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REVIEW ARTICLE

New insights into tau protein with regard to Alzheimer's disease and other tauopathies

Mohammad Mustakim Billah[1], Arif Hossin[2], Kashfia Nawrin[1], Fairuza Ahmed[3]

[1]Department of Research, Institute for Pharmaceutical Skill Development and Research, Dhaka, Bangladesh
[2]Pharmacy Discipline, Khulna University, Khulna, Bangladesh
[3]Department of Pharmacy, Brac University, Dhaka, Bangladesh

ABSTRACT

Microtubule associated protein, Tau characterizes a number of neurodegenerative disorders grouped as Tauopathies including Alzheimer's disease (AD) and tau associated frontotemporal lobar degeneration (FTLD-tau). The molecular pathogenesis of these tauopathies involves post-translational modifications of Tau such as phosphorylation and truncation. However, there are other PTMs such as acetylation, methylation, ubiquitination which contribute to the pathogenesis as well. In recent years, a remarkable number of investigations have been efforted on Tau in relation to AD or FLTD-tau which has provided a body of new insights on the possible mechanisms on tau pathology. These involve but not limited to the contexts of tau phosphorylation, Tau-RNA Interaction, MAPT translation suppression, new non-aggregative tau identification, Aβ mediated exosomal tau seed, Clusterin enhanced tau aggregation, co-factor-free tau seed, co-occurrence of tau accumulation and microglial activation, tau acetylation mediated CMA inhibition, Viral ligand-receptor interactions mediated seed transmission, autophagy etc. Early detection is considered as preliminary step in disease management. Recent studies demonstrated positron emission tomography (PET) as an efficient scanner of abnormal tau which has revealed new possibilities of predicting memory impairment, level of toxic tau, detecting previously undetected diffuse pathology and identification of tau generation and deposition. Reports also suggest new advancement on understanding of physiological management of tau pathologies by autophagy mediated tau degradation, inhibition of amyloid formation and tau accumulation. This review summarizes the recent evidences on the nature and action of tau protein with regard to AD and other tauopathies to accumulate new insights into possible mechanisms underlying, detection and diagnosis, biological management and therapeutic strategies.

Keywords

Tau,
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Correspondence

mustakimbillah@hotmail.com

INTRODUCTION

Tau is a microtubule (MTs) associated protein which supports MT assembly and stability. Tau, losing its ability to bind MTs, can misfold and initiate the pathological changes which marks characteristics of Alzheimer's disease (AD) and other Tauopathies [1]. Recent evidences indicate that pathological tau can spread between cells or anatomically connected neuronal regions where the transmission is subjected to the spread of various tau strains in the AD patient brain in a "prion-like" manner [2]. This involves a complex of multiple steps of cellular activity like secretion, cellular uptake, transcellular transfer, and/or seeding, however, the precise mechanisms of propagation of tauopathies remain unclear [3,4]. Studies suggest with compelling experimental evidence that spread of tau tangles occurs with the involvement of microglial activation over the neocortex in AD where microglial activation and tau were found to propagate jointly across Braak stages [5].

The functions of Tau in the central nervous system are controlled by manifold posttranslational modifications (PTMs) which are evident in more than fifty neuronal regions [6,7]. Normal Tau carries multiple phosphate groups in its microtubule assembly domain. An increase in phosphorylation followed by tau aggregation is commonly considered pathological hallmarks for tauopathies including AD [8,9]. Rationally, phosphorylation of insoluble Tau has been the generalized target for current AD therapies. However, recent study claims higher phosphorylation is not necessarily the lead determinant of Tau aggregation and in addition, highlight the quest for investigating well-characterized CSF Tau fragments which lack functional and mechanistic data [7].

Tau oligomerizes, but the biological functions of oligomeric tau (oTau) are still unclear [10,11]. Recent study shows Tau oligomerization facilitating fast protein aggregation are linked to RNA metabolism where oligomeric tau complexes with m6A-RNA and HNRNPA2B1 to regulate RNA translation. This was also evident by knockdown of HNRNPA2B1 which suppressed the response of pathological tau. m6A was found to gradually increase with disease severity in human brains associated with AD [12]. Another identified mechanism that promotes tau pathology propagation is acetylation which inhibits chaperone-mediated autophagy [13].

Synaptic transmission of tau has long been attributed to development of AD with in vitro and in vivo evidences [14-17], but the precise mechanisms still remain unclear. Exosomes, the extracellular vesicles, have been suggested as contributor, but tau also exists on plasma-membrane-derived EVs, microvesicles, or ectosomes [18]. New study reveals seeding activity associated exosomal tau is released from AD synapses, where amyloid beta potentiates the seeding activity [19]. Other studies demonstrated Clusterin, an extracellular chaperone, augmenting seeding of Tau aggregate in a cellular model [20]. In addition, co-factor-free tau fibrils efficiently seed tau aggregation [21]. Moreover, a new non-aggregative splicing human Tau isoform was found to be decreased in AD [22]. Viral ligand-receptor interactions have been described as mediator of efficient intercellular tau spreading [23].

Positron emission tomography (PET) studies have been efficient to scan Tau in AD brains. As a diagnostic approach a recent study profiled AD by CSF and PET imaging biomarkers which revealed PET tau as an efficient predictor of cognitive impairment [24]. The study is in line with another study where level of toxic tau has been described as the predictor of AD associated future memory decline [25]. Another PET study pointed the cortical origin of tau in AD brain [26]. Alongside, a new tau-PLA study detected an extensive previously unrecognized small-sized diffuse pathology appeared from the earliest Braak stages way before neurofibrillary tangles in preclinical AD [27]. PET study also identified tau deposition in four different routes in brains affected by AD [28].

