World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

Chemical regulation of Tau oligomers in phase separation in Alzheimer's disease

Muhammad Jehangir [1,*], Xiaohui Wang [1], Kashif kashmiri [2], Umar Ali [3] and Ke Zhu [4]

[1] *Institute of Chemical Biology and Functional Molecules, State Key Laboratory of Materials-Oriented Chemical Engineering, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, P. R. China.*
[2] *School of Pharmaceutical science, Nanjing Tech University, Nanjing211816, China.*
[3] *Department of Chemistry, Government Degree College No 2 Mardan, KPK, Pakistan.*
[4] *Hubei provincial Center for disease Control and prevention, wuhan, China.*

World Journal of Biology Pharmacy and Health Sciences, 2024, 19(02), 380–390

Publication history: Received on 07 July 2024; revised on 22 August 2024; accepted on 24 August 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.19.2.0534

Abstract

A huge number of patients suffering from certain neurodegenerative disorder, which are collectively called as tauopathies, may exhibit pathological tau protein aggregates in their brains. This category of diseases includes Alzheimer's disease (AD). In AD, post translational modifications such as phos phorylations, glycosylations, truncations, and subsequent aggregation into oligomers, paired helical filaments (PHFs), and neurofibrillary tangles (NFTs) are closely associated with cognitive decline and neurodegeneration. As a result, tau oligomers have emerged as the primary toxic species in AD and tauo pathies. Tau oligomers are soluble, self-assembled tau proteins that are formed prior to fibrils and have been demonstrated to play a pivotal role in neuronal cell death and the induction of neurodegeneration in animal models. In this succinct review, we collate and summarize literature pertaining to tau oligomer formation and its role in Alzheimer's disease. Secondly, we explore the crucial role of zinc ions (Zn^{2+}) in tau aggregation, as studies suggest that zinc induces reversible tau oligomerization and can lead to tau hyper phosphorylation. The concentration of zinc is critical, as excessive levels can promote harmful tau aggregation, while normal levels are essential for physiological functions. We also examine natural and chemical compounds that can modulate tau aggregation, and lastly, we discuss how Tau protein can undergo liquid-liquid phase separation (LLPS) in neurons, forming droplets that can later develop into toxic oligomers, which are the primary hallmark of AD. We mention some molecules, such as proteins, nucleic acids, and metal ions, that influence tau LLPS and aggregation.

Keywords: Alzheimer's Disease; Tau Protein; Oligomerization; Modulation; Zinc Ions; Liquid-Liquid Phase Separation (LLPS).

1. Introduction

Alzheimer's disease (AD) and other forms of dementia are among the top seven causes of death worldwide, affecting over 50 million individuals [1]. AD is the most prevalent cause of dementia in older people. It is estimated that annually, there are 7.7 million new cases of dementia globally, or one case every four seconds. In the United States, AD affects 5.5 million people, and projections suggest that the number of AD cases will reach 13.8 million by 2050 [2,3]. In the United States, there are approximately 7 million individuals who are 85 years old or more. Although significant advancements have been made in understanding the cellular and molecular processes involved in Alzheimer's disease (AD), there is still no effective treatment or cure for this condition. Therefore, further research is necessary in this field, and we may need to reconsider the hypothesis that aggregated proteins contribute to the neurodegeneration seen in AD. This could lead to the development of new research paradigms that enhance our understanding of the disease and enable the design of more effective therapies. Multiple mechanisms have been proposed to contribute to AD, including mitochondrial dysfunction [4]. oxidative stress [5]. imbalance of metal ions [6]. Tau is a protein that naturally lacks a

* Corresponding author: Muhammad Jehangir.

well-defined structure, and its primary role is to control the stability of microtubules and the movement of cargo along axons [7]. Under normal circumstances, tau proteins are responsible for binding to microtubules. When these proteins become detached under pathological conditions, they misfold and accumulate in the cytosol [8]. The fibrillogenesis cascade, essential in AD and tauopathies, begins with tau oligomer formation and progresses to PHFs and NFTs nucleation. NFTs and PHFs are critical histopathological markers, with NFTs being the hallmark of AD and tauopathies [9]. Recent research indicates that large insoluble fibrils are unlikely to be the main toxic form, and instead, soluble tau oligomers may be the principal toxic species [10,11]. In vitro and in vivo experiments have demonstrated that tau oligomers play a significant role in promoting neurotoxicity, which can be linked to neurodegeneration and cognitive disorders in mice [12,13]. The controversy surrounding the neurotoxic potential of filamentous tau aggregates persists. Studies indicate that neuronal dysfunction occurs prior to the formation of these insoluble fibrillar deposits, implying that earlier non-fibrillar tau aggregates may be responsible for neurotoxicity [14]. In vitro assembly assays have identified prefibrillar aggregates of recombinant tau. Additionally, tau-containing pretangle neurons lacking NFTs have been detected in Alzheimer's disease patients' brains. Recent research also indicates a four-fold increase in tau oligomers in Alzheimer's brains compared to healthy controls [15]. The recent discovery of the role of toxic soluble tau oligomers is changing our understanding of the pathogenesis of tau. Oligomers have been proposed to be the main toxic form of the tau pathology observed in tauopathies. Fibrillary tau aggregates, such as NFTs, are now considered a late event and not directly responsible for early synaptic dysfunctions [16].

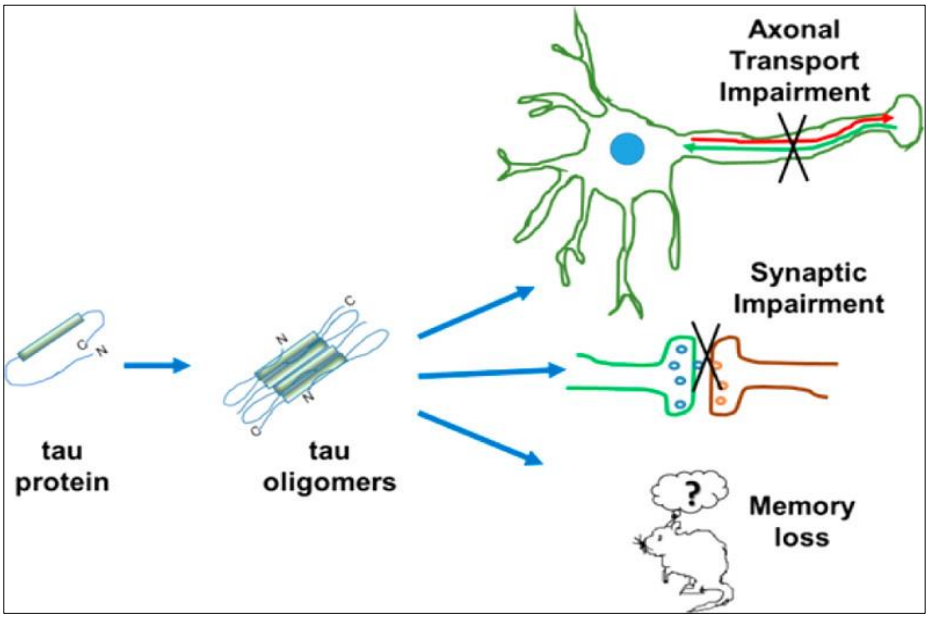

Figure 1 Mechanism of tau oligomer formation in it role in synaptic impairment and memory loss. Adopted from reference [16].

