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Secretion of full-length Tau or Tau fragments in cell culture models. Propagation of Tau *in vivo* and *in vitro*

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Abstract: The microtubule-associated protein Tau plays a crucial role in stabilizing neuronal microtubules. In Tauopathies, Tau loses its ability to bind microtubules, detach from them and forms intracellular aggregates. Increasing evidence in recent years supports the notion that Tau pathology spreading throughout the brain in AD and other Tauopathies is the consequence of the propagation of specific Tau species along neuroanatomically connected brain regions in a so-called "prion-like" manner. A number of steps are assumed to be involved in this process, including secretion, cellular uptake, trans-cellular transfer and/or seeding, although the precise mechanisms underlying propagation of Tau pathology are not fully understood yet. This review summarizes recent evidence on the nature of the specific Tau species that are propagated and the different mechanisms of Tau pathology spreading.

Keywords: secretion; spreading; Tau; Tauopathies.

List of abbreviators

AD, Alzheimer's disease; CSF, cerebral spinal fluid; FTDP-17, Frontotemporal Dementia with Parkinsonism dominantly inherited and linked to chromosome 17; MBD, microtubule binding domain; CNS, central nervous system; NFTs, neurofibrillary tangles.

Introduction

Tauopathies, including Alzheimer's disease (AD) and Frontotemporal Dementias, are a group of neurodegenerative disorders characterized by the presence of hyperphosphorylated Tau protein filaments in the affected regions of patient's brains. Tau is a microtubule-associated protein that binds to these structures and stabilizes them; however, under pathological conditions it is detached from microtubules and accumulates in the cytosol. This situation leads to the formation of aggregates or inclusions of the Tau protein that could be involved in the degeneration and neuronal death associated with these diseases (1). Neuron degeneration in specific diseases could be specifically located at different sites during the progression of the disease (2). Therefore, affected areas distant from the origin of the disease can be observed in late stages (3). There is increasing evidence strongly suggesting the involvement of extracellular Tau species as the main agent in the propagation of neurofibrillary lesions and spreading of Tau toxicity throughout different brain regions in these disorders. Understanding the precise molecular mechanism underlying Tau propagation is crucial for the development of therapeutics for this devastating disorder. This review summarizes current knowledge of recent research on the role of extracellular Tau in the spreading of Tau pathology.

Tau Protein

Tau protein belongs to the family of microtubule-associated proteins (MAP) and was first identified in the mid-1970s as an assembly factor for microtubules by Weingarten and colleagues (4).

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The human Tau gene (*MAPT*) is located on chromosome 17q21 and consists of 16 exons (5). Alternative splicing of exons 2 and 3 results in the production of isoforms containing none (0N), one (1N) or two (2N) N-terminal insertions that mediate the interaction of microtubules with the plasma membrane. Likewise, alternative splicing of exon 10 gives rise to isoforms with three (3R) or four (4R) tubulin binding domains or repeats (6). Tau is mainly expressed in the central nervous system (CNS) and a longer isoform produced by the splicing of exon 6 is primarily expressed in neurons from the peripheral nervous system. Tau is present in different locations within the neuron: axonal and somatodendritic compartments where the level of Tau phosphorylation plays an important role for its cellular distribution (7-9), although Tau has also been described in dendritic spines (10).

Four functional domains can be distinguished within Tau protein: a N-terminal projection region, a proline-rich domain, a microtubule binding domain (MBD), and a C-terminal region (11). Tau plays a crucial role in regulating microtubule dynamics in cells. In the nervous system, Tau promotes the assembly and stabilization of microtubules required for morphogenesis and axonal transport, and it is also expressed in glial cells (12). The role of Tau in the stabilization of the microtubules resides in a large part on the MBD. The 4R isoforms have a higher affinity for microtubules due to the extra repeat, so they bind and stabilize microtubules more efficiently than the 3R ones (1, 11, 13).