There have been progresses in understanding the biological management of tauopathies. Study suggests a binding of molecular chaperone JDP DnaJC7 to β-turn structural element of tau inhibits amyloidogenesis [29]. Besides, Tau pseudoacetylation with K321/K353 within KXGS motifs controls its interactions with microtubule and inhibits aggregation [30]. Tau aggregation inhibition is facilitated by UBE4B, a microRNA-9 target gene, which along with STUB1 promotes autophagy-mediated degradation of Tau [31]. Enhanced understanding on disease associated tau functions enables us to highlight new therapeutic targets.

POSSIBLE MECHANISMS OF TAUOPATHIES

Tau protein phosphorylation

The homo and heterogenous phosphorylation patterns of normal and disease-associated Tau trouble the identification of specific mutations and modifications which act as obstacles in setting the biomarkers and therapeutic target for AD [7]. While conventional concept

of Tau phosphorylation considers low-phosphorylated Tau as physiological Tau and hyperphosphorylated Tau as the pathological Tau [32], new studies by Wegmann *et al.*, 2021 described that the levels of Tau phosphorylation lack to distinguish between healthy and disease types; where it may be characterized by competitive post-translational modifications (PTMs). For instance, modification of lysine residue through acetylation or ubiquitination, adjusted addition and subtraction of labile PTMs may differentially control the interactions, functions, and aggregation of Tau in neuronal sub-compartments [7]. In fact, the toxicity of Tau oligomers and aggregates may be encoded by PTMs such as acetylation, GlcNAcetylation, methylation, ubiquitination or other molecular components, apart from phosphorylation [33,34]. Findings from this study concludes that hyperphosphorylation does not certainly lead to Tau aggregation as opposed to the common concept [7].

Tau-RNA Interaction

Tau interaction with HNRNPA2B1 and N6-methyladenosine RNA mediates the development of tauopathy [35]. Mechanistic studies performed by Jiang *et al.*, 2021 confirmed that HNRNPA2B1 acts as a connector in associating oTau with N6-methyladenosine (m6A) modified RNA transcripts [12]. Absence of HNRNPA2B1 halts oTau or oTau-c from connecting with m6A or from reducing protein synthesis and diminishes oTau-induced neurodegeneration. The brains of Alzheimer subjects and P301S tau mice were found with 5-fold increase in the levels of m6A and the m6A-oTau-HNRNPA2B1 complex. These findings reveal oTau, HNRNPA2B1, and m6A complex contributes to the oTau integrated stress response. In tauopathies including Alzheimer's disease, enhanced tau fibrillization, nuclear membrane disruption, and progressive neurodegeneration is observed, enabled by this complex. The study also highlighted that as disease severity rises in human AD brains, m6A progressively upsurges.

MIR-NATs mediated suppression of MAPT translation

Thousands of natural antisense transcripts (NAT) are expressed by human genome that can control epigenetic state, transcription, RNA stability or translation of overlapping genes [36,37]. Simone *et al.*, 2021 identified a brain-enriched NAT conserved in primates and comprised of an embedded mammalian-wide interspersed repeat (MIR) called MAPT-AS1, that represses translation of Tau by competing for pairing of ribosomal RNA with entry site MAPT mRNA internal ribosome [38]. The stabilizer of axonal microtubule, Tau, is a neuronal intrinsically disordered protein (IDP) encoded by MAPT. In Tauopathies, MAPT-AS1 expression or minimal essential sequences from MAPT-AS1 (including MIR) expression are reduced. As a consequence, neuronal tau levels are increased by silencing MAPT-AS1 expression. The study illustrated many overrepresented additional NATs with embedded MIRs (MIR-NATs) at coding genes linked to neurodegeneration and/or encoding IDPs, such as PLCG1 which is controlled by MIR-NAT-mediated translation. These results demonstrated a pivotal role for MAPT-AS1 in tauopathies revealing a presumably greater involvement of MIR-NATs to the firmly regulated IDPs6 translation, relating to proteostasis in neurodegeneration [39].

Amyloid beta mediated exosomal tau seed

Trans-synaptic spread of tau starting from entorhinal cortex through hippocampus to neocortex has long been hypothesized in AD pathology and more recently has been confirmed in vivo and in vitro [40]. A novel flow cytometry assay was conducted by Miyoshi *et al.*, 2021 to quantify depolarization of synaptosomes leading to synaptic vesicle release [19]. The study showed that C-terminal-truncated, oligomeric exosomal tau is released by AD synapses where the seeding activity is facilitated by amyloid β. These findings are consistent and in line with previous findings that describes the release of Aβ-enhanced direct prion-like heterotypic seeding activity within AD synaptic terminals, with subsequent exosomal loading of aggregated tau [41-43].

Clusterin enhanced tau aggregation

The prion-like templating of soluble Tau turns into neurotoxic aggregates when naïve cells internalize aggregate seeds released from affected cells [44,45]. The Tau aggregate seeding is strongly enhanced by an abundant extracellular chaperone, Clusterin, as demonstrated by Yuste-Checa *et al.*, 2021 [20]. Clusterin, having interaction with Tau aggregates, found to stabilize highly potent, soluble seed species [46]. The endolysosomal compartment is compromised when Tau-Clusterin complexes enter recipient cells via endocytosis allowing passage to the cytosol for propagating aggregation of endogenous Tau [47,48]. Thus, the study concludes that Tau seeding is accelerated by upregulation of Clusterin in AD patients and perhaps enhance the spreading of tauopathies.

Co-factor-free tau seed activity

Utilizing a combination of biochemical experiments and solid-state NMR spectroscopy, Chakraborty *et al.*, 2021 demonstrated that in absence of negatively charged co-factors such as heparin, full-length tau protein can be aggregated into seeding-competent amyloid fibrils which sequester RNA [21,49]. The ability to efficiently seed tau aggregation and strongly sequester RNA in absence of co-factors together provide a critical development to reveal the molecular factors that guide aggregation towards disease-specific tau strains.

