of Tau. We review here the pathways of sorting and pathological missorting of Tau.

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Cellular localization and domain organization of Tau

Tau was discovered by Marc Kirschner and colleagues in their search for microtubule (MT) assembly-promoting factors [5]. It was biochemically characterized [6] and found to be upregulated together with tubulin during neuronal differentiation [7]. Tau is present mainly in neuronal axons, in contrast to the related microtubule-associated protein MAP2 which is localized to the somatodendritic compartment [8]. Human Tau is encoded on chromosome 17q21 [9]. It exists mainly in the CNS and comprises six major and several minor alternatively spliced isoforms [10,11] (Box 1). The major CNS isoforms differ by the presence or absence of two near N-terminal inserts of 29 residues each (N1, N2), encoded by exons 2 and 3, and by the second of four repeats (R2, 31 residues) in the repeat domain (Figure 1), encoded by exon 10. Domains can be subdivided into (i) the 'assembly domain' in the C-terminal half, comprising the repeat domain plus flanking regions, which supports microtubule assembly, (ii) the 'projection domain', which does not bind to microtubules and projects away from microtubules (N-Terminal half), and (iii) the 'proline-rich domain' in the middle part (aa 150–240), which contains up to seven PXXP motifs, an interaction motif for binding proteins with SH3 domains (see below). Tau is a highly soluble and natively unfolded protein which normally resists aggregation. However, repeats R2 and R3 contain two hexapeptide motifs with increased propensity for β-structure, which can form the nucleus of amyloid-like aggregation. Otherwise the content of secondary structure is unusually low [12].

Sorting of Tau in development and physiological conditions

Tau is upregulated during embryonic development [13]. In neurogenesis, fetal 3R-Tau is expressed first in the brain [14] (temporal dynamics which are recapitulated in cell culture [15]). This fetal 3R-Tau isoform (0N3R) is initially distributed evenly in the cell body and neurites. When axons emerge and neurons are polarized, Tau becomes enriched in axons. In mammalian neurons, axonal sorting of Tau takes place within 1–2 weeks, in other words in late stage 4 and stage 5 [16] (Figures 2 and 3 and see Glossary).

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Glossary

Axon initial segment (AIS) and Tau diffusion barrier: the AIS is defined as the 'intermediate' region between the soma and the axon. It generates the action potentials, can receive synaptic input, is enriched in Na^+ and K^+ channels, and also has special cytoskeletal features (e.g., ankyrin G linked to βIV-spectrin and F-actin) [33]. The AIS colocalizes with the Tau diffusion barrier, which has the function of a rectifier: it allows Tau to pass anterogradely (i.e., from the cell body to the axon) but not retrogradely, such that Tau is retained in the axon [32].

Microtubule-associated proteins (MAPs): proteins that bind to microtubules and promote their assembly. They were originally defined by copurification with microtubules through cycles of assembly and disassembly. Structural MAPs (stabilizing the microtubule lattice) are broadly distinguished from motor MAPs (moving cellular cargoes along microtubules). Structural MAPs can be further divided into TIPs (tip-interacting or end-binding proteins) and those that bind microtubules along their lattice. The lattice-binding family is further divided into STOP (stable tubule only) proteins, the MAP1 family, and the Tau/MAP2 family, which also contains the ubiquitous MAP4 and shares similar microtubule-binding domains. In a wider sense, all proteins that associate with polymerized microtubules can be considered as MAPs. This includes enzymatically active proteins such as microtubule motor proteins (kinesins/dynein), protein kinases, or microtubule-severing proteins (e.g., katanin or spastin) [30,39,124].

Neuronal polarity, staging, and missorting of Tau: neuronal polarity refers to the asymmetric structure of a neuron, the axon versus the somatodendritic compartment, and the corresponding asymmetric distribution of cell components. Although most protein synthesis in mature mammalian neurons occurs in the soma, the axon represents up to 99% of the volume of a cell, requiring efficient transport. The process of neuritic outgrowth and cell differentiation can be subdivided into five 'Banker' stages [16,30]: (i) formation of lamellipodia; (ii) outgrowth of minor processes; (iii) formation and growth of the axon; (iv) growth of the dendrites; and (iv) maturation. With increasing maturation, Tau becomes sorted into axons (in contrast to MAP2 which is restricted to soma and dendrites). The predominance of axonal sorting of Tau may be lost permanently in certain neurons in AD and other tauopathies where Tau accumulates in the somatodendritic compartment ('missorting'), or temporarily in the brains of hibernating animals.

Spreading of Tau (pathology): the term 'spreading' or propagation can refer to different processes.