Tau is a highly soluble hydrophilic protein. However, under pathological conditions it detaches from the microtubules and accumulates in the cytosol. This situation leads to the formation of intracellular aggregates or inclusions of the Tau protein, such as the neurofibrillary tangles (NFTs) found in AD brains (14-18). It is generally thought that Tau inclusions contribute to the pathogenesis of these diseases as they occur in specific regions of the brain whose functions are altered (1). Hyperphosphorylation of Tau can cause its separation from other proteins that it binds to, and increases its tendency to form cytosolic toxic aggregates, as it has been found in cases of Tauopathies (1, 19). Additionally, in 1998 different groups identified mutations in the Tau gene (*MAPT*) associated to frontotemporal dementia, indicating that Tau dysfunction *per se* is sufficient to cause neurodegeneration and dementia (20, 21).

Although filamentous inclusions of Tau are a pathological feature of Tauopathies, recent studies suggest that the filamentous Tau is not the main responsible for the neuronal dysfunctions. It appears though that the toxicity is caused by the formation of Tau oligomers (22). In addition, it is considered that soluble Tau and non-inclusions are responsible for the activation of pro-apoptotic pathways (1). Therefore, it is thought that Tau inclusions are not the main toxic species and that neuronal toxicity would be caused by a smaller soluble aggregates or by a specific conformation of the Tau protein (1).

Since Tau inclusions are characteristic of Tauopathies, Tau processing has been extensively examined in both *in vitro* and *in vivo* models. The investigations have focused either on posttranslational modification of Tau (23) or on mechanisms of Tau degradation (24).

Tau Posttranslational modifications

Tau protein is subject to a wide range of posttranslational modifications, including phosphorylation, isomerization (25, 26), glycation (27, 28), nitration, O-GlcNAc modification, acetylation (29), oxidation (30), crosslinking (31), truncation (32), polyamination, deamination (33), SUMOylation (34), Lysine methylation and ubiquitination (35) (reviewed in (1, 36).

One of the most studied modifications and for which more data is available in the literature has been phosphorylation due to its possible involvement in the induction of Tauopathies (37). Tau contains up to 85 putative phosphorylation sites, including 45 serine, 35 threonine, and 5 tyrosine residues (38). Tau can be phosphorylated by microtubule affinity-regulating kinases (MARKs; also known as PAR1 kinases), cyclic AMP-dependent protein kinase (PKA) and Ca^{2+}- or calmodulin-dependent protein kinase II (CaMKII), tyrosine kinases such as the src family members, among others (8). Phosphorylation can regulate the binding of Tau to microtubules and membranes (39), modulate axonal transport (40), and modify actin cytoskeleton (41). However, hyperphosphorylation of Tau may induce pathology through different mechanisms.

On the other hand, protein phosphatase 1 (PP1), PP2A, PP2B, PP2C and PP5 have all been implicated in the dephosphorylation of Tau (8). Among them, PP2A is the main phosphatase (42) acting on a greater number of phosphorylation sites (42, 43).

Tau Degradation

Several studies have demonstrated that two major proteolytic systems contribute to Tau degradation inside cells, the ubiquitin–proteasome system and the autophagy–lysosomal system (24, 44, 45). The contribution

of each of these pathways to Tau turnover and which forms of Tau are degraded by each pathway is not entirely clear. Whereas full-length Tau is cleared by the proteasome system (46, 47), the mutated and truncated forms of Tau protein appear to be degraded by the autophagy-lysosomal pathway (48, 49).

Caspase-3, calpain and cathepsin L are able to cleave Tau protein at several sites and the resulting fragments increase Tau aggregation (1, 49, 50). In some mouse models expressing mutated human Tau (P301L 4R0N), activation of caspases precedes the formation of filaments, so that this truncated Tau may be important for the formation of aggregates in NFTs *in vivo*.

Recently, numerous studies have shown the existence of a secretory process for unfolded proteins (51, 52). These findings suggest a resemblance of these molecular mechanisms of neuroanatomical spreading in some neurodegenerative diseases, such as Parkinson's, Huntington's, Alzheimer's, and whith those of the prion-like transmission. In this process, two consecutive steps are required for trans-cellular spreading of protein aggregates (3):

1. Secretion: protein aggregates must be released to the extracellular medium. This may occur either through a passive release of apoptotic cells or may require active mechanisms involving conventional or non-conventional secretory pathways.
2. Uptake: extracellular protein aggregates have to get inside of neighboring cells. This can happen through several processes: direct penetration through the plasma membrane, fluid phase endocytosis or receptor-mediated endocytosis.

