Molecular Mechanisms Underlying Tau Pathology and Disease Progression in Alzheimer's Disease and Chronic Traumatic Encephalopathy: Deciphering Molecular Characteristics for Therapeutic Target in Tauopathies

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Abstract

Tauopathies, a division of neurodegenerative diseases defined by the deposition and aggregation of abnormal tau protein, include a diverse array of conditions that pose a relevant and withstanding concern in neurobiology and medicine. While associated tauopathies may share similar pathological features such as abnormal aggregation of tau protein, they differ in their clinical presentation, molecular mechanisms, and neuropathological patterns. Thus, highlighting the similarities and differences in the isoform variations and molecular pathology of tauopathies is crucial for advancing knowledge in the field and implying therapeutics. This review will comparatively outline the important molecular characteristics of Alzheimer's Disease (AD) Chronic Traumatic Encephalopathy (CTE) by identifying their neuropathology, dominant isoform significance, post-translational modifications, and cellular response. Thus, this review aims to provide a detailed analysis of the current knowledge surrounding tauopathies, highlight areas for future research, and emphasize the broader implications for the field of neurodegenerative disease. With enhanced comprehension of the mechanisms that underlie these diseases, diagnostic measures, potential biomarkers, treatments, and preventions may be improved through identifying unifying characteristics. Conversely, understanding the molecular differences of tauopathies may not only enhance our understanding of these diseases, but also differential treatment mechanisms specific to each tauopathy.

Introduction

I. Function of Tau in the Neuron

Tau is an essential microtubule-associated protein (MAP) predominantly expressed in nerve cells, where it plays a crucial role in promoting the assembly and stabilization of microtubules (Weingarten et al., 1975). Microtubules, abundant in neurons, form an integral part of the cell's cytoskeleton, influencing its shape and function (Lasser et al., 2018). Studies isolating tau have revealed its significance in regulating axonal and intracellular dynamics. Within the neuron, Tau protein is concentrated in axons, where it attaches to microtubules to stabilize their function. Microtubule stabilization allows for kinesis-mediated transportation of cargo in neurons, therefore influencing neurotransmission (see Figure 1). Tau protein's N-terminal and C-terminal regions interact with proteins involved in cytoskeleton control, as well as motor proteins kinesins and dyneins. Thus, tau regulates intraneuronal dynamics, allowing for variable cytoskeleton rearrangement and synaptic transmission (Bodea et al., 2016). Broadly speaking, in cases of pathology, abnormal alterations of tau lead to the development of neurodegenerative diseases known as tauopathies (Hernandez & Avila, 2007).

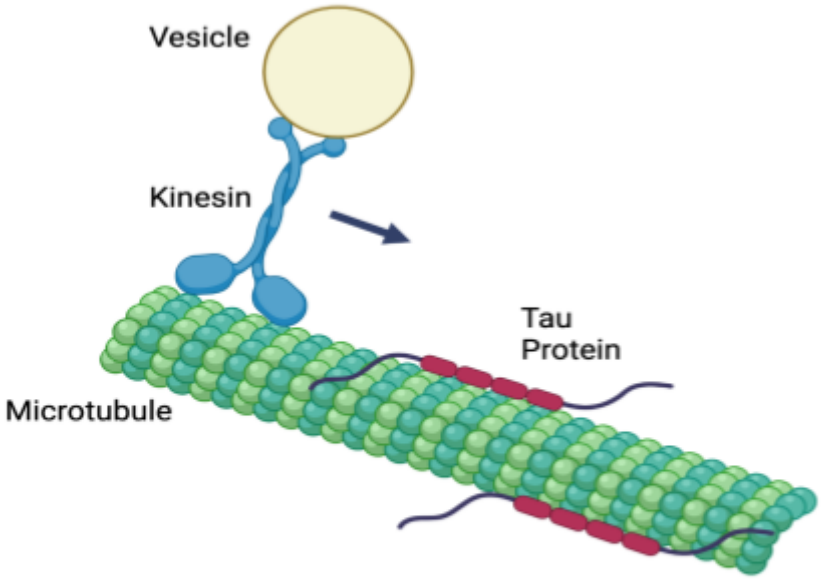

Figure 1. Schematic of Tau protein and microtubule. Tau protein is required for microtubule stabilization, which sets a precedent for the kinesis facilitated transport of cargo in neurons.