1.1. Tau oligomers

Since tau aggregates and hyperphosphorylation increase with time in AD brains, they may play a significant role in cognitive decline as they have a positive correlation with neurodegeneration and synaptic loss [17]. Tau is a multifunctional protein that has the ability to have both beneficial and negative effects on cells [18]. Tau NFTs are more strongly correlated with neural loss and clinical symptoms [19]. Tau regulates the dynamics and stability of microtubules and is involved in numerous physiological processes, including DNA protection, glucose metabolism, iron homeostasis, myelination, axonal transport, neurogenesis, motor function, learning and memory, and neuronal excitability [20]. Furthermore, hyperphosphorylated tau proteins self-assemble into paired helical filaments and tangled tau strands, two dangerous opaque aggregates. because AD symptoms don't show up for decades after the tauopathy first manifests [21]. The tau protein belongs to the group of proteins called microtubule-associated proteins (MAPs). It affects axonal growth and transport, neuronal polarization, and ultimately normal brain and neuron function [22]. Many post-translational changes, most notably tau hyperphosphorylation, have been linked to AD and have been shown to have a significant impact on microtubule assembly and tau aggregation. The hyperphosphorylation of tau results in a conformational shift. NFTs are created when tau oligomerizes from tau monomer and aggregates into pair helical filaments [23]. Tau oligomers primarily consist of monomeric or dimeric units derived from the protein that has been either pathologically truncated or highly phosphorylated. However, it is also thought that tau can assemble into two distinct dimers and higher-order oligomers at its full length. Granular tau oligomers, contains approximately 40 tau

protein molecules, have also been detected in the brain tissue of many Alzheimer's disease patients [24]. By lowering levels of critical synaptic proteins, upsetting mitochondrial balance, and contributing to DNA and RNA damage, tau oligomers accumulate in synapses and interfere with proteostatic processes, ultimately resulting in synaptic dysfunction [25]. Additionally, tau oligomers may nonspecifically promote the aggregation of other disease-related proteins via the biophysical mechanism known as LLPS, which has been used to explain a number of pathomechanisms involving aggregation-prone proteins [26]. In a physiological state, tau is soluble and non-toxic, but in pathological conditions, it may alter and acquire toxic properties despite its solubility. Tau's dissociation from microtubules may be one effect of post-translational modifications, leading to the disintegration of MTs in axons [27]. When cut off from MTs, tau diffuses quickly into other neuronal compartments and can lead to aberrant sorting within neuronal cells, which can cause synaptic dysfunction. Furthermore, a decrease in synaptic vesicles and, eventually, the loss of synapses are the outcomes of pathological Tau forms entering dendrites and postsynaptic compartments [28].

1.2. Structural features

Tau Oligomers has a progressively ordered (β-sheet) structure. It is currently unclear how exactly Tauo forms. Model peptide research emphasizes the significance of membranes in oligomerization. The most hazardous species of tau are believed to be granular tau oligomers (gTauO), a form of tau that can be extracted from AD brains [29]. Tau protein, which is generally unstructured, can adopt a misfolded beta-sheet conformation that aggregates into fibrils with a filament core made of MTBRs. As illustrated in (Figure 2) [30]. this conformation enables the N-terminus to make contact with the core domains and form paired helical filaments (PHFs), which subsequently assemble into NFTs. New research suggests that soluble tau oligomers, rather than these large insoluble fibrils, may be the main toxic tau species, even though NFTs have long been acknowledged as the histological hallmark of AD and tauopathies [31]. Furthermore, the formation of inactive tau fibrils has been suggested to have neuroprotective effects by enclosing harmful tau oligomers [32]. At first, NFTs were thought to be the toxic species causing neuronal loss. The toxicity of tau fibrils is dependent on its disintegration into short fibrils and small soluble oligomers, as demonstrated by recent studies. For example, sonicating tau fibrils increased their cytotoxicity in vitro. Furthermore, due to its ability to trigger a translational stress response, oligomeric tau—rather than fibrillar tau—was demonstrated to be physiologically active in both in vitro and in vivo studies [33].

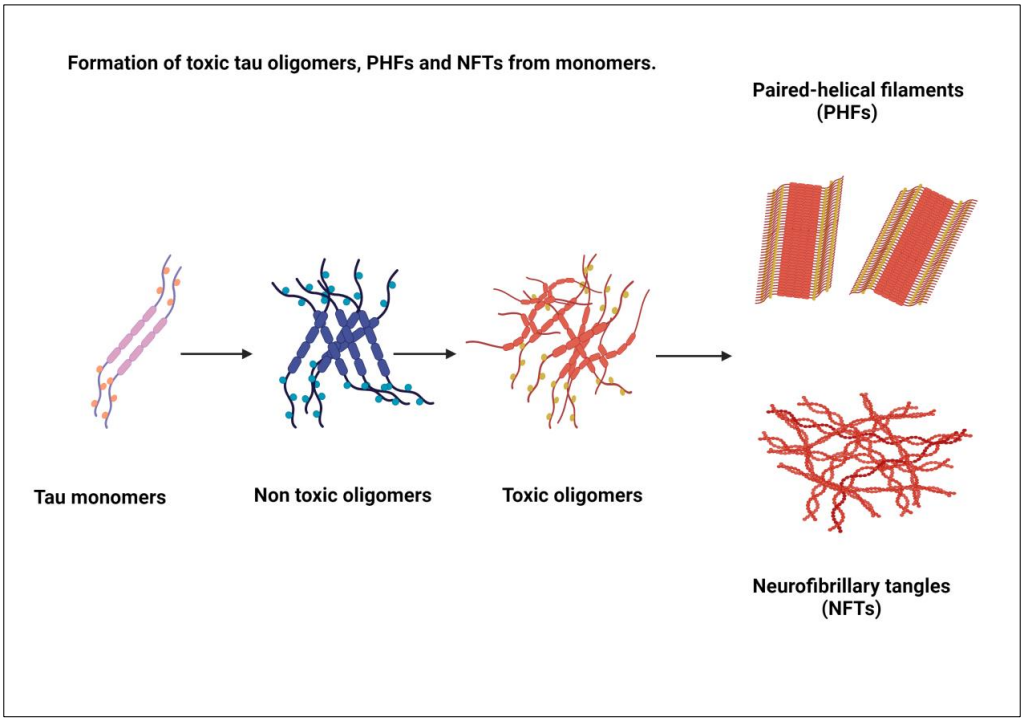

Figure 2 Formation of Paired helical filaments (PHFs) and Neurofibrillary tangles (NFTs).