(i) Spreading of Tau pathology refers to the progressive appearance of pathological features of Tau in the brain (such as missorting, aggregation, phosphorylation), as described for AD by the Braak staging [43]). In principle, the spreading of Tau pathology could occur by different mechanisms, such as chemical signaling, inflammatory processes, excitotoxicity, loss of trophic support [87]. Tau pathology could also spread by direct transfer of Tau molecules or oligomers. This can take place in two ways:

(ii) Tau and its pathological features can spread intra-neuronally, for instance from axons to the somatodendritic compartment. This process of missorting can be accompanied by progressive abnormal phosphorylation, folding, and aggregation. For example, expression of aggregation-prone mutants of Tau can undergo self-assembly and nucleate the co-assembly of endogenous wild type Tau [70]

(iii) Tau can also spread outside cells and inter-neuronally. Putative mechanisms include release from one neuron and uptake into another, involving transfer by exo/endocytosis, exosomes, membrane leakiness etc. [89,125]. This spreading tends to follow nerve trajectories, implying synaptic release and postsynaptic reuptake, but may also occur by release into the interstitial fluid (ISF) and subsequent diffusion [85]. If the transferred Tau carries a pathological aggregation-prone conformation (for example as an oligomer with β-structure), this may cause the nucleation and aggregation of Tau in the receiving neurons. This process is referred to as 'prion-like' propagation of Tau pathology.

Tau contains 85 phosphorylatable residues (80 S+T, 5 Y). Because of the unfolded structure of Tau, many of these sites can be phosphorylated, and ~45 have been found experimentally [17]. 17 of the sites are in SP or TP motifs which are preferential targets of proline-directed kinases. These phospho-sites are enriched in AD-Tau and, because they are recognized by several antibodies raised against AD-Tau, are thus of diagnostic value. However, with few exceptions the effects of phospho-sites on the functions of Tau are still ambiguous, and many of these sites are present during development and in hibernating animals (see below and [18]).

Interestingly, in hibernating animals, the polar distribution of Tau is lost, and Tau becomes ubiquitously distributed and phosphorylated at phospho-sites similar as in AD [19]. These changes correlate with decreased dendritic length, arborization, and spine density [20]. Similarly, in anesthesia-induced hypothermia Tau becomes phosphorylated at AD-epitopes [21]. Much of these effects can be ascribed to the downregulation of phosphatases, particularly protein phosphatase 2a (PP2a). In contrast to AD, the redistribution and hyperphosphorylation of Tau is rapidly reversible (~2 h) during arousal, indicating that these effects can be reversed in physiological conditions and are not necessarily pathological (Figure 4).

Sorting mechanisms

Several models have been proposed to explain the polarization of Tau. They can be broadly subdivided as RNA-based and protein-based mechanisms. One RNA-based mechanism postulates preferential transport of Tau mRNA into axons mediated by a 3′- untranslated region (UTR) axonal localization signal [22]. Another model is the preferential translation of Tau mRNA on ribosomes in axons owing to a 5′-UTR oligopyrimidine tract which mediates mTOR-governed protein synthesis in developing axons [23].

Protein-based mechanisms postulate either (i) preferential degradation of Tau in non-axonal compartments, (ii) stabilization in axons, or (iii) retention of Tau in axons by a 'barrier' between the axon and the soma. Compartment-specific degradation of Tau was suggested by results from microinjection of tagged Tau into primary neurons. Initially, Tau is distributed over all cell compartments, but after 4 days labeled Tau is present only in axons [24]. This could be explained by differential interactions with degradation pathways (proteasome, autophagy [25,26]) or folding pathways (chaperones), depending for example on post-translational modifications (phosphorylation) or chaperones (e.g., C-terminus of Hsc70 interacting protein, CHIP) [27,28]. Axonal stabilization of Tau or retention of Tau in axons could be explained by a high affinity of Tau for axonal MTs, and low affinity for dendritic MTs, as shown with fixed permeabilized cells [29]. This could be due to differential phosphorylation and other post-translational modifications in axons versus dendrites (reviewed in [30]). For example, missorted dendritic Tau is preferentially phosphorylated at the KXGS motifs, which makes Tau more diffusible and less able to bind to microtubules [31]. By contrast, axonal Tau is less phosphorylated at these sites so that Tau is 'trapped' on axonal microtubules. Preferential retention of Tau in the axon can be explained by a Tau diffusion barrier, which lies within the axon initial segment (AIS), a region where action potentials are generated. The efficiency of the Tau barrier roughly correlates with the gradual establishment of the AIS [32]. The mechanisms that control the AIS assembly appear to be different from the Tau diffusion barrier because the Tau barrier depends on microtubules and is independent of F-actin, in contrast to the AIS [32,33].

In all cases that depend on compartment-specific turnover of Tau (i.e., translation and degradation), Tau diffusion needs to be slow relative to its turnover. If diffusion is too fast, no compartment specific changes should be observable. This is indeed the case; Tau propagation is

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