A new non-aggregative Tau isoform

A new non-aggregative human-specific truncated isoform of Tau was identified using qPCR by García-Escudero *et al.*, 2021 which is formed by retention of intron 12 in human neuroblastoma cells [22]. Western blotting of AD brain revealed diminished level of this Tau isoform in all Braak stages indicating its key role in AD pathology. The nature of this Tau is identical with other Tau isoforms exhibiting similar PTMs by phosphorylation and tangling but differ in the binding affinity being less prone to aggregate with other Tau(s). The study provided evidence that this non aggregative tau could be related to GSK3β inhibition which induces intron 12 retention, seemingly modulated by the inhibition of SRSF2 [50-52].

Co-occurrence of Tau accumulation and microglial activation

In Alzheimer's disease, microglial activation acts as a precursor in the propagation of tau tangles over the neocortex [17,53]. Pascoal *et al.*, 2021 described colocalization of microglial activation and tau accumulation in a Braak-like pattern [5]. Using positron emission tomography brain imaging, 130 individuals with aging and AD clinical spectrum were studied for microglial activation, Aβ and tau pathologies where their co-occurrence was found as the strongest predictor of cognitive impairment. The study suggested that pathways of longitudinal tau propagation depended on the network of baseline microglia rather than that of the tau circuits. The findings indicated a model where tau spread is influenced by the interaction of Aβ and activated microglia across Braak stages.

Tau acetylation mediated CMA inhibition

Tau homeostasis is disrupted in tauopathies [54-56]. Early pathological event in tauopathy, in part, includes acetylation of soluble tau [57,58]. A study executed by Caballero *et al.*, 2021 observed that chaperone-mediated autophagy (CMA) is responsible for degrading a large fraction of neuronal tau however, on acetylation, tau is found to be competitively degraded by macroautophagy and endosomal microautophagy [13,59]. Redirecting of acetylated tau towards other autophagic pathways to an extent caused from the inhibitory effect of acetylated tau itself on CMA which results in its extracellular release. The experimental disruption of CMA which promotes cell-to-cell propagation of pathogenic tau in a mice model of tau pathology is further demonstrated in tauopathy human brain by lysosomal analysis. This study revealed tau homeostasis is disturbed in tauopathy brains with CMA dysfunctions which can potentially aggravate disease progression [13].

Viral ligand-receptor interactions

Pathogenic protein aggregates have the ability to affect unaffected cells through intercellular transmission, thereby templates their own aberrant conformation onto soluble homotypic proteins [60,61]. Proteopathic seeds appear to involve release into extracellular space through extracellular vesicle (EV) secretion or communicated by direct cell-to-cell contact by cytonemes, contributing to the prion-like spreading of protein misfolding [62-65]. Both direct cell contact- or EV- dependent exchange of cellular cargo is associated with receptor-ligand interactions [66]. Using different cellular models spreading cytosolic prions or pathogenic Tau aggregates, Liu *et al.*, 2021 reasoned that proteopathic aggregate induction was increased by vesicular stomatitis virus glycoprotein VSV-G and SARS-CoV-2 spike S via cell contact or ligand-decorated EV [23]. The findings suggested receptor-ligand interactions as strong controller of intercellular proteopathic seed transfer and highlighted the possibility that viral infections (glycoprotein expression) contribute to spreading of protein misfolding by facilitating intercellular cargo transfer.

Autophagy and Tau Protein

Autophagic vacuoles are observed in abundance around the senile plaque in swollen axons which suggests the distribution of autophagy function across AD brain [67-69]. Using neuronal cellular model of tauopathy (M1C cells) of wild Tau, Hamano *et al.*, 2021 assessed the effects of autophagy inhibitors chloroquine and 3 methyladenine (3MA) and lysosomotrophic agent NH4Cl and found that Tau accumulation was elevated remarkably by these

agents [70]. The result indicated that Tau degradation mechanism is disturbed by the disturbances of autophagy lysosomal system and autophagy is also affected by phosphorylation and C terminal truncation.

DIAGNOSIS & DETECTION OF TAUOPATHIES

Tau PET best predicts memory impairment in AD

Finding biomarkers with predictive value for cognitive decline in AD is necessary for early detection of the disease. Biomarker status for Aβ42 (A) or tau (T) deposition and neurodegeneration (N) can aid in profiling the affected individuals [71]. A comparative study in each ATN category was performed by Bucci *et al*., 2021 between the cerebrospinal fluid (CSF) and imaging (PET/MR) biomarkers to assess their potential to predict longitudinal cognitive decline [24]. Though amyloid-β outcomes were similar using CSF or imaging, results for tau and neurodegeneration were not substitutable. CSF p-Tau181 and PET amyloid-β were found inferior to PET tau positivity indicating PET tau as the best predictor for cognitive decline in AD.

Levels of toxic Tau predicts cognitive decline in AD

Using a newer type of positron emission tomography (PET) imaging that is capable of locating toxic tau protein in the brain, Martersteck *et al*., 2021 discovered that PET Tau can foresee the level of cognitive decline in AD patients associated with primary progressive aphasia (PPA) or other types associated with memory problems [25]. The pace of the disease progression can be predicted and detected with the help of tau-based biomarkers. The study was among the first to exhibit that a person's decline in cognitive performance leading to associated brain atrophy is proportional to the higher level of toxic tau in the brain as demonstrated in a one year follow up.

Extensive previously undetected tau pathology

Given that tau fibrillation can occur independently of hyperphosphorylation and can be associated with other post-translational modifications (PTMs), early pathological tau multimers can be discovered by direct visualization of tau multimerization [7,72,73]. Bengoa-Vergniory *et al*., 2021 used a novel tau-proximity ligation assay (tau-PLA) which directly detected tau multimers, was in fact, the first method with high specificity for both in situ and in vitro visualization [27]. The study describes tau multimerization as extensive from the earliest presymptomatic Braak stages as a diffuse pathology in previously unrecognized medial temporal/hippocampal areas which appears way before neurofibrillary tangles.