2. Role in Alzheimer's pathology

In AD, tau protein makes up the majority of NFTs [34,35]. Although tau is mostly found in axons in neurons, it is also present in other cellular compartments [36]. In multistructure, tau is also expressed. Oligomers then develop into NFTs, PHFs (paired helical filaments), and straight helical filaments. Loss of microtubule binding and hyperphosphorylation of tau are associated with this progression [37]. Notably, there are structural variations in oligomeric tau between in vivo and in vitro preparations [38]. The in vivo toxicity of different oligomeric tau preparations has been confirmed by a number of functional studies, indicating the presence of common pathogenic elements in otherwise distinct oligomeric configurations. For instance, the injection of tau oligomers derived from the recombinant full-length human tau into the hippocampal region of wild-type mice results in defects in recognition memory, neuronal damage, mitochondrial dysfunction, and synaptic dysfunction [39]. More recent studies have revealed that answerable tau blocks Aβ-dependent hyperactivity, thereby leading to disabled neuronal circuit function despite the presence of NFTs [40]. also, several answerable tau species which differ in sowing exertion, phosphorylation, and oligomerization rather than tau accumulation have been described to determine the diversity in announcement progression 41. These reports suggest that answerable tau species are the main protagonists of announcement [42]. Studies have also shown that specific Tau species in the CSF or Tau pathology in the brain detected through positron emission tomography (PET) imaging can be indicators of the disease. In pathological conditions, insoluble tau aggregates can accumulate inside neurons, in the extracellular space, and in other brain cells like astrocytes and oligodendrocytes [43]. The formation of stable material is caused by abnormally modified and truncated tau proteins that self-aggregate and mature into paired helical filaments (PHF) and neurofibrillary tangles (NFT), which are characteristic of several neurodegenerative diseases [44]. Inflammation is present when these aggregates form, which may facilitate their removal but may also aggravate underlying pathological processes. Frontotemporal dementia and other neurodegenerative diseases, such as Alzheimer's disease, are primarily caused by tau pathology [45].

3. Chemical regulation of Tau oligomerization

A typical phosphorylation of tau results in a loss of affinity for MTs in tau pathologies like AD. The consequence of this is a primary lesion known as tau mislocalization from the axon to the cytoplasm and dendrites, which leads to function loss [46]. Thus, pathogenic forms such as soluble oligomers, insoluble fibrils, and NFTs are formed by the mislocalized tau proteins aggregating [47]. While each of these tau aggregates is harmful to the brain, tau pathologies are primarily caused by the oligomers. Consequently, research on tau oligomerization and TO characterization with respect to aberrant phosphorylation is highly valuable in order to facilitate the development of treatments for diseases associated with tau aggregation [48]. Much work has been done in recent years to try and modify AD pathology by focusing on Aβ, but the results have been dismal. Tau-targeting studies and strategies are therefore gaining a lot of attention [49]. A recent research study has focused on the impact of zinc on Tau physiology and aggregation. Specifically, studies have shown that zinc can cause a temperature-dependent, reversible oligomerization of Tau, which occurs in the absence of heparin [50]. Additionally, study shows that Zn2+ binds to Tau and activates Tau phosphorylation kinases, inactivating protein phosphatase and promoting Tau's hyperphosphorylation. But according to recent pre clinical research, Zn2+ may influence Tau pathology through a phosphorylation-independent mechanism by directly binding to Tau and thereby encouraging its aggregation [51]. The range of physiological Zn2+ concentration in cells is 1 nM to 10 nM, while the pathological Zn2+ concentration in cells is between 10–300 μM. Therefore, we are interested in learning whether and how a pathological concentration of Zn2+ influences the cytotoxicity and fibrillization of a pathological mutant ΔK280 of human Tau that is associated with frontotemporal dementia, a tauopathy [52]. This buildup could be connected to zinc-bound protein function, which can be compromised by pathological changes in neuronal metabolism [53]. A physiological setting, where zinc concentrations are lower, has also highlighted the significance of zinc binding to tau [54]. Therefore, at low levels of zinc within neurons, zinc's interaction with tau could produce physiological effects [55]. while at high concentrations, it may have an impact on the pathological aggregation observed in tauopathies. Because zinc homeostasis is crucial for physiopathology, the concentration of zinc may therefore be a significant contributing factor to tau aggregation [56]. In addition to zinc and a few other inhibitors of tau aggregation, monoclonal antibodies 2B10 and 6H1, which are specific to tau oligomers, are useful in preventing tau from aggregating in vitro and halting the growth of tau at the oligomer state. These antibodies are particularly effective in stopping the formation of tau aggregates and are widely used in research and therapeutic applications [57]. Tau aggregates have demonstrated both dis aggregation and aggregation inhibition by azaphilones, a class of fungal metabolites. Strong inhibitors of Tau aggregation are the secondary metabolites of Aspergillus nidulans, such as 2,ω-Dihydroxyemodin, Asperthecin, and Asperbenzaldehyde, which possess aromatic rings [58]. Research has also demonstrated the critical role curcumin derivative molecules play in tau oligomers. By interacting with the toxic TauO, curcumin derivatives change it into higher molecular weight aggregates, which reduces its toxicity [59]. According to additional research, isobavachalcone interacts with tau protein to prevent neuronal apoptosis brought on by tau oligomers, inhibit tau protein aggregation,

and lessen tau protein hyperphosphorylation. It is said that isobavachalcone inhibits the aggregation of tau proteins. In vitro, it has the ability to disassemble tau filaments and stop tau proteins from aggregating. a substance that protects the tau protein from aggregating into harmful forms may be useful in preventing AD [60]. Two distinct pharmacological approaches have been created with the goal of preventing tau aggregation. One is the direct binding to tau, which prevents it from aggregating by maintaining an interaction-incompetent conformation [61]. The other tactic relies on interactions that support the stabilization of non-toxic species—direct binding is not necessary [62]. Additionally, MB has been proven to reduce the buildup of abnormal tau proteins in mice with the P301L mutation. It was the first compound to be investigated in clinical trials as a suppressor of tau aggregation [63]. In vitro, purpurin's interaction with the PHF6 segment inhibited heparin-induced tau fibrillization and disintegrated pre-formed fibrils. In Drosophila overexpressing human tau, purpurin prevented eye neurodegeneration. Observed purpurin permeability in the cultured blood-brain barrier (BBB) model suggests potential for treating tau-related dementia [64]. Both the autophagylysosome and the ubiquitinproteasome systems break down tau, and when AD disrupts either of these systems, aberrant tau forms appear. Previous studies have shown that activating the autophagy lysosome system or the ubiquitin–proteasome system directly or indirectly can greatly improve the removal of harmful tau variants, leading to improvements in synaptic function and neuronal health [65].