At the beginning of each Tauopathy, Tau pathology is found in determined area of the brain and progresses to other areas throughout the time (2). Consequently, affected areas distant from the origin can be observed in late stages of the disease (3). The classic explanation for this condition has been based on the concept of selective vulnerability (53). According to this idea, the different areas of the brain would have different resistance to the disease, so that only a few of them would be affected. This implies the assumption of a model of disease in which the affectation or non-affectation of a neural cell depends only on its own characteristics.

In recent years, a growing body of literature has supported the idea of cell-to-cell transmission of Tau aggregates (fibrillary or oligomers). This extracellular Tau could enter cells through several mechanisms and seed the recruitment of soluble Tau into growing new aggregates.

In summary, Tau is a microtubule-associated protein. It is an intrinsically disordered protein and that feature facilitates its binding to several molecules or to be subjected to different post-translational modifications along its unstructured molecule.

Tau Secretion

The presence of phosphorylated Tau and intracellular NFTs in the cerebral spinal fluid (CSF) of AD patients it was long believed to be a consequence of the death of the affected neurons (54). However, Tau has been detected at the pre- and post-synapse in control human brains (55) as well at the post-synapse in mouse brains (56). This suggests that propagation of Tau pathology is an active process and Tau release from healthy neurons could be a physiological process that might be disrupted in diseased brain.

Some groups have reported Tau in the extracellular space under physiological conditions (57-59) and endogenous Tau to be actively secreted from human (60) and rat neurons (61). These observations fit well with the detection of Tau tangles in the entorhinal cortex in early stages of AD and spreading of tangles into the hippocampus and cortex as the diseases progresses (62). Recent studies with *in vivo* models in which human Tau was specifically overexpressed in the entorhinal cortex have shown that secretion and spreading of Tau followed along synaptic circuitry and Tau pathology progression from the entorhinal cortex, through the hippocampus, and into the cortex (47, 63, 64). In addition, comparative analysis of CSF from AD and healthy subjects showed a clear increase of amino-terminal (N-terminal) Tau fragments in AD, with no evidence of full-length or carboxyl-terminal (C-terminal) Tau (65). However, other groups have founded full length Tau in the interstitial fluid of P301L mice (59) or C-terminally truncated forms of Tau are released from neurons (66).

Mechanisms of Tau secretion

In the last few years, some hypotheses of Tau release have been proposed. The first one suggested that monomeric and aggregated Tau may be released upon axonal degeneration and neuronal death, being detectable in CSF (54). However, studies in animal and cell cultures suggest that Tau aggregates can propagate from neuron to neuron in the absence of cell death (63, 67, 68). The nucleation of

Tau aggregates could be facilitated by post translational modifications like truncation (32). In this way, caspase cleavage of Tau has been also suggested as a possible link between amyloid and Tau aggregates (32). These studies were performed in Tau overexpression models (58, 60, 69, 70), non-transfected cells (60, 71, 72), or analyzed Tau in the culture medium of immature primary cortical rodent neurons (61, 72). According to these studies, some authors described unconventional mechanisms of non-vesicular Tau secretion in a constitutive way, possibly by direct translocation through the plasma membrane since this transport is only inhibited by cold and not by inhibitors of the Golgi-RE pathway (60). On the other hand, other authors have proposed that the overexpression of Tau protein produces its secretion through exosomes (58, 73, 74) or ectosomes (64). Further studies will be required to determine whether aggregates of Tau are only released passively or if there are specific active release processes.

The mechanisms regulating Tau secretion remain unknown. Pooler et al. (61) described that neuronal activity could regulate physiological secretion of endogenous Tau by cortical neurons. This process was calcium-dependent and modulated by phosphorylation. More recently, Mohamed et al. (75) have demonstrated that Golgi dynamics were linked to a modulation of Tau secretion by both primary cortical neurons and HeLa cells. On the other hand, some authors implicate mitochondrial damage on Tau secretion (22).