Cortical Origin of Tau in AD brain

Positron emission tomography (PET) effectively detects Tau depositions in the AD pathology brain. Early TAU deposition may occur prior Aβ expression in a specific site of the medial temporal lobe [74]. Sanchez *et al*., 2021 described an automated anatomic sampling method which quantified Tau PET signals in AD patients of different ages [26]. The study concluded that initial Tau signal found in rhinal sulcus which was not associated with Aβ whereas, Age, Aβ, and APOE status facilitated the subsequent Tau propagation in the temporal neocortex. Further longitudinal data confirmed the Tau network as well as the association of baseline Tau with subsequent Tau dissemination. The study implied to a precise tracking of Tau progression in the temporal lobe in patients with AD.

Four distinct trajectories of tau deposition

Using tau-positron emission tomography scans, Vogel *et al*., 2021 identified four distinct trajectories of tau deposition in relation to Alzheimer's disease including limbic-predominant and medial temporal lobe-sparing patterns and posterior and lateral temporal patterns [28]. Distinct demographic and cognitive profiles were presented by these subtypes which differed in longitudinal outcomes. In each subtype, the initiation and spreads of tau pathology was mediated via distinct corticolimbic networks.

BIOLOGICAL MANAGEMENT OF TAUOPATHIES

DnaJC7 binds natively folded tau structural elements

Molecular chaperones such as Hsp70/J-domain protein (JDP) families act centrally in binding substrates and prevent their aggregation [75,76]. Hou *et al*., 2021 reported a novel mechanism of tau aggregation regulation where suppression of tau aggregation was observed in vitro and in cells by interaction between a molecular chaperone JDP DnaJC7 and tau [29]. DnaJC7 shows strong affinity towards natively folded wild-type tau, however exhibits low binding affinity for disease-associated Tau mutants. The study identified that using a single TPR domain, DnaJC7 spots Tau's amyloid motif containing β-turn structural element. Regarding non-mutant wild-type tau, β-turn structural elements can suppress binding of full-length tau to DnaJC7. The study

suggested a preferential binding of Tau to DnaJC7 which stabilizes the natively folded Tau conformations and prevents amyloids formation by inhibiting tau conversion.

UBE4B promotes autophagy-linked Tau degradation

Suppression of Tau overexpression is essential to alleviate neurodegeneration. Subramanian *et al.*, 2021 identified miR-9 family as suppressors of human tau overexpression phenotypes using a microRNA (miR) library in Drosophila [31]. CG11070 (miR-9a target) and its mammalian orthologue UBE4B (E3/E4 ubiquitin ligase) was found to pacify eye neurodegeneration, synaptic bouton defects, and crawling phenotypes induced by human tau overexpression in Drosophila models. CG11070 or UBE4B overexpression also led to decrease total and phosphorylated Tau levels. Overexpression of UBE4B and STUB1 encoding the E3 ligase CHIP, ubiquitinated and degraded Tau in mammalian neuroblastoma cells and increased oligomeric Tau degradation in Tau-BiFC mouse model where autophagy-lysosome system was found as key Tau degradation pathway. The findings concluded that autophagy-mediated Tau degradation was promoted by UBE4B and STUB1 together.

Tau K321/K353 pseudoacetylation within KXGS motifs

Tau tangles are enriched in post-translational modifications including acetylation at multiple sites [77]. Though majority of the reports describe Tau acetylation as detrimental as it can promote tau aggregation, few suggest that specific Tau acetylation within KXGS motifs (K259, K290, K321, K353) can protect from disease by inhibition of Tau aggregation [78,79]. On a cell-based assays for microtubule binding and tau aggregation performed by Xia *et al.*, 2021, Tau was expressed with acetylmimetics K259Q, K290Q, K321Q, and K353Q in HEK293T cells where diminished Tau-MT interaction was observed within KXGS motif [30]. More specifically, K321Q, and K353Q at pathogenic P301L tau mutation context inhibited prion-like seeded aggregation.

THERAPEUTIC STRATEGIES

Many of the above context not only describes the findings but also implied to new therapeutic strategies. Finding the molecular components and PTM activity in the Tau strain would enable the therapeutic target identification occurring at early disease cascade at a state of restricted neuronal loss [2]. The presence and level of tau-based biomarkers might predict how aggressive the disease is going to be, providing indicators necessary for precision-medicine interventions [25]. For biomarker predicted cognitive decline in AD, FDA approved aducanumab was proposed to treat mild disease stage. The finding of extensive previously undetected pathology opens a new scope to the study of early tau pathology, providing potential suggestions in early diagnosis and design of therapeutic strategies [27]. In the context of the disturbances of autophagy lysosomal system, autophagy upregulation and modulation were recommended as next target of AD therapeutics [33]. In this regard, autophagy modulators, rapamycin, mTOCR1 inhibitor and its analogues, lithium, metformin, clonidine, curcumin, nicotinamide, bexaroten, and torehalose were proposed. The new less aggregation-prone Tau recommends further research to develop future therapies for AD and related tauopathies [22]. The novel mechanism of Tau aggregation regulation can be evaluated for diagnosis and therapeutic approaches [29]. Site-specific acetylation of tau (K321Q and K353Q) could indicate a native protective mechanism against aggregation of tau and could lead to a potential therapeutic target [30].