4. Chemical regulation of Tau oligomers in phase separation

LLPS is essential for a variety of cellular functions, such as gene expression, cellular stress response, and mitotic spindle assembly [66]. Additionally, pathological processes like virus replication and protein aggregation are linked to LLPS [67]. Diseases may therefore arise as a result of LLPS dysregulation [68]. According to some research, tau aggregation begins with LLPS [69]. Tau is primarily the subject of LLPS research in AD. The gene encoding tau, an intrinsically disordered protein (IDP) associated with microtubules and LLPS, is known as the microtubule-associated protein tau (MAPT) gene [70]. IDPs, like the well-known AD molecule tau are principally involved in this protein misfolding. Because it serves as a link between various stages, toxic oligomerization is an essential component of the toxicity mechanism. Tau, for example, undergoes LLPS in tauopathies to form condensates, which then aggregate into droplets and oligomers. Because oligomers are somewhat toxic, they can exacerbate neuronal damage, which can eventually result in neurodegeneration and traumatic brain injury [71]. A number of studies have confirmed that neurofibrillary tangles, the typical pathological change and basis for diagnosis in AD, are caused by pathological aggregation of tau, and that LLPS may provide a pathological mechanism to explain these tangles. Analogously, LLPS also influences other molecules involved in the development of AD disease and the production of Aβ amyloid plaques. Some LLPS-prone proteins have even been shown in studies to form fibrils with structural motifs and stability that are essentially distinct from those of classical amyloid proteins [72]. Research conducted on additional LLPS-prone proteins demonstrated that liquid droplets undergo a transformation over time known as droplet aging. A network of amyloid fibrils forms as a result of this aging process for some proteins [73,74]. Determining how LLPS affects tau's aggregation characteristics is therefore very important, since the buildup of intracellular tau filaments is a defining feature of AD and other tauopathies [75]. The exact roles of liquid tau droplets created through liquid-liquid phase separation in the progression of Alzheimer's disease are still not fully understood. The recruitment of tubulin into these tau droplets helps in the formation of micro tubules. [76,77] Additionally, tau condensates that form on the surface of micro tubules play a role in regulating their functions [78]. There is evidence suggesting that the liquid-liquid phase separation of tau may play a role in tau aggregation and the creation of stress granules [79,80]. Various tau-binding molecules, such as proteins, nucleic acids, organic compounds, and metal ions, are involved in regulating both the liquid-liquid phase separation and aggregation of tau, further emphasizing the close relationship between the two processes. One such molecule, the green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG), known for its antioxidant and anti-inflammatory properties, shows promise in treating neurodegenerative diseases [81,82]. According to studies, the green tea polyphenol EGCG has a unique function that involves tau LLPS promotion. While EGCG encourages the formation of amorphous aggregates, or protein hazes, at acidic pH values, we discovered that this polyphenol also encourages the formation of liquid tau droplets at neutral pH values [83]. According to recent reports, LLPS speeds up the aggregation of Tau. It is evident from the data that acetylation reduces or eliminates Tau LLPS. Our study support a model of aggregation mediated by LLPS, but they do not establish the existence of such a mechanism in vivo. Unlike hyperphosphorylation, which has been shown to increase or directly cause condensation-mediated aggregation, we conclude that acetylation in vivo is unlikely to enhance or cause Tau to undergo LLPS [84]. A Tau-rich condensed phase has been demonstrated to be able to attract tubulin dimers and promote their assembly through a mechanism known as Tau LLPS. Tau is involved in microtubule formation and stabilization. This function would be affected by both acetylation that blocks Tau from partitioning into a Tau-rich phase and acetylation at critical Tau sites that obstruct tubulin binding. LLPS-mediated microtubule assembly initiation, and decreased binding to tubulins/microtubules; **figure 3)** [85].

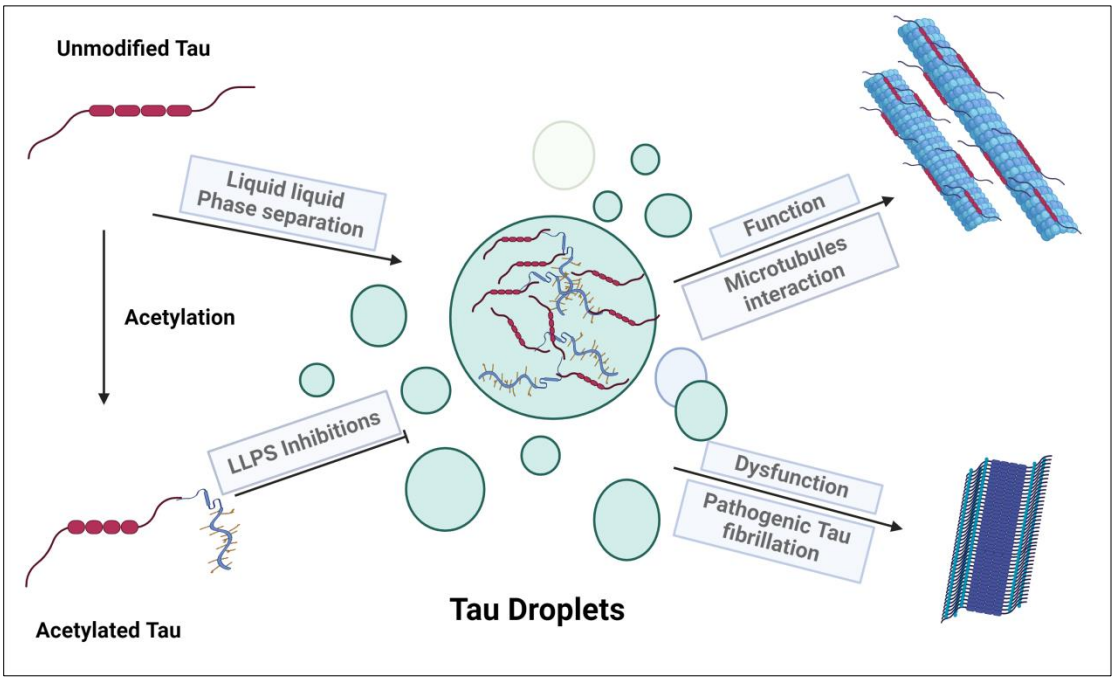

Figure 3 Model for Tau' loss of physiologic function and gain of pathologic dysfunction linked to its ability to undergo LLPS as modulated by acetylation.

