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REVIEW

Cellular factors modulating the mechanism of tau protein aggregation

Sarah N. Fontaine · Jonathan J. Sabbagh · Jeremy Baker · Carlos R. Martinez-Licha · April Darling · Chad A. Dickey

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Abstract Pathological accumulation of the microtubule-associated protein tau, in the form of neurofibrillary tangles, is a major hallmark of Alzheimer's disease, the most prevalent neurodegenerative condition worldwide. In addition to Alzheimer's disease, a number of neurodegenerative diseases, called tauopathies, are characterized by the accumulation of aggregated tau in a variety of brain regions. While tau normally plays an important role in stabilizing the microtubule network of the cytoskeleton, its dissociation from microtubules and eventual aggregation into pathological deposits is an area of intense focus for therapeutic development. Here we discuss the known cellular factors that affect tau aggregation, from post-translational modifications to molecular chaperones.

Keywords Tau · Alzheimer's disease · Tauopathy · Aggregation

Introduction

A major hallmark of a number of neurodegenerative diseases is accumulation of the microtubule (MT)-associated protein tau. Though tau was initially identified as a component of the pathological neurofibrillary tangles associated with Alzheimer's disease (AD) [1], several neurodegenerative disorders present tau pathology in the absence of amyloid pathology. There are a number of these tauopathies, including AD, frontotemporal dementia with parkinsonism associated with chromosome 17 (FTD-17), corticobasal degeneration (CBD), Pick's disease, chronic traumatic encephalopathy (CTE), argyrophilic grain disease, and progressive supranuclear palsy (PSP). Genetic analyses of non-AD tauopathies revealed these patients possessed missense, silent and deletion mutations in the *MAPT* gene; in familial FTD-17 alone over 40 different *MAPT* mutations have been reported, as reviewed in [2]. The identification of these mutations, in addition to broader understanding of the genetics of neurodegenerative disorders, has implications for the analysis of mechanisms of tau aggregation and function in vitro.

Thorough immunohistochemical analyses using conformational epitope antibodies, as well as biochemical and electron microscopy assessments performed on post-mortem tissue, indicate tau accumulations that are present in both neuronal and glial cells with a wide variety of morphologies and distribution patterns for the different tauopathies [3–11]. Here, we review what is known about cellular factors that influence the mechanism of tau aggregation to define potential areas for therapeutic intervention across these differing tauopathies.

Tau structure and function

The tau protein is an intrinsically disordered protein encoded by a single gene (*MAPT*) residing on chromosome 17q21 in humans [12]. The protein is robustly expressed in neuronal axons in the central nervous system (CNS), while evidence exists for expression in additional CNS cell types [13]. In humans, tau mRNA is alternatively spliced resulting in the presence or absence of three regions encoded by exon 2, exon 3 and exon 10, yielding six distinct

S. N. Fontaine · J. J. Sabbagh · J. Baker · C. R. Martinez-Licha · A. Darling · C. A. Dickey (✉)
Department of Molecular Medicine, College of Medicine, Byrd Alzheimer's Institute, University of South Florida, Tampa, FL 33613, USA
e-mail: cdickey@health.usf.edu

isoforms of tau [14]. Alterative splicing of exon 10 results in tau with either 3 or 4 MT-binding repeats, both of which are found in tangles in the brains of tauopathy patients [15, 16].

MAPT mutations associated with inherited tauopathies largely can be classed into two categories: those which are solely impactful at the protein level or those that affect mRNA splicing, resulting in increased production of 4R tau. Further, several mutations located in exon 10 can have effects at both protein and RNA levels [17] (Table 1).

Recombinant tau protein can be readily produced in *E. coli*, allowing for a wide array of biochemical and biophysical assessments on the protein, furthering the study of tau biology [46, 80–84]. Tau contains multiple domains including an acidic N-terminal domain, a central proline-rich region, a predominantly basic repeat region responsible for binding to MTs, and a C-terminal domain comprised of mostly neutral residues. The tau repeat domain contains 3 or 4 repeats, depending on splicing of exon 10, and each repeat domain contains a KXGS consensus site. Phosphorylation of the serine in these motifs disrupts tau binding to the MT and serves to regulate tau-mediated MT assembly [85]. In solution, a variety of spectroscopic techniques including circular dichroism (CD), Fourier transform infared (FTIR) and nuclear magnetic resonance (NMR) spectroscopy have shown both brain-derived and recombinant purified full-length tau lacks secondary and tertiary structure and is therefore classed as an intrinsically disordered protein (IDP) [86, 87]. The tau protein consists of several charged residues ($\sim$29 % of the residues are charged) yet uniquely for an IDP, has a low net charge of