Tau is fundamental to the proper functioning of all neuronal subtypes. Notably, within the hippocampus, it is crucial for memory formation and the regulation of axonal transport and synaptic plasticity within hippocampal neurons (Wu et al., 2021). There, tau interacts with motor proteins such as kinesins to facilitate the movement of vesicles, mitochondria, and other cellular materials along microtubules, thus regulating synaptic transmission and long term potentiation (LTP) (Sinsky et al., 2021). Interestingly, studies have shown that tau dysfunction can impair LTP in hippocampal neurons, suggesting that tau is necessary for synaptic plasticity, therefore learning (Kimura et al., 2014). Also prominent in the cerebral cortex, tau has crucial function in cortical neurons. It is specifically vital in reserving the shape and physical stability of nerve cells, maintaining the organizational and connective integrity of neurons (Bodea et al., 2016). In subcortical subtypes of neurons such as the thalamus and basal ganglia, tau also modulates sensory relay processing and motor function (Bosch-Bouju et al., 2013). While tau is typically found in these particular neurons of the central nervous system (CNS), specific isoforms such as “big tau” are primarily expressed in the peripheral nervous system (PNS) (Boyne et al., 1995; Goedert et al., 1989). Little is known of the function of big tau in neuronal pathology; however, dysfunction and abnormal accumulation of tau are primarily known to cause CNS neurodegenerative disorders (Medeiros et al., 2011).

Interestingly, recent research has shown that tau may play a physiological role in dendrites and other synaptic interactions (Mietelska-Porowska et al., 2014). Aside from its axonal function, tau protein additionally occurs in pre and post synapses in a smaller concentration (Sinsky et al., 2021). In abnormal tau formation, tau protein aggregates damage tripartite synapses, disrupting the normal synaptic function (Stevenson et al., 2020). Furthermore, microglia have regular interactions with synapses, therefore released extracellular

tau could be capable of interactions with proteins present in the synaptic clefts, influencing synaptic functions (Sinsky et al., 2021). Thus, recognizing the complex interaction between tau protein and synaptic function is essential for understanding the pathophysiology of tau associated neurodegeneration and developing interventions aimed at preserving synaptic integrity.

II. Tau Gene Mutations and Isoforms

Previous studies have demonstrated that in humans, the normal functioning tau protein is encoded by the microtubule associated protein tau (MAPT) gene on chromosome 17q21 (Neve et al., 1986). This gene in particular serves as an interesting subject of inquiry due to its many alterations that may occur in both healthy and abnormal tau production associated with tauopathies, such as isoforms and mutations (Rawat et al., 2022).

One mechanism of the MAPT gene and other genes associated with tau pathology would be expressed through missense mutations (Strang, 2019). Particularly in genes encoding tau proteins or their precursors, heritable and dominant forms of respective diseases may occur through these mutations (Wolfe, 2012). Furthermore, several other proteins have also been isolated and shown association with tau its pathology.

However, the most prominent and relevant alterations to the MAPT gene are isoforms produced as a result of alternative mRNA splicing (Goedert et al., 1989). As shown in Figure 2, the human tau gene forms a primary RNA transcript, which upon further processing, produces isoforms. Alternative mRNA splicing of the MAPT gene produces six major isoforms known as 0N3R, 0N4R, 1N3R, 1N4R, 2N3R, and 2N4R (Goedert et al., 1989). In order for tau to serve its optimal function, it is necessary that these 3R and 4R isoforms are distributed in a balance essential to drive proper function within specific brain regions (Vourkou et al., 2022). Studies have shown that 4R isoforms are more prone to forming neurotoxic aggregates than 3R isoforms (Hedieh Shahpasand-Kroner, 2022).