EFhd2 exhibits similar molecular and biochemical properties to intrinsically disordered proteins that have been linked to neurodegenerative disorders. This implies that the pathophysiology of neurodegenerative diseases may involve EFhd2. Further evidence that EFhd2 may regulate the formation of pathological protein aggregates other than tau comes from its association with poly-GA C9Orf72 aggregates in amyotrophic lateral sclerosis and frontotemporal lobar degeneration [86]. Furthermore, tau phase separation at physiological protein concentrations can be driven by its interaction with RNA and the RNA binding protein TIA1, without the need for artificial crowding agents like PEG, according to other studies. By using this system, the researchers show that TIA1 also encourages the vitrification and oligomerization of tau. The discovery that TIA1 can selectively copartition with tau in physiological settings is noteworthy and highlights the significance of TIA1 in tau biology [87]. When combined with RNA, tau rapidly forms oligomers and gradually transforms into fibrils. Initially, tau appears uniformly distributed within TIA1 droplets, indicating miscibility. Over time, tau becomes gelated and consolidates into microdomains that exclude TIA1. These tau microdomains may act as centers for oligomeric tau formation. Inhibiting the transition from tau oligomers to fibrils, as TIA1 does, promotes tau oligomerization and is associated with accelerated tau vitrification. [88].

5. Conclusion

This review article underscores the crucial part played by tau oligomers in the progression of Alzheimer's disease (AD), and tauopathies, Showing their substantial impact on neurodegeneration and cognitive decline. Various post translational modifications, such as phosphorylation, glycosylation, and truncation, promote tau aggregation into paired helical filaments (PHFs) and neurofibrillary tangles (NFTs), which are the main causes of Alzheimer's diseases with oligomers emerging as the most detrimental species. The dual role of zinc in tau physiology beneficial at normal levels but harmful when elevated emphasis the importance of precise regulation of metal ions. Additionally, this review article examines the influence of natural and chemical compounds on tau aggregation and investigates the process of liquid-liquid phase separation (LLPS) in tau aggregation, which is affected by proteins, nucleic acids, and metal ions. Developing therapies that target early toxic tau forms and their regulatory mechanisms presents promising prospects for improving the treatment of Alzheimer's disease and related tauopathies.

Compliance with ethical standards

Acknowledgments

The National Natural Science Foundation of China financed this work, and I express my heartfelt gratitude to Professor Wang Xiao Hui from the School of Chemistry and Molecular Engineering at Nanjing Tech University for their indispensable advice and support throughout the entire endeavor.

Disclosure of conflict of interest

The authors hereby confirm that they have no conflicting interests with the contents of the manuscript.

Reference

[1] World Health Organization (WHO). The Top 10 Causes of Death. 2020. Available online: https://www.who.int/news-room/fact-sheets (accessed on 15 September 2022).

[2] Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*, *80*(19), 1778-1783.

[3] H Greig, N., & K Lahiri, D. (2014). Advances in understanding Alzheimer's disease, and the contributions of current Alzheimer research: ten years on and beyond. *Current Alzheimer Research*, *11*(2), 107-109.

[4] Constantinescu, R. (2013). *Cerebrospinal Fluid Biomarkers in Neurodegenerative Movement Disorders: Parkinsonian Disorders and Huntington's Disease*.

[5] Zambrano, C. A., Egaña, J. T., Núñez, M. T., Maccioni, R. B., & González-Billault, C. (2004). Oxidative stress promotes τ dephosphorylation in neuronal cells: the roles of cdk5 and PP1. *Free Radical Biology and Medicine*, *36*(11), 1393-1402.

[6] Maynard, C. J., Bush, A. I., Masters, C. L., Cappai, R., & Li, Q. X. (2005). Metals and amyloid-β in Alzheimer's disease. International journal of experimental pathology, 86(3), 147-159.

[7] Avila, J., Lucas, J. J., Perez, M. A. R., & Hernandez, F. (2004). Role of tau protein in both physiological and pathological conditions. Physiological reviews.

[8] Bramblett, G. T., Goedert, M., Jakes, R., Merrick, S. E., Trojanowski, J. Q., & Lee, V. M. (1993). Abnormal tau phosphorylation at Ser396 in Alzheimer's disease recapitulates development and contributes to reduced microtubule binding. Neuron, 10(6), 1089-1099.

[9] Ballatore, C., Lee, V. M. Y., & Trojanowski, J. Q. (2007). Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nature reviews neuroscience, 8(9), 663-672.

[10] Liang, S. Y., Wang, Z. T., Tan, L., & Yu, J. T. (2022). Tau toxicity in neurodegeneration. Molecular Neurobiology, 59(6), 3617-3634.

[11] Cárdenas-Aguayo, M. D. C., Gómez-Virgilio, L., DeRosa, S., & Meraz-Ríos, M. A. (2014). The role of tau oligomers in the onset of Alzheimer's disease neuropathology. ACS chemical neuroscience, 5(12), 1178-1191.

[12] Castillo-Carranza, D. L., Nilson, A. N., Van Skike, C. E., Jahrling, J. B., Patel, K., Garach, P., ... & Kayed, R. (2017). Cerebral microvascular accumulation of tau oligomers in Alzheimer's disease and related tauopathies. Aging and disease, 8(3), 257.

[13] Gerson, J., Castillo-Carranza, D. L., Sengupta, U., Bodani, R., Prough, D. S., DeWitt, D. S., ... & Kayed, R. (2016). Tau oligomers derived from traumatic brain injury cause cognitive impairment and accelerate onset of pathology in Htau mice. Journal of neurotrauma, 33(22), 2034-2043.

[14] Himmelstein, D. S., Ward, S. M., Lancia, J. K., Patterson, K. R., & Binder, L. I. (2012). Tau as a therapeutic target in neurodegenerative disease. Pharmacology & therapeutics, 136(1), 8-22.