Table 1 Effects of *MAPT* mutation on tau aggregation

Mutation	Effect on aggregation	Associated Tauopathy	Reference
R5L	Increases tau aggregation	PSP	[18, 19]
R406W	Increases aggregation of tau reduces the binding of tau to MTs	FTDP-17	[20–30]
	Increased pS202 levels (increased aggregation)	AD	[31–36]
P301L	Increases aggregation of tau reduces the binding of tau to MTs	FTDP-17	[5, 18, 24–27, 30, 40–56]
	Increased pS202 levels (increased aggregation)		
P301S	Increases aggregation of tau reduces the binding of tau to MTs	FTDP-17	[57–62]
G272 V	Increases aggregation of tau reduces the binding of tau to MTs	FTDP-17	[18, 20, 24–26, 30, 63–66]
	Increased pS202 levels (increased aggregation)	Pick's disease	
V337M	Increases aggregation of tau reduces the binding of tau to MTs	FTDP-17	[18, 20, 21, 27]
	Increased pS202 levels (increased aggregation)		
ΔK280	Increases aggregation of tau reduces the binding of tau to MTs	FTDP-17	[27, 46]
G335V	Increases aggregation of tau reduces the binding of tau to MTs	FTDP-17	[67]
N279K	Increases tau aggregation. reduces the binding of 4Rtau but not 3Rtau to MTs.	FTDP-17	[38, 68]
ΔN296	Increases aggregation of tau reduces the binding of tau to MTs	Parkinson's disease, PSP	[69]
G303V	Increases tau aggregation	PSP	[70]
	Increases the binding of tau to MTs		
Exon 10+3 (IVS10+3G>A)	Increases tau aggregation reduces the binding of 4Rtau to MTs	FTDP-17	[71]
Exon 10+14 (IVS10+14C>T)	Increases tau aggregation	FTDP-17	[38]
N296H	Increases aggregation of tau reduces the binding of tau to microtubules	FTDP-17	[72]
I260V	Increases aggregation of tau reduces the binding of tau to MTs	FTDP-17	[73]
L266V	Increases aggregation of tau	Pick's disease	[74]
	Reduces the binding of tau to MTs		[75]
R5K	Increases aggregation of tau reduces the binding of tau to MTs	FTDP-17	[76]
Exon 10+12 (IVS10+12C>T)	Increases aggregation of tau	FTDP-17	[77, 78]
Exon 10+13 (IVS10+13A>G)	Increases aggregation of tau	FTDP-17	[24, 79]

+2 and is not significantly hydrophobic [88, 89]. These distinctive properties of tau protect the protein structure from chemical alterations of its immediate surroundings, including changes in ionic environment, pH, and denaturation [88]. Despite the absence of globular structure, tau is still able to form long-range self-contacts as evidenced by the successful development of conformational epitope antibodies [90, 91]. FTIR and NMR measurements indicate that tau can adopt conformations wherein both termini are folded to be in proximity to the MT repeat region [92–94].

From a functional viewpoint, the first reports of tau indicate it functions to promote MT assembly [95]. Currently, this predominant function of tau in cytoskeletal regulation is widely accepted: tau has high affinity for MTs [96], and upon binding to the MT via the MT repeat regions, stabilizes the MTs at the plus end, providing stability to the MTs during growth phases, while the N-terminal domain of tau may serve as a "spacer" between MTs to ensure adequate distance between them [97–100]. Further, a significant amount of evidence corroborates the MT-stabilizing and assembly enhancing function of tau, as tauopathy-related tau mutations alter the tau-MT association. Several mutations such as P301L, P301S, G272V, L315R, G335V, V337M, R406W, and ΔK280 result in tau being less able to interact with the MT, resulting in reduced MT assembly [67, 81, 98, 101–103]. This might be due to alterations in the functional phosphorylation/dephosphorylation balance necessary for helping to control tau-MT interactions as these mutations have been shown to have differential phosphorylation patterns [21, 63], as well as alteration in the local domain structure of the MT-binding site. Two identified missense mutations, N279K and S305N, do not reduce tau-MT interactions but do lead to increased splicing of exon 10, which is known to affect this interaction [104]. Expression of the recently described FTD mutation G55R in recombinant 4R tau results in enhanced MT assembly, though this is not the case when this mutation is expressed on a 3R tau background [105].