Among others, Asai et al. suggested that microglial cells may promote Tau propagation through exosome-dependent mechanisms (76) whereas Fontaine et al. concluded that Tau was released from cells through an exosome-independent pathway that required heat shock cognate 70, its co-chaperone DnaJ, and synaptosomal-associated protein 23 (77). Despite of results obtained by different groups described above, further investigations are required to elucidate the mechanism or mechanisms involved in Tau secretion.

Species of Tau that are secreted

There are many controversies around which specific Tau species are released to the extracellular space. Some studies have shown that Tau propagation could involve species ranging from small soluble monomers to large insoluble fibrils *in vivo* or *in vitro* (78-80). Experiments in cell cultures suggest that the protein has to be in some specific state of oligomerization or fibrillation to be endocytosed and transported by the neuron. Kfoury et al. showed that intracellular Tau fibrils could be directly released into extracellular space in culture cells and then be taken up by the co-cultured cells in the medium via cell-cell transfer in exosomes or tunneling nanotubes (78). In addition, different groups have injected synthetic Tau fibrils into the brain of transgenic mice, and observed the propagation of Tau pathology to regions distant from the injection areas (81, 82). Clavaguera et al. (67) showed that abnormally phosphorylated, filamentous Tau derived from the brains of human P301S Tau transgenic mice was sufficient to induce the formation of silver-positive Tau inclusions in ALZ17 mice that overexpress wild-type human Tau, but do not develop Tau inclusions. In addition, Ahmed et al., using the same transgenic mice than Clavaguera et al., infused unilaterally with brain extract containing Tau aggregates. They observed Tau inclusions as early as 2 weeks post-infusion and showed contralateral hippocampal spread after 1 month (83). More recently, Guo et al. found that intracerebral inoculation of Tau fibrils purified from AD brains resulted in the formation of abundant Tau inclusions in anatomically connected brain regions in non-transgenic mice (84). Additionally, they suggested that spread was dependent on synaptic connectivity rather than spatial proximity. All of these findings suggest the possibility that Tau fibrils could act as a seed to propagate pathology between neurons *in vivo*.

On the other hand, other groups have identified non-fibrillary small particles as necessary for propagation (79, 85). Lasagna-Reeves et al. confirmed Tau propagation after injecting populations of Tau oligomers directly from the cerebral cortex of AD brain into the hippocampus of wild type mice (79). Recently, Usenovic et al. have demonstrated that wild-type full-length human Tau oligomers are able to induce Tau aggregation in human neurons with no Tau mutations or overexpression (85). Their observation reflects that the Tau fibrils could not be transported from one neuron to another. Surprisingly, Wu et al. observed that Tau monomers could not be taken up by neurons (86).

Role of phosphorylation on Tau release

In Tauopathies, Tau presents different posttranslational modifications being the hyperphosphorylation one of the most important ones (87). Hence, several groups have focused on studying the role of phosphorylation on Tau secretion. The amount of phosphorylated Tau in the CSF has been measured (54) and an increase in phosphorylation at T181 (88) or T231 (89) has been described in AD patients. However, some studies have

also reported that phosphorylation decreases with the progression of AD (90). The phosphorylation in CSF at other sites such as S199, S202, T205 S396 and S404 remains controversial (91). Plouffe et al. (70) demonstrated that hyperphosphorylation and cleavage of Tau increase its secretion *in vitro* in Hela cells. On the other hand, several observations suggest that Tau in the extracellular space would be desphosphorylated in AD brain by tissue non-specific alkaline phosphatases (92).