[15] Patterson, K. R., Remmers, C., Fu, Y., Brooker, S., Kanaan, N. M., Vana, L., ... & Binder, L. I. (2011). Characterization of prefibrillar Tau oligomers in vitro and in Alzheimer disease. Journal of Biological Chemistry, 286(26), 23063-23076.

[16] Cárdenas-Aguayo, M. D. C., Gómez-Virgilio, L., DeRosa, S., & Meraz-Ríos, M. A. (2014). The role of tau oligomers in the onset of Alzheimer's disease neuropathology. ACS chemical neuroscience, 5(12), 1178-1191.

[17] Eftekharzadeh, B., Daigle, J. G., Kapinos, L. E., Coyne, A., Schiantarelli, J., Carlomagno, Y., ... & Hyman, B. T. (2018). Tau protein disrupts nucleocytoplasmic transport in Alzheimer's disease. Neuron, 99(5), 925-940.

[18] Tapia-Rojas, C., Cabezas-Opazo, F., Deaton, C. A., Vergara, E. H., Johnson, G. V., & Quintanilla, R. A. (2019). It's all about tau. Progress in neurobiology, 175, 54-76.

[19] Hanseeuw, B. J., Betensky, R. A., Jacobs, H. I., Schultz, A. P., Sepulcre, J., Becker, J. A., ... & Johnson, K. (2019). Association of amyloid and tau with cognition in preclinical Alzheimer disease: a longitudinal study. JAMA neurology, 76(8), 915-924.

[20] Kent, S. A., Spires-Jones, T. L., & Durrant, C. S. (2020). The physiological roles of tau and Aβ: implications for Alzheimer's disease pathology and therapeutics. Acta neuropathologica, 140(4), 417-447.

[21] Kim, K., & Park, C. B. (2020). Femtomolar sensing of Alzheimer's tau proteins by water oxidation-coupled photoelectrochemical platform. Biosensors and Bioelectronics, 154, 112075.

[22] Sinsky, J., Pichlerova, K., & Hanes, J. (2021). Tau protein interaction partners and their roles in Alzheimer's disease and other tauopathies. International journal of molecular sciences, 22(17), 9207.

[23] Chong, F. P., Ng, K. Y., Koh, R. Y., & Chye, S. M. (2018). Tau proteins and tauopathies in Alzheimer's disease. Cellular and molecular neurobiology, 38, 965-980.

[24] Niewiadomska, G., Niewiadomski, W., Steczkowska, M., & Gasiorowska, A. (2021). Tau oligomers neurotoxicity. Life, 11(1), 28.

[25]]Zheng, J., Akbari, M., Schirmer, C., Reynaert, M. L., Loyens, A., Lefebvre, B., ... & Bohr, V. A. (2020). Hippocampal tau oligomerization early in tau pathology coincides with a transient alteration of mitochondrial homeostasis and DNA repair in a mouse model of tauopathy. Acta neuropathologica communications, 8(1), 1-23.

[26] Darling, A. L., & Shorter, J. (2021). Combating deleterious phase transitions in neurodegenerative disease. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1868(5), 118984.

[27] Mroczko, B., Groblewska, M., & Litman-Zawadzka, A. (2019). The role of protein misfolding and tau oligomers (TauOs) in Alzheimer's disease (AD). International journal of molecular sciences, 20(19), 4661.

[28] Griner, S. L., Seidler, P., Bowler, J., Murray, K. A., Yang, T. P., Sahay, S., ... & Eisenberg, D. S. (2019). Structure-based inhibitors of amyloid beta core suggest a common interface with tau. Elife, 8, e46924.

[29] Penke, B., Szűcs, M., & Bogár, F. (2020). Oligomerization and conformational change turn monomeric β-amyloid and tau proteins toxic: Their role in Alzheimer's pathogenesis. Molecules, 25(7), 1659.

[30] Gibbons, G. S., Kim, S. J., Wu, Q., Riddle, D. M., Leight, S. N., Changolkar, L., ... & Lee, V. M. (2020). Conformation-selective tau monoclonal antibodies inhibit tau pathology in primary neurons and a mouse model of Alzheimer's disease. Molecular Neurodegeneration, 15, 1-19.

[31] Liang, S. Y., Wang, Z. T., Tan, L., & Yu, J. T. (2022). Tau toxicity in neurodegeneration. Molecular Neurobiology, 59(6), 3617-3634.

[32] Limorenko, G., & Lashuel, H. A. (2022). Revisiting the grammar of Tau aggregation and pathology formation: how new insights from brain pathology are shaping how we study and target Tauopathies. Chemical Society Reviews, 51(2), 513-565.

[33] Jiang, L., Zhao, J., Cheng, J. X., & Wolozin, B. (2020). Tau oligomers and fibrils exhibit differential patterns of seeding and association with RNA binding proteins. Frontiers in Neurology, 11, 579434.

[34] Vogels, T., Leuzy, A., Cicognola, C., Ashton, N. J., Smolek, T., Novak, M., ... & Schöll, M. (2020). Propagation of tau pathology: integrating insights from postmortem and in vivo studies. Biological psychiatry, 87(9), 808-818.

[35] Majdi, A., Sadigh-Eteghad, S., Rahigh Aghsan, S., Farajdokht, F., Vatandoust, S. M., Namvaran, A., & Mahmoudi, J. (2020). Amyloid-β, tau, and the cholinergic system in Alzheimer's disease: Seeking direction in a tangle of clues. Reviews in the Neurosciences, 31(4), 391-413.

[36] Chang, C. W., Shao, E., & Mucke, L. (2021). Tau: Enabler of diverse brain disorders and target of rapidly evolving therapeutic strategies. Science, 371(6532), eabb8255.

[37] Barbier, P., Zejneli, O., Martinho, M., Lasorsa, A., Belle, V., Smet-Nocca, C., ... & Landrieu, I. (2019). Role of tau as a microtubule-associated protein: structural and functional aspects. Frontiers in aging neuroscience, 11, 204.

[38] Vaquer-Alicea, J., Diamond, M. I., & Joachimiak, L. A. (2021). Tau strains shape disease. Acta neuropathologica, 142, 57-71.

[39] Rayman, J. B. (2023). Focusing on oligomeric tau as a therapeutic target in Alzheimer's disease and other tauopathies. Expert Opinion on Therapeutic Targets, 27(4-5), 269-279.

[40] Busche, M. A., Wegmann, S., Dujardin, S., Commins, C., Schiantarelli, J., Klickstein, N., ... & Hyman, B. T. (2019). Tau impairs neural circuits, dominating amyloid-β effects, in Alzheimer models in vivo. Nature neuroscience, 22(1), 57-64..