In addition to a key role in regulation of the MT network, tau can interact with the plasma and membrane via adaptor proteins [106, 107] and functions in cargo transport in a MT-independent fashion, through kinesin motors [108]. Several mutations in 4R tau (ΔN296, P301L, R406W) result in altered kinesin-motor transport in vitro when compared to 4R WT tau [109] and it is reported that some tau mutations result in impaired axonal mitochondrial transport [110, 111]. Tau can also be found localized in the nucleus [112], bound to AT-rich polynucleotide sequences and has been reported to protect DNA from stress-induced damage [113] and function in nucleolar organization [114].

New insights into how an IDP can adopt a highly aggregated conformation are more readily available as biophysical methods to assess protein aggregation structure and mechanism become more sensitive. Primary methods of biochemically assessing tau aggregation in vitro rely on using light-scattering [115] and amyloid fibril structure-sensing dyes, such as Congo Red, and thioflavin T or S dyes for kinetic analyses [80–83, 116], and electron microscopy and atomic force microscopy for gross aggregate morphology measurements [117, 118]. More sensitive methods such as NMR and X-ray scattering yield higher resolution data, and have highlighted key structural features required for forming the fibril core down to the specific peptide [119–121]. For more information regarding the biochemical mechanism of tau aggregation, a detailed review of the biochemistry of tau aggregation was recently published [122].

In vitro, recombinant tau aggregation can be initiated using polyanions like heparin, heparan sulfate, tRNA, and polyglutamate [123–126] fatty acids such as arachidonic acid and docosahexaenoic acid [123, 125, 127, 128], and treating either sequentially or with a mixture of purified kinases [129, 130]. Recent evidence indicates heparin binding to tau may facilitate a conformational transition by simultaneously diminishing long-range contacts and compacting the MT-binding region, resulting in a conformation of tau with higher propensity for aggregation [94]. When isolated, specific domains of tau can adopt distinct secondary structure and conformations, which may correlate to their propensity for aggregation [94, 131, 132]. Isolated modeling and analysis of the K18 peptide (spanning all 4 MT repeats) and K19 (peptide spanning 3 MT repeats) revealed these peptides contain a mixture of ordered and disordered structures including β-sheet-prone structures which may serve as a core or seed for full-length tau aggregation [133, 134]. Toward that end, minimal fibrillation domains have been determined in vitro, primarily within the MT repeat region: amino acids 317–335, 391–407 [135], 275–280, 306–311 [83], and 314–320 [136]. When the MT repeat region is flanked by the C-terminal domain, tau aggregation is reduced [129, 136]. Together, it seems the residues within the MT repeat region are important not only for tau function but also instrumental in the initiation of tau aggregation.

Cellular factors influencing tau aggregation

Among cellular factors which have been reported to affect tau aggregation, we will discuss post-translational modifications (PTMs) (Fig. 1) including phosphorylation, acetylation, and proteolysis, as well as the molecular chaperone machinery..