Tau secretion can occur via different mechanisms depending on the Tau variant to be released. Saman et al. (73) showed an exosome-mediated secretion of human Tau phosphorylated at Thr-181. It is still unclear whether phosphorylation regulates Tau secretion since both phosphorylated and unphosphorylated Tau species have been detected in the extracellular space. Plouffe et al. reported that a Tau mutant mimicking phosphorylation was more efficiently secreted than one mimicking dephosphorylation in Hela cells (70). Tau secreted by exosomes was shown to be phosphorylated at several sites found in AD (54, 73). Although some studies in primary cortical neurons showed release of unphosphorylated Tau in control conditions (61), other groups have however reported that several Tau species were secreted phosphorylated and unphosphorylated by cortical neurons upon various insults (70). Further investigations are necessary to elucidate the role of Tau phosphorylation in its secretion.

Role of truncation on Tau release

Abnormal Tau cleavage is found in the neurofibrillary degeneration characteristic of AD and related Tauopathies. Kim et al. (69) found that Tau protein fragments containing the Tau N-terminal domain could be secreted to the extracellular space in an *in situ* lamprey model via two distinct mechanisms. Moreover, this secreted Tau is largely dephosphorylated, which would be in agreement with the phosphatase activity described by Diaz-Hernandez and co-workers (92). However, Kanmert et al. (66) using four distinct neuronal cultures observed that C-terminal-truncated forms of Tau were released by mechanisms that are both dependent and independent of cell death. Secreted Tau cleaved at the C-terminal has been reported either in cell culture (69) as well as in transgenic mouse models expressing human Tau (59, 93). Plouffe et al. suggested that cleavage at D421 as well as phosphorylation increased the rate of Tau secretion (70). In addition, Solokow et al. demonstrated depolarization-induced release of a 20 kDa Tau fragment from AD synapses (94). More recently, Pérez et al. showed that Tau fragments lacking the proline-region are either not secreted or secreted in a distinct manner to the full-length molecule (95).

In summary, it seems that both full-length and truncated Tau can be released by different mechanisms.

Role of mutations on Tau release

In 1994, Wilhelmsen et al. defined a form of Frontotemporal Dementia with Parkinsonism dominantly inherited and linked to chromosome 17 (FTDP-17). The chromosomal region 17q21-22 comprises the Tau gene, demonstrating for the first time that a mutation in the *MAPT* gene could lead to neurodegeneration (13, 20).

Most of the mutations in the *MAPT* coding regions are found in exons 1, 9, 10, 11, 12, and 13 whereas intronic mutations are located near the alternative splicing site of intron 10, increasing the expression of the 4R isoform with respect to that of 3R. *MAPT* mutations reduce the ability of Tau to interact with microtubules. This partial loss of Tau function may be responsible for the anomalous aggregation of the protein. Some mutations also promote the assembly of Tau into filaments (11, 13).

As in patients with Alzheimer's disease, CSF from symptomatic FTDP-17 patient shows elevated Tau levels but it is significantly lower than in AD patients (54, 96). Studies in cell cultures demonstrated that Tau was released via the unconventional secretory pathway and Tau mutations influenced the rate of Tau secretion, being 4R Tau isoforms less abundant that 3R Tau isoforms (72). These results suggest a role of Tau mutations in influencing the retention of certain Tau isoforms within the cell.

In summary, an increase in intracellular Tau could facilitate Tau secretion. That secretion could be regulated by posttranslational modifications: phosphorylation, truncation or by the presence of aggregated intracellular Tau.

Cellular Uptake of Tau

With regards to the uptake processes, poorly folded or fibrillary Tau after being released can be internalized by the surrounding cells where it could induce polymerization of the native protein (68). Once inside the cell, Tau can be located along the endocytic pathway in both late and early endosomes. It has also been described the association of these Tau species to lysosomal vesicles in a retrograde pathway in axons, which would reinforce the idea of trans-synaptic transmission of Tau (68, 86).

Tau can be released into the extracellular space either in a free form (60, 97) or associated to vesicles (58, 73, 74). Many groups have studied how extracellular Tau can be taken up by surrounding neurons (reviewed in (98, 99)), although the precise mechanism by which aggregated extracellular Tau binds to and enters cells are still unknown. Tau could be taken up via receptor-mediated endocytosis (79, 86, 100), dynamin-driven endocytosis of non-fibrillary, soluble Tau aggregates (86), or even actin-dependent, proteoglycan-mediated macropynocytosis (101). Furthermore, it has been observed that extracellular Tau might bring about a receptor-activated increase in intracellular calcium through M1/M3 muscarinic receptor stimulation (57, 92) and that such receptor activation could lead to endocytosis of extracellular Tau. On the other hand, some groups have suggested tunneling nanotubes as a possible mechanism of Tau spreading (102). Also, Takahashi et al. have implied that the extracellular domain of APP might be involved in the incorporation of Tau fibrils into cells (103).