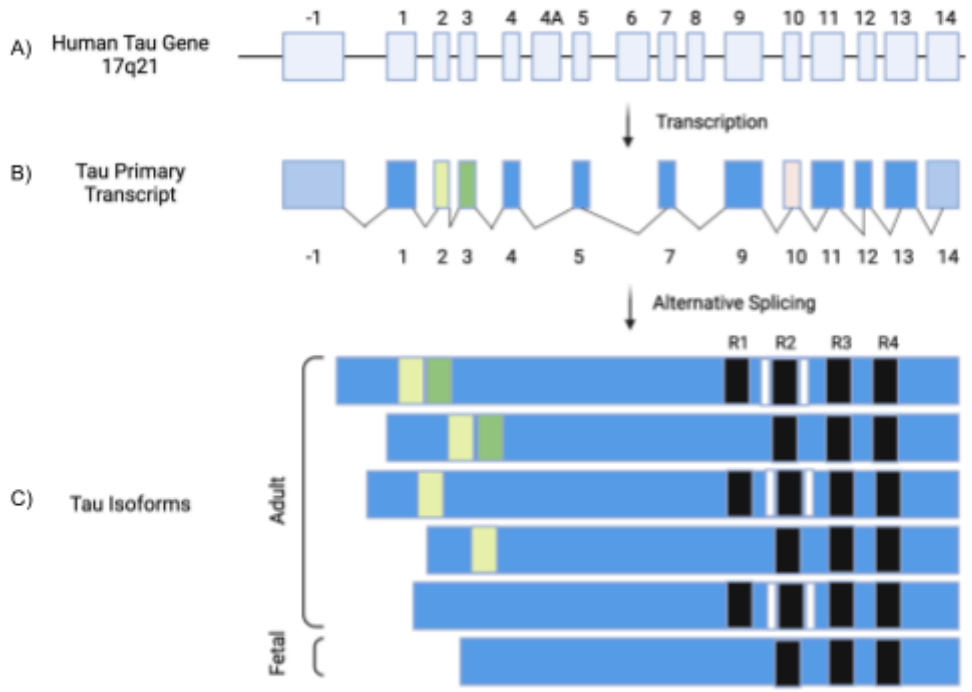

Figure 2. The human tau gene, tau primary transcript, and six tau isoforms that may result from alternative RNA splicing. A) the human tau gene spans approximately 100 kilobases and consists of 16 exons. B) In its primary transcript, all exons and introns are included. C) Following alternative splicing events, six isoforms are produced typically through the inclusion or exclusion of exons 2, 3, and 10.

Furthermore, the distribution of tau isoforms within specific brain regions may contribute to increased vulnerability to different tauopathies. In other words, certain isoforms may be more prevalent in regions affected by different tauopathies (Vourkou et al., 2022). Thus, these imbalances have been implicated in the clinical manifestations of neurodegeneration, making them a promising source to identify biomarkers and develop isoform specific interventions for associated tauopathies (Buchholz & Zempel, 2024).

III. Post-Translational Modifications

Further, another alteration to tau that is commonly associated with the specialization of the protein through post-translational modifications (PTMs) (Haj-Yahya & Lashuel, 2018). PTMs are essential to normal tau protein function, as their main purpose is to regulate and increase tau's functional diversity. This allows it to perform specialized tasks in neurons, regulating its diverse functions (VandeVrede et al., 2022). The most prominent examples of tau PTMs include phosphorylation, truncation, nitration, glycation, and glycosylation (Pevalova et al., 2006). When these modifications are disturbed, they can play a serious role in the pathogenesis of various neurodegenerative diseases (Blagov et al., 2022). The most prominent of these, and most commonly associated with common tauopathies, is phosphorylation. In normal tau, the protein is phosphorylated for many important functions. For example, it regulates microtubule binding following phosphorylation, and its affinity for microtubules decreases allowing disassembly and reorganization. These processes are necessary for axonal growth and synaptic plasticity (Jahan et al., 2023). Normal phosphorylation regulates tau's involvement in axonal transport by