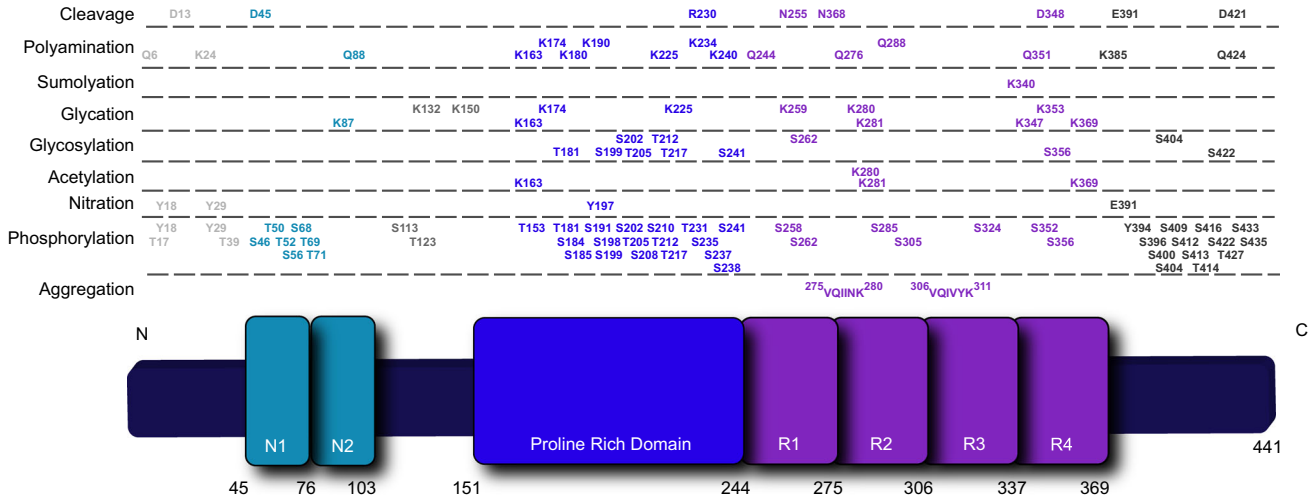

Fig. 1 Schematic diagram of the longest isoform of human tau and the locations of post-translational modifications important for aggregation relative to important protein domains. Pro-aggregation peptides 275–280 and 306–311 [83] are shown for comparison

Post-translational modifications

Phosphorylation

The longest isoform of human tau contains 79 serine/threonine residues along the 441 amino acid stretch (Fig. 1). Of these residues, 20 different sites have been reported to correlate with tau function [137]. Generally, it is thought that tau is phosphorylated and dephosphorylated as a regulatory mechanism to control the association of tau with the MT: tau de-phosphorylation promotes MT binding whereas phosphorylation decreases the affinity of tau for tubulin and stimulates the activity of tau phosphatases, facilitating the disassociation of tau from the MT [138–140]. This theory is supported by the finding that physiological tau can be phosphorylated at residues S199, S202, T231, S262 and S404 in normal adult brain [141]. It may be possible that the multi-site phosphorylation status of tau can confer ultrasensitivity to the molecule, priming tau for a multitude of responses from interacting proteins [142, 143]. In this way, hyperphosphorylated tau found in diseases could be indicative of an inability of tau to respond correctly to a stimulus, such that tau becomes trapped in a state that is conducive to eventual misfolding and aggregation.

There are three classes of kinases which have been shown to phosphorylate tau, the first of which contains proline-directed kinases such as glyocen synthase kinase-3 (GSK3) [144], mitogen-activated protein kinases (MAPKs) such as ERK1/2, JNK and p38, and cyclin-dependent protein kinase-5. The second class of kinases consists of non-proline-directed kinases such as tau-tubulin kinase, microtubule affinity-regulating kinases (MARKs), casein kinase, and dual-specificity tyrosine phosphorylation-regulated kinase 1A/2 (DYRK 1A/2). The final class of kinases which affect tau is tyrosine protein kinases such as Src family kinases and c-Ableson (c-Abl) kinases, which may play a role in tau aggregation as tyrosine-phosphorylated tau is found in tau aggregates in both transgenic mouse models and AD patient brains [145]. These kinases (and others), their effects on tau, and their suitability as drug targets have been extensively reviewed previously [146–148].

In most tauopathies, pathological tau is hyperphosphorylated at serine/threonine residues [1, 149], particularly within KXGS motifs in the MT-binding region [150]. This suggests a mechanism where excessive hyperphosphorylation confers a structural predisposition to aggregate, despite the fact that in vitro at least, tau that is not phosphorylated can be induced to polymerize [151–153]. Studies of dephosphorylated, brain-derived tau suggest the phosphorylation state of tau is critical for fibril formation [129] and in fact, recombinant human tau readily aggregates when hyperphosphorylated (above 10 mol phosphate/mol protein) in vitro [20, 154]. Further, analysis of 27 different phosphomimetic mutants of recombinant tau found that phosphorylation sites nearer to the N-terminus tend to suppress tau aggregation, whereas phosphorylation sites nearer to the C-terminus, including those sites located around domains of tau which are purported to have local β-sheet competent structure, have a stimulatory effect on in vitro filament formation [155]. These data suggest that hyperphosphorylation may lead to aggregation by neutralizing inherent anti-polymerizing structural properties of tau. Hyperphosphorylation changes to the local environment and spatial arrangement of the acidic and basic regions of tau may impact tau self-polymerization, and it has been demonstrated that hyperphosphorylation may neutralize the basic charges and inherent anti-aggregation properties of

tau within the acidic N-terminal inserts, allowing for tau filament formation [129].