In cultured cells, uptake of Tau aggregates depends on the presence of heparan sulfate proteoglycans at the cell surface and may occur through macropinocyotsis (101). More recently, other groups have suggested the role of components of the extracellular matrix such as heparin or hyaluronic acid on Tau pathology (104, 105).

Based on the reports in the literature, Tau uptake seems to depend on both the conformation and size of the Tau aggregates. Wu et al. also showed that both oligomers and short fibrils which bind to the membrane, but not monomers, long fibrils, or long filaments, could be internalized by the neuronal cell through a receptor-independent mechanism (86). Furthermore, a recent study has demonstrated that accumulation of intracellular Tau depends on the isoform composition of the Tau extracellular oligomers (106). The authors propose that the extracellular Tau oligomers disrupt anterograde and retrograde fast axonal transport by causing accumulation of endogenous intracellular Tau.

In summary, cellular uptake of Tau could be through a receptor-dependent or through a receptor-independent mechanism. Also, the uptake could take place not only in neurons but also in other brain cells like microglia (107). Also, Tau uptake could be done through nanotubes in a similar way to the transport taking place between T cells. In cultured neurons, that transport has been described (3, 108, 109).

Relation between β-Amyloid Spreading and Tau Spreading

Senile plaques (consisted of β-amyoid peptide) and neurofibrillary tangles (made up of Tau) are the hallmarks of AD. However, several lines of researches suggest that Aβ and Tau oligomers may act synergistically for the development of AD. It is proposed the trans-synaptic transmission of these species as the cause of the spreading of pathology in AD (110).

Growing evidence propose a close relationship between Aβ and Tau. Gotz et al. showed a huge increase of Tau neuropathology when fibrillary AB42 is injected into the brains of transgenic mice expressing human P301L Tau (111). In the same way, Jin et al. observed that soluble Aβ oligomers isolated from the AD brain stimulated Tau hyperphosphorylation at AD-relevant epitopes, and hence promote neurodegeneration in primary hippocampal neurons from rats (112). Afterwards, other groups have demonstrated that the accumulation and subsequent deposition of Aβ could induce the phosphorylation and aggregation of Tau in neurons (113, 114) and facilitate the propagation and toxicity of Tau inside neurons (115, 116). It is known that the accumulating Aβ42 oligomers activate a set of protein kinases, such as GSK-3β, a kinase that phosphorylates Tau (117). This hyperphosphorylated Tau could aggregate and induce neurodegeneration. All these works suggest a close relationship between β-amyloid and Tau on the spreading of AD pathology.

Recent studies in transgenic animals have suggested an enhancement of Tau pathology spreading and toxicity by mutant APP (113). Furthermore, heterotypic seeding of Tau fibrils by Aβ pre-aggregates and further cerebral injection of Ab-seeded Tau in mice leads to increased Tau propagation *in vivo* (114), suggesting a cross-seeding mechanism. Interestingly, similar cross seeding had been previously reported between Tau and α-synuclein (118). Although progression of amyloid and Tau pathologies in AD is anatomically and temporally different in early stages of the disease, the overlap in later stages might reflect some sort of cross-talk. Nevertheless, whether or not these findings are relevant for the propagation of Tau pathology in AD and other human Tauopathies remains to be elucidated.