CONCLUSION AND PROSPECTS

The characterizations of tau in AD or other tauopathies are unbound and thus, still under investigation. The findings accumulated above provides a summary of evidences which enrich the current understanding with newly exposed pathological nature of the tau, advances in pathological tau detection and natural management of tauopathies along with scopes for therapeutic interventions. Though lots of effort have been made to treat AD however none can be considered adequately effective [80]. Previous studies reported hyper phosphorylated tau as the disease progressive tau, but new report suggested the level of phosphorylation seem inadequate to attribute to disease progression. Transmission of pathological tau in AD brain is due to various tau strains and microglial activation. Moreover, viral ligand-receptor interactions mediate intercellular tau dissemination. Tau-RNA interactions facilitate response to pathological tau. AD synapses release exosomal tau and its seeding is enhanced by Aβ. Clusterin and co-factor-free tau fibrils also enhance tau aggregation seed. The newly identified human tau isoform has less affinity to aggregate but decreases in AD condition. These recent insights have opened new scopes for further investigation and indicated therapeutic interventions for Alzheimer's and other tau associated diseases.

Abbreviations

MT: Microtubule; AD: Alzheimer's Disease; FTLD-tau: Tau associated Frontotemporal Lobar Degeneration; PTM: Posttranslational Modifications; CSF: Cerebrospinal Fluid; oTau: oligomeric Tau; oTau-c: optically induced tau-Cry2 oligomers; RNA: Ribonucleic Acid; HNRNPA2B1: Heterogeneous Nuclear Ribonucleoprotein A2/B1; m6A-RNA: N6-methyladenosine-RNA; EV: Extracellular Vesicles; Aβ: Amyloid Beta; PET: Positron Emission Tomography; Tau-PLA: Tau-Proximity Ligation Assay; JDP: J-Domain Proteins; DnaJC7: DnaJ Heat Shock Protein Family (Hsp40) Member C7; KXGS motif: Conserved Tau Phosphorylation Motif; UBE4B: Ubiquitin Conjugation Factor E4 B; STUB1: STIP1 Homology and U-Box Containing Protein 1; GlcN: Glucosamine; NAT: Natural Antisense Transcripts; MIR: Mammalian-Wide Interspersed Repeat; MAPT-AS1: Microtubule-Associated Protein Tau-Antisense RNA 1; mRNA: Messenger RNA; IDP: Intrinsically Disordered Protein; PLCG1: Phospholipase C Gamma 1; NMR: Nuclear Magnetic Resonance; qPCR: quantitative Polymerase Chain Reaction; GSK3β: Glycogen Synthase Kinase-3β; SRSF2: Serine and Arginine Rich Splicing Factor 2; CMA: Chaperone-Mediated Autophagy; VSV-G: Vesicular Stomatitis Virus G; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; PET/MR: Positron Emission Tomography/Magnetic Resonance; p-Tau181: Plasma Tau Phosphorylated at Threonine 181; PPA: Primary Progressive Aphasia; APOE: Apolipoprotein E; Hsp70: 70 Kilodalton Heat Shock Proteins; TPR: Tetratricopeptide Repeat; miR: microRNA; CHIP: Carboxy-Terminus of Hsc70 Interacting Protein; Tau-BiFC: Tau-Bimolecular Fluorescence Complementation; FDA: Food and Drug Administration; mTOCR1: Mammalian Target of Rapamycin Complex 1.

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Authors MMB and KN designed and organized the project. MMB, AH, KN and FA collected the findings and prepared the manuscript in parts.

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Competing Interests

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REFERENCES

1. Medeiros R, Baglietto-Vargas D, LaFerla FM. The Role of Tau in Alzheimer's Disease and Related Disorders. *CNS Neuroscience & Therapeutics*. 2011;17(5):514-524. doi:10.1111/j.1755-5949.2010.00177.x
2. Wegmann S, Biernat J, Mandelkow E. A current view on Tau protein phosphorylation in Alzheimer's disease. *Current Opinion in Neurobiology*. 2021; 69:131-138. doi:10.1016/j.conb.2021.03.003
3. Le MN, Kim W, Lee S, McKee AC, Hall GF. Multiple mechanisms of extracellular tau spreading in a non-transgenic tauopathy model. *Am J Neurodegener Dis*. 2012;1(3):316-333.
4. Mohamed NV, Herrou T, Plouffe V, Piperno N, Leclerc N. Spreading of tau pathology in Alzheimer's disease by cell-to-cell transmission. *European Journal of Neuroscience*. 2013;37(12):1939-1948. doi:10.1111/ejn.12229
5. Pascoal TA, Benedet AL, Ashton NJ, *et al*. Microglial activation and tau propagate jointly across Braak stages. *Nat Med*. 2021;27(9):1592-1599. doi:10.1038/s41591-021-01456-w
6. Cleveland DW, Hwo SY, Kirschner MW. Physical and chemical properties of purified tau factor and the role of tau in microtubule assembly. *Journal of Molecular Biology*. 1977;116(2):227-247. doi:10.1016/0022-2836(77)90214-5
7. Wegmann S, Biernat J, Mandelkow E. A current view on Tau protein phosphorylation in Alzheimer's disease. *Current Opinion in Neurobiology*. 2021; 69:131-138. doi:10.1016/j.conb.2021.03.003
8. Braak H, Braak E. Staging of alzheimer's disease-related neurofibrillary changes. *Neurobiology of Aging*. 1995;16(3):271-278. doi:10.1016/0197-4580(95)00021-6
9. Iqbal K, Liu F, Gong CX. Tau and neurodegenerative disease: the story so far. *Nat Rev Neurol*. 2016; 12(1):15-27. doi:10.1038/nrneurol.2015.225
10. Scheltens P, Blennow K, Breteler MMB, *et al*. Alzheimer's disease. *Lancet*. 2016;388(10043):505-517. doi:10.1016/S0140-6736(15)01124-1
11. Zhou W, Wang Y. Candidate genes of idiopathic pulmonary fibrosis: current evidence and research. *TACG*. 2016;9:5-13. doi:10.2147/TACG.S61999
12. Jiang L, Lin W, Zhang C, *et al*. Interaction of tau with HNRNPA2B1 and N6-methyladenosine RNA

mediates the progression of tauopathy. *Molecular Cell*. 2021;81(20):4209-4227.e12. doi:10.1016/j.molcel.2021.07.038