The development of phosphorylation specific epitopes in tau has allowed researchers to correlate paired helical filament (PHF) or tau accumulation events with the phosphorylation state of tau. In fact, tau hyperphosphorylation correlates well with AD disease severity [150]. Among the first epitopes to be phosphorylated in the initial stages of tau aggregation are the KXGS motifs contained within the MT-binding region, and Ser262 in particular. Tau phosphorylated at S262 can be found in normal adult brain [141], perhaps as a regulatory modification, as it negatively affects the tau-MT association [156]. However, pS262 tau can be found free of MTs dispersed throughout the neuron [157, 158] in amorphous, aggregated state [159], suggesting this modification is a preliminary step towards tau aggregation. Following pS262 phosphorylation, pT231 is detected in many early, pre-tangle aggregated forms of tau [159]. Like pS262 tau, pT231 has reduced affinity for MTs [160] and also can be detected in non-tauopathy brains [141], potentially providing an early phopho-indicator of aggregation-prone or aggregated tau. Following phosphorylation at these sites, tau aggregates are positive for phosphoepitopes pS199, pS202, pT205, pS208 [161] as well as pS396 and pS404 [162], and the reactivity of these epitopes in tauopathy patient brains is well described [160]. Moreover, phosphorylation at pS199, pS202, pT205 promotes tau aggregation [163, 164], indicating that the modification of these residues promotes tau aggregation. The presence of mature tau aggregates such as PHFs containing seemingly regulatory phosphorylated tau at pS262 and pT231, suggests that phosphorylation which promotes tau disassembly from the MT may play an important role in the initial stages of cellular tau aggregation.

More insight regarding tau phosphorylation and aggregation can be obtained from studies using familial FTDP-17 tau mutations. Tau proteins containing G272V, P301L, V337M are more readily phosphorylated in vitro [20] while, the mutation R406W lacks several key phosphorylation sites at residues T231, S235, S396, S400, and S404 [165]. G272V, P301L, V337M and R406W all have enhanced phosphorylation at S202 compared to WT tau [20, 21]. This enhanced pS202 signature results in a conformational change (observed in vitro in gel shift mobility assays) [21] and can facilitate tau aggregation and recruitment of the normally microtubule-associated tau [20, 21]. Together, the literature indicates that the phosphorylation state of tau is linked to its aggregation and accumulation, and these effects are enhanced in the presence of familial tau mutations.

Acetylation

Acetylated tau was first identified by Min and colleagues in patients with light to moderate tau pathology, and was suggested to be a preliminary step in the accumulation of phosphorylated tau in neurofibrillary tangles [166]. While there are ~23 lysine residues in tau that are candidates for acetylation, mass spectroscopy revealed the primary acetylated residue in tau is K280 [167]. Tau acetylated at K280 is predisposed to aggregate in vitro, and can be found in tau deposits in a number of tauopathies, including PSP and AD [167], suggesting a role for tau acetylation in aggregation. However, there are some conflicting data regarding the true role of tau acetylation, as it is also reported that AD and tau transgenic mouse brains contain tau which is hypoacetylated and hyperphosphorylated specifically at KXGS motifs in the MT-binding region [168]. Further analysis reveals the deacetylase acting on these residues is histone deacetylase 6 (HDAC6) [168]. This is of note as HDAC6 protein expression is increased in AD and tau transgenic mice [169, 170], while HDAC6 inhibition promotes tau clearance [168] and rescues behavioral deficits in a tauopathy model [171]. These findings suggest a mechanism where enhanced deacetylation of tau within KXGS motifs predisposes these residues to hyperphosphorylation.

The precise mechanisms regulating tau acetylation are complex. Acetyl-transferases p300, pCAF, and CBP (CREB binding protein) have all been reported to acetylate tau, and deacetylases SIRT1 and HDAC6 have been shown to modulate deacetylation of tau at specific residues [166, 168]. Further, HDAC6 inhibition results in decreased tau-mediated toxicity, while SIRT1 levels are reduced in AD brains and correlate with an increased number of tau aggregates [172]. Finally, there is evidence that tau itself is capable of auto-acetylation [173, 174], which may have further implications for the balance of phosphorylation and acetylation in regulating tau aggregation.