Expert opinion

In this review, we summarize the recent studies on the Tau secretion in cellular systems. Exploration of this

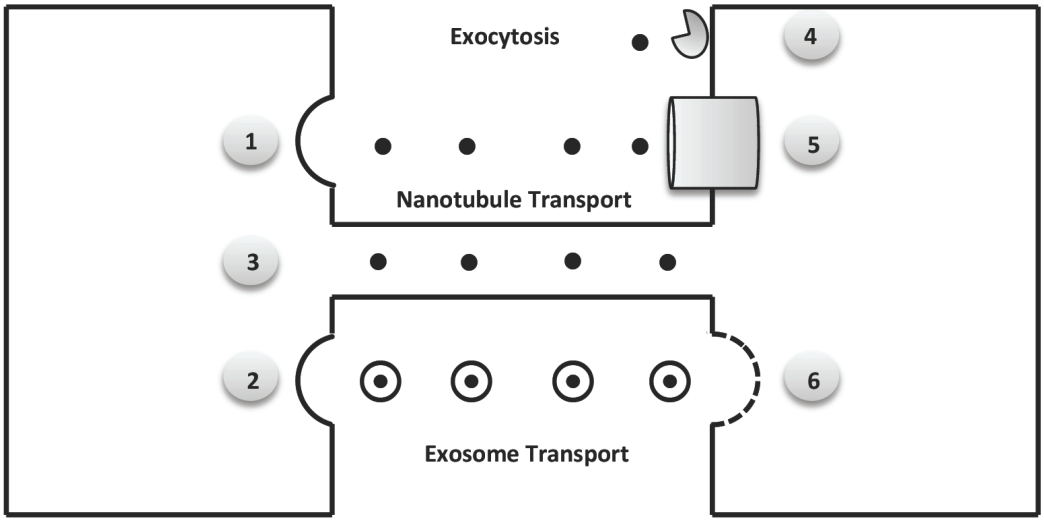

Figure 1: Schematic drawing of possible mechanims for Tau spreading: 1) exocytosis, 2) exosome release and 3) tunneling nanotubules (see the end of the Section "cellular uptake of Tau"); and for Tau uptake through: 4) dynamin-mediated endocytosis, 5) M1/M3-mediated receptors and 6) proteoglycas-mediated macropinocytosis.

process let us understand better the pathology of many neurodegenerative disorders where protein secretion could also take place. Several mechanisms have been proposed: constitutive secretion, ectosomes o exosomes, natotubes and macropinocytosis, but the exact mechanisms of Tau secretion and Tau propagation are unresolved yet. The debate is not closed, and most likely reflects the difficulty of accurately describing how the spreading of Tau takes place, which may depend on a combination of factors, including model systems used, Tau species secreted and other ones.

Outlook

The transcellular propagation of Tau in neurodegenerative diseases (Tauopathies) is still unknown. Future studies should aim to better understand the molecular mechanisms underlying Tau release, propagation and uptake in these pathologies (Figure 1). We must also improve our ability to detect the Tau species secreted. All these investigations will give us the clues to develop new therapies for the treatment of many disorders. These new strategies will include the reduction of Tau secretion, the enhancement of extracellular clearance of Tau in soluble or aggregated form and the inhibition of cell uptake. Also, further elucidation of Tau physiology will lead to a better understanding on of its biology and of the benefits of therapies designed to this process.

Highlights

- Recent investigations have been focused on studying the role of extracellular Tau in pathology of neurodegenerative diseases.
- Recent studies performed in non-neuronal and neuronal cell lines overexpressing human Tau have proposed that Tau could be secreted by several mechanisms: non-vesicular secretion in a constitutive way, vesicular secretion, exosomes, ectosomes or tunneling nanotubes.
- Some Tau species have been detected in the extracellular space: Tau phosphorylated, Tau truncated and Tau mutated. Data from these studies have suggested that the nature of Tau secreted could depend on the cell type tested.
- The mechanisms involved in Tau uptake are poorly understood. Tau endocytosis could occur via receptor-mediated endocytosis, dynamin-driven endocytosis of non-fibrillary, soluble Tau, or uptake of Tau aggregates by macropinocitosis.
- The observations that Tau can be secreted and taken up by adjacent cells set the basis to develop new strategies to block the propagation of Tau pathology in many neurodegenerative disorders.
- Some aspects for specific tau uptake such as the neuronal selectivity, the nature of the extracellular tau species involved, or the precise seeding mechanisms could require of further studies.

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