13. Caballero B, Bourdenx M, Luengo E, *et al*. Acetylated tau inhibits chaperone-mediated autophagy and promotes tau pathology propagation in mice. *Nat Commun*. 2021;12(1):2238. doi:10.1038/s41467-021-22501-9
14. Mohamed NV, Herrou T, Plouffe V, Piperno N, Leclerc N. Spreading of tau pathology in Alzheimer's disease by cell-to-cell transmission. *European Journal of Neuroscience*. 2013;37(12):1939-1948. doi:10.1111/ejn.12229
15. Kfoury N, Holmes BB, Jiang H, Holtzman DM, Diamond MI. Trans-cellular Propagation of Tau Aggregation by Fibrillar Species*. *Journal of Biological Chemistry*. 2012;287(23):19440-19451. doi:10.1074/jbc.M112.346072
16. Medina M, Avila J. The role of extracellular Tau in the spreading of neurofibrillary pathology. *Frontiers in Cellular Neuroscience*. 2014;8:113. doi:10.3389/fncel.2014.00113
17. de Calignon A, Polydoro M, Suárez-Calvet M, *et al*. Propagation of Tau Pathology in a Model of Early Alzheimer's Disease. *Neuron*. 2012;73(4):685-697. doi:10.1016/j.neuron.2011.11.033
18. Dujardin S, Bégard S, Caillierez R, *et al*. Ectosomes: A New Mechanism for Non-Exosomal Secretion of Tau Protein. *PLOS ONE*. 2014;9(6):e100760. doi:10.1371/journal.pone.0100760
19. Miyoshi E, Bilousova T, Melnik M, *et al*. Exosomal tau with seeding activity is released from Alzheimer's disease synapses, and seeding potential is associated with amyloid beta. *Lab Invest*. Published online August 30, 2021:1-13. doi:10.1038/s41374-021-00644-z
20. Yuste-Checa P, Trinkaus VA, Riera-Tur I, *et al*. The extracellular chaperone Clusterin enhances Tau aggregate seeding in a cellular model. *Nat Commun*. 2021;12(1):4863.doi:10.1038/s41467-021-25060-1
21. Chakraborty P, Rivière G, Liu S, *et al*. Co-factor-free aggregation of tau into seeding-competent RNA-sequestering amyloid fibrils. *Nat Commun*. 2021;12(1):4231. doi:10.1038/s41467-021-24362-8
22. García-Escudero V, Ruiz-Gabarre D, Gargini R, *et al*. A new non-aggregative splicing isoform of human Tau is decreased in Alzheimer's disease. *Acta Neuropathol*. 2021;142(1):159-177. doi:10.1007/s00401-021-02317-z
23. Liu S, Hossinger A, Heumüller SE, *et al*. Highly efficient intercellular spreading of protein misfolding mediated by viral ligand-receptor interactions. *Nat Commun*. 2021;12(1):5739. doi:10.1038/s41467-021-25855-2
24. Bucci M, Chiotis K, Nordberg A. Alzheimer's disease profiled by fluid and imaging markers: tau PET best predicts cognitive decline. *Mol Psychiatry*. Published online October 1, 2021:1-11. doi:10.1038/s41380-021-01263-2
25. Martersteck A, Sridhar J, Coventry C, Weintraub S, Mesulam MM, Rogalski E. Relationships among tau burden, atrophy, age, and naming in the aphasic variant of Alzheimer's disease. *Alzheimer's & Dementia*. n/a(n/a). doi:10.1002/alz.12445
26. Sanchez JS, Becker JA, Jacobs HIL, *et al*. The cortical origin and initial spread of medial temporal tauopathy in Alzheimer's disease assessed with positron emission tomography. *Sci Transl Med*. 2021;13(577):eabc0655. doi:10.1126/scitranslmed.abc0655
27. Bengoa-Vergniory N, Velentza-Almpani E, Silva AM, *et al*. Tau-proximity ligation assay reveals extensive previously undetected pathology prior to neurofibrillary tangles in preclinical Alzheimer's disease. *Acta Neuropathologica Communications*. 2021;9(1):18. doi:10.1186/s40478-020-01117-y
28. Vogel JW, Young AL, Oxtoby NP, *et al*. Four distinct trajectories of tau deposition identified in Alzheimer's disease. *Nat Med*. 2021;27(5):871-881. doi:10.1038/s41591-021-01309-6
29. Hou Z, Wydorski PM, Perez VA, *et al*. DnaJC7 binds natively folded structural elements in tau to inhibit amyloid formation. *Nat Commun*. 2021;12(1):5338. doi:10.1038/s41467-021-25635-y
30. Xia Y, Bell BM, Giasson BI. Tau K321/K353 pseudo-acetylation within KXGS motifs regulates tau–microtubule interactions and inhibits aggregation. *Sci Rep*. 2021;11(1):17069. doi:10.1038/s41598-021-96627-7
31. Subramanian M, Hyeon SJ, Das T, *et al*. UBE4B, a microRNA-9 target gene, promotes autophagy-mediated Tau degradation. *Nat Commun*. 2021;12(1):3291. doi:10.1038/s41467-021-23597-9
32. Wattmo C, Blennow K, Hansson O. Cerebro-spinal fluid biomarker levels: phosphorylated tau (T) and total tau (N) as markers for rate of progression in Alzheimer's disease. *BMC Neurology*. 2020;20(1):10. doi:10.1186/s12883-019-1591-0
33. Wesseling H, Mair W, Kumar M, *et al*. Tau PTM Profiles Identify Patient Heterogeneity and Stages of Alzheimer's Disease. *Cell*. 2020;183(6):1699-1713.e13. doi:10.1016/j.cell.2020.10.029
34. Morris M, Knudsen GM, Maeda S, *et al*. Tau post-translational modifications in wild-type and human amyloid precursor protein transgenic mice. *Nat Neurosci*. 2015;18(8):1183-1189. doi:10.1038/nn.4067
35. Zaccara S, Ries RJ, Jaffrey SR. Reading, writing and erasing mRNA methylation. *Nat Rev Mol Cell Biol*.