Proteolytic cleavage

Finally, proteolytic cleavage of tau may play an important role in tau aggregation. Tau can be cleaved by caspases 3 and 6 at residues D421 and D348 though caspase 3 is the more effective protease [175], and tau cleaved at D421 has been identified in AD patient brain [175–177]. Further, this D421 truncated tau is prone to aggregation at a much faster rate than full-length tau [175] and can act as a seed to initiate aggregation of full-length tau, possibly as a preliminary step in tangle formation [178, 179]. Caspase cleavage of tau does not preclude hyperphosphorylation, as both modifications are often identified in tau accumulations in post-mortem brain [175] and D421-cleaved tau can be phosphorylated by GSK3β in vitro [178].

In addition to capsase-mediated proteolytic cleavage of tau, tau can be cleaved by calpains, thrombin, and cathepsins [180–183]. In response to beta amyloid (Aβ),

tau is truncated to a fragment spanning residues 45–230 by calpain 1 [180], and calpain cleavage may be a common event in several tauopathies [184]. This 45–230 tau fragment is neurotoxic, though a similarly sized fragment produced by calpain 2 is not [180, 185], and can form small aggregates in the presence of arachodonic acid that partially inhibits aggregation of full-length tau [184]. Finally, it has recently been demonstrated that tau can be cleaved by legumain/mammalian asparagine endopeptidase (AEP), a cysteine protease that cleaves the C-terminal of asparagine proteases, independently of calpain or caspase cleavage [186]. Tau is cleaved by mammalian AEP at N255 and N368, and the resulting fragments bind poorly to MTs yet aggregate readily in heparin-stimulated aggregation assays, possibly because this fragmentation leaves intact the key peptides sequences for tau aggregation (residues 275–280, 306–311) [186]. Interestingly, these AEP-cleaved tau fragments are capable of becoming hyperphosphorylated [186]. Thus, tau can be cleaved by a variety proteases, and the fragments resulting from these proteolytic events have pro-aggregatory and pro-toxicity properties, suggesting tau cleavage is likely an important determining PTM in pathological tau accumulation.

Nitration, glycosylation, glycation and other post-translational modifications of tau

In addition to acetylation and phosphorylation, tau has been reported to be modified by glycosylation [187, 188], glycation or non-enzymatic glycosylation [189, 190], prolyl-isomerization [191], nitration [192], polyamination [193], sumolyation [194], oxidation [195], ubiquitination [196, 197]. Of these PTMs, glycosylation, nitration, sumolyation, glycation and polyamination are associated with mechanisms of tau aggregation.

Tau extracted from AD patient brain is found to be glycosylated [187, 188] and deglycosylation of this material disaggregates tau and restores MT functionality to the protein [188]. In fact, O-linked glycosylation of tau has been linked to decreased phosphorylation and aggregation [198, 199], suggesting that glycosylated tau may be important in preventing unwanted aggregation of phosphorylated tau. Glycation of tau can occur at 12 different sites on tau, 7 of which are located within the MT-binding region [189, 190]; while glycation itself does not initiate tau aggregation [200], this modification appears to promote the accumulation of aggregated tau [201].

Tau derived from AD brain is normally glycosylated but de-glycosylated brain-purified tau does still assemble into fibrils [188]. Tau nitrated at residues Y18 and Y29 have been found in tangle pathology of AD patients [202–204], suggesting a role for nitration in tau accumulation. Nitration can occur at 4 sites on tau (Fig. 1) and in vitro, nitration at Y197 and E391 promotes tau polymerization [202]. These data suggest that nitration may influence tau conformation and promote aggregation. Tau sumolyated at K340 by SUMO-1, -2 and -3 has been found in tau aggregates in mutant amyloid precursor protein (APP) transgenic mice but not in transgenic tau mice, suggesting amyloid pathology is key to sumolyation of tau [194, 205]. Sumolyation therefore may represent an amyloid-driven PTM of tau that can occur at some stage during tau accumulation, and may promote the accumulation of tau in tangles. Polyamination results in an isopeptide bond and facilitates protein cross-linking [206], and polyaminated tau has been observed in P301L mice as well as in AD brains [207, 208]. Polyaminated tau may represent a tau isoform that is cross-linked in a way that facilitates aggregation, as this modification can be detected on tau prior to accumulation [193]. Together, these PTMs represent modifications of tau which may impart the structural predisposition to aggregation. As there is a host of evidence suggesting that multiple PTMs can occur on tau simultaneously, it may be that a delicate balance of tau modification is required for normal tau function and any slight deviation from this balance predisposes it toward aggregation and accumulation.