[41] Dujardin, S., Commins, C., Lathuiliere, A., Beerepoot, P., Fernandes, A. R., Kamath, T. V., ... & Hyman, B. T. (2020). Tau molecular diversity contributes to clinical heterogeneity in Alzheimer's disease. Nature medicine, 26(8), 1256-1263.

[42] Hameed, S., Fuh, J. L., Senanarong, V., Ebenezer, E. G. M., Looi, I., Dominguez, J. C., ... & Simon, O. (2020). Role of fluid biomarkers and PET imaging in early diagnosis and its clinical implication in the management of Alzheimer's disease. Journal of Alzheimer's disease reports, 4(1), 21-37.

[43] Perea, J. R., López, E., Díez-Ballesteros, J. C., Ávila, J., Hernández, F., & Bolós, M. (2019). Extracellular monomeric tau is internalized by astrocytes. Frontiers in neuroscience, 13, 442.

[44] Kovacs, G. G. (2018). Tauopathies. Handbook of clinical neurology, 145, 355-368.

[45] Sinsky, J., Pichlerova, K., & Hanes, J. (2021). Tau protein interaction partners and their roles in Alzheimer's disease and other tauopathies. International journal of molecular sciences, 22(17), 9207.

[46] Limorenko, G., & Lashuel, H. A. (2022). Revisiting the grammar of Tau aggregation and pathology formation: how new insights from brain pathology are shaping how we study and target Tauopathies. Chemical Society Reviews, 51(2), 513-565.

[47] Congdon, E. E., & Sigurdsson, E. M. (2018). Tau-targeting therapies for Alzheimer disease. Nature Reviews Neurology, 14(7), 399-415.

[48] Cheng, Y., Tian, D. Y., & Wang, Y. J. (2020). Peripheral clearance of brain-derived Aβ in Alzheimer's disease: pathophysiology and therapeutic perspectives. Translational Neurodegeneration, 9, 1-11.

[49] Roman, A. Y., Devred, F., Byrne, D., La Rocca, R., Ninkina, N. N., Peyrot, V., & Tsvetkov, P. O. (2019). Zinc induces temperature-dependent reversible self-assembly of tau. Journal of molecular biology, 431(4), 687-695.

[50] Moreira, G. G., Cristóvão, J. S., Torres, V. M., Carapeto, A. P., Rodrigues, M. S., Landrieu, I., ... & Gomes, C. M. (2019). Zinc binding to tau influences aggregation kinetics and oligomer distribution. International Journal of Molecular Sciences, 20(23), 5979.

[51] Hu, J. Y., Zhang, D. L., Liu, X. L., Li, X. S., Cheng, X. Q., Chen, J., ... & Liang, Y. (2017). Pathological concentration of zinc dramatically accelerates abnormal aggregation of full-length human Tau and thereby significantly increases Tau toxicity in neuronal cells. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1863(2), 414-427.

[52] Tsvetkov, P. O., Roman, A. Y., Baksheeva, V. E., Nazipova, A. A., Shevelyova, M. P., Vladimirov, V. I., ... & Zernii, E. Y. (2018). Functional status of neuronal calcium sensor-1 is modulated by zinc binding. Frontiers in Molecular Neuroscience, 11, 459.

[53] Xie, Z., Wu, H., & Zhao, J. (2020). Multifunctional roles of zinc in Alzheimer's disease. Neurotoxicology, 80, 112-123.

[54] Moreira, G. G., Cristóvão, J. S., Torres, V. M., Carapeto, A. P., Rodrigues, M. S., Landrieu, I., ... & Gomes, C. M. (2019). Zinc binding to tau influences aggregation kinetics and oligomer distribution. International Journal of Molecular Sciences, 20(23), 5979.

[55] Xie, Z., Wu, H., & Zhao, J. (2020). Multifunctional roles of zinc in Alzheimer's disease. Neurotoxicology, 80, 112-123.

[56] Chandupatla, R. R., Flatley, A., Feederle, R., Mandelkow, E. M., & Kaniyappan, S. (2020). Novel antibody against low-n oligomers of tau protein promotes clearance of tau in cells via lysosomes. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 6(1), e12097.

[57] Sonawane, S. K., Balmik, A. A., Boral, D., Ramasamy, S., & Chinnathambi, S. (2019). Baicalein suppresses Repeat Tau fibrillization by sequestering oligomers. Archives of biochemistry and biophysics, 675, 108119.

[58] Lo Cascio, F., Puangmalai, N., Ellsworth, A., Bucchieri, F., Pace, A., Palumbo Piccionello, A., & Kayed, R. (2019). Toxic tau oligomers modulated by novel curcumin derivatives. Scientific reports, 9(1), 19011.

[59] Xiao, S., Wu, Q., Yao, X., Zhang, J., Zhong, W., Zhao, J., ... & Zhang, M. (2020). Inhibitory effects of isobavachalcone on tau protein aggregation, tau phosphorylation, and oligomeric tau-induced apoptosis. ACS Chemical Neuroscience, 12(1), 123-132.

[60] Seidler, P. M., Boyer, D. R., Rodriguez, J. A., Sawaya, M. R., Cascio, D., Murray, K., ... & Eisenberg, D. S. (2018). Structure-based inhibitors of tau aggregation. Nature chemistry, 10(2), 170-176.

[61] Martinelli, A. H., Lopes, F. C., John, E. B., Carlini, C. R., & Ligabue-Braun, R. (2019). Modulation of disordered proteins with a focus on neurodegenerative diseases and other pathologies. International journal of molecular sciences, 20(6), 1322.

[62] Dominguez-Meijide, A., Vasili, E., & Outeiro, T. F. (2020). Pharmacological modulators of tau aggregation and spreading. Brain Sciences, 10(11), 858.

[63] Viswanathan, G. K., Shwartz, D., Losev, Y., Arad, E., Shemesh, C., Pichinuk, E., ... & Segal, D. (2020). Purpurin modulates Tau-derived VQIVYK fibrillization and ameliorates Alzheimer's disease-like symptoms in animal model. Cellular and Molecular Life Sciences, 77, 2795-2813.

[64] Soeda, Y., & Takashima, A. (2020). New insights into drug discovery targeting tau protein. Frontiers in Molecular Neuroscience, 13, 590896.

[65] Terlecki-Zaniewicz, S., Humer, T., Eder, T., Schmoellerl, J., Heyes, E., Manhart, G., ... & Grebien, F. (2021). Biomolecular condensation of NUP98 fusion proteins drives leukemogenic gene expression. Nature structural & molecular biology, 28(2), 190-201.