2019;20(10):608-624. doi:10.1038/s41580-019-0168-5

36. Pelechano V, Steinmetz LM. Gene regulation by antisense transcription. *Nat Rev Genet*. 2013;14(12):880-893. doi:10.1038/nrg3594
37. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol*. 2021;22(2):96-118. doi:10.1038/s41580-020-00315-9
38. Simone R, Javad F, Emmett W, *et al*. MIR-NATs repress MAPT translation and aid proteostasis in neurodegeneration. *Nature*. 2021;594(7861):117-123. doi:10.1038/s41586-021-03556-6
39. Gsponer J, Futschik ME, Teichmann SA, Babu MM. Tight Regulation of Unstructured Proteins: From Transcript Synthesis to Protein Degradation. *Science*. 2008;322(5906):1365-1368. doi:10.1126/science.1163581
40. Braak H, Del Tredici K. Alzheimer's pathogenesis: is there neuron-to-neuron propagation? *Acta Neuropathol*. 2011;121(5):589-595. doi:10.1007/s00401-011-0825-z
41. Sokolow S, Henkins KM, Bilousova T, *et al*. Pre-synaptic C-terminal truncated tau is released from cortical synapses in Alzheimer's disease. *Journal of Neurochemistry*. 2015;133(3):368-379. doi:10.1111/jnc.12991
42. Stopschinski BE, Diamond MI. The prion model for progression and diversity of neurodegenerative diseases. *The Lancet Neurology*. 2017;16(4):323-332. doi:10.1016/S1474-4422(17)30037-6
43. Schneider A, Simons M. Exosomes: vesicular carriers for intercellular communication in neurodegenerative disorders. *Cell Tissue Res*. 2013;352(1):33-47. doi:10.1007/s00441-012-1428-2
44. Peng C, Trojanowski JQ, Lee VMY. Protein transmission in neurodegenerative disease. *Nat Rev Neurol*. 2020;16(4):199-212. doi:10.1038/s41582-020-0333-7
45. Sibilla C, Bertolotti A. Prion Properties of SOD1 in Amyotrophic Lateral Sclerosis and Potential Therapy. *Cold Spring Harb Perspect Biol*. 2017;9(10):a024141. doi:10.1101/cshperspect.a024141
46. Wyatt AR, Yerbury JJ, Ecroyd H, Wilson MR. Extracellular Chaperones and Proteostasis. *Annual Review of Biochemistry*. 2013;82(1):295-322. doi:10.1146/annurev-biochem-072711-163904
47. Flavin WP, Bousset L, Green ZC, *et al*. Endocytic vesicle rupture is a conserved mechanism of cellular invasion by amyloid proteins. *Acta Neuropathol*. 2017;134(4):629-653. doi:10.1007/s00401-017-1722-x
48. Chen JJ, Nathaniel DL, Raghavan P, *et al*. Compromised function of the ESCRT pathway promotes endolysosomal escape of tau seeds and propagation of tau aggregation. *Journal of Biological Chemistry*. 2019;294(50):18952-18966. doi:10.1074/jbc.RA119.009432
49. Zhang W, Falcon B, Murzin AG, *et al*. Heparin-induced tau filaments are polymorphic and differ from those in Alzheimer's and Pick's diseases. Grigorieff N, Wolberger C, Grigorieff N, Stahlberg H, Fändrich M, eds. *eLife*. 2019;8:e43584. doi:10.7554/eLife.43584
50. Hernández F, Gómez de Barreda E, Fuster-Matanzo A, Lucas JJ, Avila J. GSK3: A possible link between beta amyloid peptide and tau protein. *Experimental Neurology*. 2010;223(2):322-325. doi:10.1016/j.expneurol.2009.09.011
51. Hernández F, Pérez M, Lucas JJ, Mata AM, Bhat R, Avila J. Glycogen Synthase Kinase-3 Plays a Crucial Role in Tau Exon 10 Splicing and Intranuclear Distribution of SC35: implications for alzheimer's disease. *Journal of Biological Chemistry*. 2004;279(5):3801-3806. doi:10.1074/jbc.M311512200
52. Bhat R, Xue Y, Berg S, *et al*. Structural Insights and Biological Effects of Glycogen Synthase Kinase 3-specific Inhibitor AR-A014418 *. *Journal of Biological Chemistry*. 2003;278(46):45937-45945. doi:10.1074/jbc.M306268200
53. Spillantini MG, Goedert M. Tau pathology and neurodegeneration. *The Lancet Neurology*. 2013;12(6):609-622. doi:10.1016/S1474-4422(13)70090-5
54. Dennissen FJA, Kholod N, van Leeuwen FW. The ubiquitin proteasome system in neurodegenerative diseases: Culprit, accomplice or victim? *Progress in Neurobiology*. 2012;96(2):190-207. doi:10.1016/j.pneurobio.2012.01.003
55. Scrivo A, Bourdenx M, Pampliega O, Cuervo AM. Selective autophagy as a potential therapeutic target for neurodegenerative disorders. *The Lancet Neurology*. 2018;17(9):802-815. doi:10.1016/S1474-4422(18)30238-2
56. Nixon RA. The role of autophagy in neurodegenerative disease. *Nat Med*. 2013;19(8):983-997. doi:10.1038/nm.3232
57. Irwin DJ, Cohen TJ, Grossman M, *et al*. Acetylated tau, a novel pathological signature in Alzheimer's disease and other tauopathies. *Brain*. 2012;135(3):807-818. doi:10.1093/brain/aws013
58. Irwin DJ, Cohen TJ, Grossman M, *et al*. Acetylated Tau Neuropathology in Sporadic and Hereditary Tauopathies. *The American Journal of Pathology*. 2013;183(2):344-351. doi:10.1016/j.ajpath.2013.04.025
59. Caballero B, Wang Y, Diaz A, *et al*. Interplay of pathogenic forms of human tau with different autophagic pathways. *Aging Cell*. 2018;17(1):e12692. doi:10.1111/acel.12692