Molecular chaperones

Cellular proteostasis is tightly controlled by a class of proteins known as molecular chaperones. The major chaperones that control proteostasis, heat shock proteins (Hsps) 90 kDa (Hsp90) and 70 kDa (Hsp70), function to regulate nascent chain protein folding, re-fold incorrect conformers of mature proteins, and if these actions fail, target the misfolded proteins to the proteasome for degradation. Therefore, chaperone proteins are ideally situated to deal with aberrant tau conformers, and the increased aggregation of tau may be linked to inappropriate tau sorting within the chaperone system. The first link of chaperones to tau biology by Dou et al. [209] found Hsp90 and tau accumulation are inversely correlated in mice overexpressing an FTD-17 mutant: brain regions containing high levels of aggregated tau had decreased Hsp90 levels, and regions with low to absent tau aggregation expressed higher levels of Hsp90. This inversely correlative trend also proved true for Hsp70 and was further confirmed in cells by Hsp90 and Hsp70 knockdown [209].

Hsp90

Hsp90 family members are encoded by 17 genes in humans which account for the predominantly cytosolic Hsp90, mitochondrial tumor necrosis factor receptor-associated protein 1 (TRAP-1), and endoplasmic reticulum (ER) resident glucose-regulated protein 94 (Grp94), each

of which has a distinct set of clients and functions [210]. Early in vitro work with purified Hsp90 revealed it binds tubulin dimers and inhibits MT polymerization [211], with more recent studies implicating Hsp90 in tau regulation and MT-tau interactions [209, 212]. The findings that Hsp90 inhibitors reduced tau levels and phosphorylation through induction of the heat shock response [212, 213] or CHIP-mediated ubiquitination [214] further confirmed a role for Hsp90 in tau biology. These studies and others [215] suggest Hsp90 promotes tau refolding, leading to the facilitation and maintenance of aberrant tau. In fact, Hsp90 was demonstrated to directly interact with tau, which promoted a conformational change in tau and enhanced its propensity to aggregate [216]. Important structural modeling work revealed that Hsp90 binds to a long stretch of tau which includes the aggregation-prone MT-binding repeat domains [217], providing mechanistic insight into how Hsp90 may facilitate tau accumulation.

The importance of co-chaperones in cellular function has been gaining increasing attention. Hsp90 co-chaperones such as FK506-binding protein 51 (FKBP51), FKBP52, cell division cycle protein 37 (Cdc37), and protein phosphatase 5 (PP5) have been shown to regulate tau stability, aggregation, and clearance. FKBP51 and FKBP52 are immunophilins with both a tetratricopeptide repeat (TPR) and peptidyl-prolyl isomerase (PPIase) domain, permitting them to interact with tau in concert with Hsp90 or alone through cis–trans isomerization of proline residues [218]. This latter action of FKBP51 stabilizes the tau-MT interaction by altering the phosphorylation pattern of tau, an effect that can occur independently of Hsp90 [218]. However, FKBP51 and Hsp90 together have a synergistic effect on tau, preventing its clearance through the proteasome and promoting its aggregation [219]. FKBP52 also binds directly to tau, especially phosphorylated tau, inhibiting MT polymerization and tau aggregation [220]. Cdc37, which has been linked to kinase regulation, stabilizes tau and prevents its clearance through both Hsp90 and the regulation of important tau kinases [221]. Not surprisingly, the phosphatase PP5 dephosphorylates tau at several disease-relevant sites and its activity is decreased in AD brains [222, 223]. Although little data exist about how Hsp90 and PP5 regulate tau together, given the known role of each in tau biology, it is likely that they work in concert to control tau phosphorylation and proteostasis.

Hsp70

The other major cellular chaperone family is the Hsp70 family. There are over 10 members of the Hsp70 family, some with very specific subcellular locations and functions [224]. Hsp70 family proteins have been shown to bind to the MT-binding region of tau [209, 225–227]. These binding sites overlap with regions of tau important for aggregation [226] and tau binds to Hsc70 directly after MT disassembly [228], suggesting Hsc70 plays an important role in correctly directing tau after it initially disengages from the MT, which may provide insight into how Hsp70s can modulate tau aggregation. Hsp70s have a host of co-factors including DnaJ/Hsp40 family proteins, nucleotide exchange factors such as BAG proteins, and the E3 ubiquitin ligase CHIP [224]; several of these cofactors have demonstrated interactions with tau and in some cases modulate its aggregation [225, 229–232]. CHIP, responsible for ubiquitination of Hsp70 clients, is capable of binding to and ubiquitinating phosphorylated tau [225, 229] and has been shown to co-localize with pathological accumulated tau in AD, Pick's disease, PSP, and CBD [229], suggesting tau which is ubiquitinated by CHIP can be recruited into the deposits of abnormally aggregated tau. In fact, overexpression of CHIP in cells increased tau aggregation, whereas overexpression of Hsp70 reduced tau aggregation [229, 233].