[66] Boyko, S., Surewicz, K., & Surewicz, W. K. (2020). Regulatory mechanisms of tau protein fibrillation under the conditions of liquid–liquid phase separation. Proceedings of the National Academy of Sciences, 117(50), 31882-31890.

[67] Jiang, S., Fagman, J. B., Chen, C., Alberti, S., & Liu, B. (2020). Protein phase separation and its role in tumorigenesis. Elife, 9, e60264.

[68] Kanaan, N. M., Hamel, C., Grabinski, T., & Combs, B. (2020). Liquid-liquid phase separation induces pathogenic tau conformations in vitro. Nature communications, 11(1), 2809.

[69] Fu, Q., Zhang, B., Chen, X., & Chu, L. (2024). Liquid–liquid phase separation in Alzheimer's disease. Journal of Molecular Medicine, 1-15.

[70] Babinchak, W. M., & Surewicz, W. K. (2020). Liquid–liquid phase separation and its mechanistic role in pathological protein aggregation. Journal of molecular biology, 432(7), 1910-1925.

[71] Babinchak, W. M., & Surewicz, W. K. (2020). Liquid–liquid phase separation and its mechanistic role in pathological protein aggregation. Journal of molecular biology, 432(7), 1910-1925.

[72] [163]Nedelsky, N. B., & Taylor, J. P. (2019). Bridging biophysics and neurology: aberrant phase transitions in neurodegenerative disease. Nature Reviews Neurology, 15(5), 272-286.

[73] Mathieu, C., Pappu, R. V., & Taylor, J. P. (2020). Beyond aggregation: Pathological phase transitions in neurodegenerative disease. Science, 370(6512), 56-60.

[74] Savastano, A., Flores, D., Kadavath, H., Biernat, J., Mandelkow, E., & Zweckstetter, M. (2021). Disease-associated tau phosphorylation hinders tubulin assembly within tau condensates. Angewandte Chemie International Edition, 60(2), 726-730.

[75] Tan, R., Lam, A. J., Tan, T., Han, J., Nowakowski, D. W., Vershinin, M., ... & McKenney, R. J. (2019). Microtubules gate tau condensation to spatially regulate microtubule functions. Nature cell biology, 21(9), 1078-1085.

[76] Lin, Y., Fichou, Y., Longhini, A. P., Llanes, L. C., Yin, P., Bazan, G. C., ... & Han, S. (2021). Liquid-liquid phase separation of tau driven by hydrophobic interaction facilitates fibrillization of tau. Journal of molecular biology, 433(2), 166731.

[77] Kang, S. G., Han, Z. Z., Daude, N., McNamara, E., Wohlgemuth, S., Molina-Porcel, L., ... & Westaway, D. (2021). Pathologic tau conformer ensembles induce dynamic, liquid-liquid phase separation events at the nuclear envelope. BMC biology, 19(1), 1-21.

[78] Gao, Y. Y., Zhong, T., Wang, L. Q., Zhang, N., Zeng, Y., Hu, J. Y., ... & Liang, Y. (2022). Zinc enhances liquid-liquid phase separation of Tau protein and aggravates mitochondrial damages in cells. International Journal of Biological Macromolecules, 209, 703-715.

[79] Wang, K., Liu, J. Q., Zhong, T., Liu, X. L., Zeng, Y., Qiao, X., ... & Liang, Y. (2020). Phase separation and cytotoxicity of tau are modulated by protein disulfide isomerase and S-nitrosylation of this molecular chaperone. Journal of molecular biology, 432(7), 2141-2163.

[80] Gonçalves, P. B., Sodero, A. C. R., & Cordeiro, Y. (2021). Green tea epigallocatechin-3-gallate (EGCG) targeting protein misfolding in drug discovery for neurodegenerative diseases. Biomolecules, 11(5), 767.

[81] Fernandes, L., Cardim-Pires, T. R., Foguel, D., & Palhano, F. L. (2021). Green tea polyphenol epigallocatechin-gallate in amyloid aggregation and neurodegenerative diseases. Frontiers in neuroscience, 15, 718188.

[82] Chen, J., Ma, W., Yu, J., Wang, X., Qian, H., Li, P., ... & Huang, Y. (2023). (−)-Epigallocatechin-3-gallate, a Polyphenol from Green Tea, Regulates the Liquid–Liquid Phase Separation of Alzheimer's-Related Protein Tau. Journal of Agricultural and Food Chemistry, 71(4), 1982-1993.

[83] Wegmann, S., Eftekharzadeh, B., Tepper, K., Zoltowska, K. M., Bennett, R. E., Dujardin, S., ... & Hyman, B. T. (2018). Tau protein liquid–liquid phase separation can initiate tau aggregation. The EMBO journal, 37(7), e98049.

[84] Ferreon, J. C., Jain, A., Choi, K. J., Tsoi, P. S., MacKenzie, K. R., Jung, S. Y., & Ferreon, A. C. (2018). Acetylation disfavors tau phase separation. International journal of molecular sciences, 19(5), 1360.

[85] Vega, I. E., Umstead, A., & Kanaan, N. M. (2019). EFhd2 affects Tau liquid–liquid phase separation. Frontiers in neuroscience, 13, 845.

[86] Ash, P. E., Lei, S., Shattuck, J., Boudeau, S., Carlomagno, Y., Medalla, M., ... & Wolozin, B. (2021). TIA1 potentiates tau phase separation and promotes generation of toxic oligomeric tau. Proceedings of the National Academy of Sciences, 118(9), e2014188118.

[87] Wittmer, Y., Jami, K. M., Stowell, R. K., Le, T., Hung, I., & Murray, D. T. (2023). Liquid droplet aging and seeded fibril formation of the cytotoxic granule associated RNA binding protein TIA1 low complexity domain. Journal of the American Chemical Society, 145(3), 1580-1592.

[88] Shin, Y., Berry, J., Pannucci, N., Haataja, M. P., Toettcher, J. E., & Brangwynne, C. P. (2017). Spatiotemporal control of intracellular phase transitions using light-activated otoDroplets. Cell, 168(1), 159-171.

Author's Short Biography

	**Muhammad Jehangir**: Specialized in Organic synthesis and Organic synthesis chemistry, Currently doing his Master's degree in Material and chemical engineering, at department of chemistry and Molecular engineering, Nanjing Tech University, China.
	**Kashif Kashmiri**: Specialized in health Science and Medicine, he is currently studying for his master's degree in Pharmacology at School of Pharmaceutical science under the supervision of Professor Zhao Ye at Nanjing Tech University, China.