60. Jucker M, Walker LC. Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases. *Nat Neurosci*. 2018;21(10):1341-1349. doi:10.1038/s41593-018-0238-6
61. Brunello CA, Merezhko M, Uronen RL, Huttunen HJ. Mechanisms of secretion and spreading of pathological tau protein. *Cell Mol Life Sci*. 2020;77(9):1721-1744. doi:10.1007/s00018-019-03349-1
62. Victoria GS, Zurzolo C. The spread of prion-like proteins by lysosomes and tunneling nanotubes: Implications for neurodegenerative diseases. *Journal of Cell Biology*. 2017;216(9):2633-2644. doi:10.1083/jcb.201701047
63. Rostami J, Holmqvist S, Lindström V, *et al*. Human Astrocytes Transfer Aggregated Alpha-Synuclein via Tunneling Nanotubes. *J Neurosci*. 2017;37(49):11835-11853. doi:10.1523/JNEUROSCI.0983-17.2017
64. Tardivel M, Bégard S, Bousset L, *et al*. Tunneling nanotube (TNT)-mediated neuron-to neuron transfer of pathological Tau protein assemblies. *Acta Neuropathologica Communications*. 2016;4(1):117. doi:10.1186/s40478-016-0386-4
65. Lim YJ, Lee SJ. Are exosomes the vehicle for protein aggregate propagation in neurodegenerative diseases? *Acta Neuropathologica Communications*. 2017;5(1):64. doi:10.1186/s40478-017-0467-z
66. Mathieu M, Martin-Jaular L, Lavieu G, Théry C. Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication. *Nat Cell Biol*. 2019;21(1):9-17. doi:10.1038/s41556-018-0250-9
67. Nixon RA, Wegiel J, Kumar A, *et al*. Extensive Involvement of Autophagy in Alzheimer Disease: An Immuno-Electron Microscopy Study. *Journal of Neuropathology & Experimental Neurology*. 2005;64(2):113-122. doi:10.1093/jnen/64.2.113
68. Kanazawa T, Taneike I, Akaishi R, *et al*. Amino Acids and Insulin Control Autophagic Proteolysis through Different Signaling Pathways in Relation to mTOR in Isolated Rat Hepatocytes *. *Journal of Biological Chemistry*. 2004;279(9):8452-8459. doi:10.1074/jbc.M306337200
69. Nixon RA. Autophagy, amyloidogenesis and Alzheimer disease. *Journal of Cell Science*. 2007;120(23):4081-4091. doi:10.1242/jcs.019265
70. Hamano T, Enomoto S, Shirafuji N, *et al*. Autophagy and Tau Protein. *International Journal of Molecular Sciences*. 2021;22(14):7475. doi:10.3390/ijms22147475
71. Delmotte K, Schaeverbeke J, Poesen K, Vandenberghe R. Prognostic value of amyloid/tau/neurode-generation (ATN) classification based on diagnostic cerebrospinal fluid samples for Alzheimer's disease. *Alz Res Therapy*. 2021;13(1):84. doi:10.1186/s13195-021-00817-4
72. Ercan-Herbst E, Ehrig J, Schöndorf DC, *et al*. A post-translational modification signature defines changes in soluble tau correlating with oligomerization in early stage Alzheimer's disease brain. *acta neuropathol commun*. 2019;7(1):192. doi:10.1186/s40478-019-0823-2
73. Kaufman SK, Thomas TL, Del Tredici K, Braak H, Diamond MI. Characterization of tau prion seeding activity and strains from formaldehyde-fixed tissue. *acta neuropathol commun*. 2017;5(1):41. doi:10.1186/s40478-017-0442-8
74. Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. *Nat Rev Neurosci*. 2018;19(11):687-700. doi:10.1038/s41583-018-0067-3
75. Kampinga HH, Craig EA. The HSP70 chaperone machinery: J proteins as drivers of functional specificity. *Nat Rev Mol Cell Biol*. 2010;11(8):579-592. doi:10.1038/nrm2941
76. Tiwari S, Kumar V, Jayaraj GG, Maiti S, Mapa K. Unique Structural Modulation of a Non-Native Substrate by Cochaperone DnaJ. *Biochemistry*. 2013;52(6):1011-1018. doi:10.1021/bi301543g
77. Min SW, Cho SH, Zhou Y, *et al*. Acetylation of Tau Inhibits Its Degradation and Contributes to Tauopathy. *Neuron*. 2010;67(6):953-966. doi:10.1016/j.neuron.2010.08.044
78. Cook C, Carlomagno Y, Gendron TF, *et al*. Acetylation of the KXGS motifs in tau is a critical determinant in modulation of tau aggregation and clearance. *Human Molecular Genetics*. 2014;23(1):104-116. doi:10.1093/hmg/ddt402
79. Carlomagno Y, Chung D eun C, Yue M, *et al*. An acetylation–phosphorylation switch that regulates tau aggregation propensity and function. *Journal of Biological Chemistry*. 2017;292(37):15277-15286. doi:10.1074/jbc.M117.794602
80. Fish PV, Steadman D, Bayle ED, Whiting P. New approaches for the treatment of Alzheimer's disease. *Bioorganic & Medicinal Chemistry Letters*. 2019;29(2):125-133. doi:10.1016/j.bmcl.2018.11.034