Hsp70 preferentially interacts with oligomeric species of tau aggregates [233, 234]. Hsp70 can rescue tau aggregation-induced deficits in axonal transport [235], highlighting the importance of the molecular chaperone machinery in clearing tau aggregation to restore function. Due to the number of Hsp70 isoforms, it is important to delineate how each Hsp70 isoform treats tau. While tau can bind to both the constitutively expressed Hsc70 and the stress-inducible Hsp72 [226], these isoforms have opposite effects on tau: Hsp72 facilitates tau clearance, while Hsc70 stabilizes tau levels [226]. Interestingly, AD patients have greatly increased Hsc70 levels compared to Hsp72 [226]. Perhaps most strikingly, small molecule inhibitors of Hsp70 facilitate tau clearance from cells and in tau transgenic models [236, 237], and rescue deficits in synaptic plasticity [237], suggesting Hsc70-mediated stabilization of tau levels can create an environment conducive to the accumulation of tau aggregates.

Small heat shock proteins

In addition to the major cellular chaperones, other Hsps are also implicated in tau aggregation. Small Hsps such as Hsp27 (also known as HspB1) and αB crystallin (αBC/Hsp25 in rats) protect cells against stress-induced protein accumulation by interacting with misfolded proteins and preventing protein aggregation, a function dependent on the phosphorylation state of these Hsps. Small Hsps are found in both the intracellular and extracellular space [238]. The involvement of small Hsps in tauopathy is of interest, particularly since Hsp27 can bind directly to phosphorylated tau [239, 240] and Hsp27 transgenic mice

have increased levels of phosphorylated tau along with the kinase, GSK3β [241]. Hsp27 is expressed in neurons bearing tau tangles in brain regions commonly affected by AD pathology [242–244] and both Hsp27 and αBC are found co-localized with hyperphosphorylated tau in glial and astrocytic cells in several tauopathies [245–247].

In terms of tau aggregation, tau fibril formation in vitro is prevented by the addition of recombinant Hsp27, while in vivo Hsp27 overexpression results in decreased tau levels and strikingly, rescue of synaptic plasticity in a transgenic tau model [240]. In fact, Hsp27 does not disaggregate preformed tau aggregates, but acts specifically to inhibit fibril formation [240]. This activity was dependent on the large multimeric conformation of the Hsp27, as a phosphomimetic mutant of Hsp27 less robustly prevented tau aggregation. This mutant form of Hsp27 stabilized tau levels in mouse neurons, while wild-type Hsp27 facilitated tau clearance, suggesting that the phosphorylation dynamics of Hsp27 are critical for tau aggregation kinetics in vivo [240]. These data therefore indicate that ATP-independent small Hsps play a role in modulating tau aggregation. A recent proteomics study has indicated Hsp27 and αBC are differentially phosphorylated in brains (all cell types represented) of patients with AD compared to control brains [248]. Together, these data suggest differences in signaling pathways regulating kinases and the small Hsps in neurodegenerative disease may contribute to modulation of aggregating tau in tauopathies.

Conclusion: implications for designing effective therapies targeting cellular modulators of tau aggregation

In conclusion, tau aggregation can be affected not only by mutations associated with disease but also by a number of modifications. Direct modifications to the tau protein that alter its aggregation include tau phosphorylation, cleavage, glycosylation, nitrosylation and acetylation. Indirect modifications by binding partners such as chaperones can also have diverse effects on tau aggregation. Therefore, there are multiple mechanisms that control tau aggregation in the brain, each of which could be exploited for therapeutic development. But it remains to be seen if inhibiting tau aggregation will be effective in the clinic for AD and other tauopathies. In fact, given the diverse mechanisms through which tau aggregation can be controlled in the cell, it is possible that some types of tau aggregation could be protective while others are toxic. Thus, new investigational compounds targeting these distinct tau aggregation mechanisms could provide important insights about the pathogenesis of tau.

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