affecting tau's interaction with motor proteins and microtubules, all modulating axonal transport (Stern et al., 2017). Further, tau phosphorylation is implicated in neuronal plasticity through its prominent role in signaling pathways eminent to learning and memory formation (Rawat et al, 2022).

Although phosphorylation of tau is a normal PTM, in cases of pathology, hyperphosphorylation may contribute to the onset of neurodegenerative disease (Rawat et al., 2022). There are 40 phosphorylation sites on the protein tau that are associated with disease, all with their own unique functions (Kimura, et al., 2018). Specifically, hyperphosphorylated tau loses its ability to bind and stabilize microtubules effectively, thus leading to impaired dynamics of microtubules. As a result, free tau molecules may aggregate and form neurofibrillary tangles (NFTs) (Gong & Iqbal,. 2008). When NFT aggregates accumulate in neurons, various cellular functions are disrupted. In a broad sense, hyperphosphorylated tau may accumulate in both dendrites and synaptic terminals, interfering with neurotransmission (Rajmohan & Reddy, 2018). Recent studies have also shown that this all may contribute to neuroinflammation, including activation of microglia and astrocytes, and the propagation of tau spreading in a prion-like manner (Amro et al., 2021). In a broad sense, NFTs result in physiological impairments, apoptosis, and neuronal loss reflected as cognitive impairment. While the specifics of these characteristics differ in various tauopathies, these are the mechanisms contributing to tau pathology and the onset of neurodegenerative diseases (Sinksky et al., 2021). In a broad sense, neurodegenerative disorders are characterized by damaged neurons and a loss of neuronal connectivity, thus dramatically compromising affected individuals' execution of daily tasks, often termed as dementia (Cunningham et al., 2015). Table 1 below outlines the significant characteristics of CTE and AD, respectively.

Characteristic	**CTE**	**AD**
Isoform	Tau protein (3R and 4R)	Tau protein (3R and 4R), Beta-amyloid
Brain Region	Frontotemporal lobes, amygdala, hippocampus	Hippocampus, cerebral cortex
Cause	TBI and repetitive head trauma	Unknown
Phosphorylation Sites	Ser202, Thr205, Ser396, Ser404	Ser202, Thr205, Ser396, Ser404
Symptoms	Memory loss, confusion, impaired judgment, aggression, abnormal mood changes, progressive dementia	Memory loss, confusion, communication difficulties, abnormal mood changes, progressive dementia

Table 1. Comparative table detailing characteristics of Chronic Traumatic Encephalopathy, Alzheimer's Disease, and Progressive Supranuclear Palsy. Table compares significant isoforms, affected brain regions, known causes of disease, tau phosphorylation sites, and associated symptoms.

Alzheimer's Disease (AD)

Currently, over 55 million people worldwide are living with dementia, most of these individuals having been diagnosed with AD. Further, it has been projected that by 2050, this number will continue to increase to around 152 million cases globally (Alzheimer's Disease International). This information is imperative because dementia, most frequently caused by AD, is currently the seventh leading cause of death, and a significant concern associated with aging (National Institute on Aging, 2023). Specifically, according to the Alzheimer's Association, in the United States alone, it is estimated that 6.9 million Americans currently have AD specifically (Alzheimers & Dementia, 2024). AD is defined as a progressive neurodegenerative dementia that impairs memory, thinking, and behavior, typically becoming severe enough to interfere with daily tasks (Kumar et al., 2024).

I. Clinical Presentation

The clinical aspects of dementia that are associated with AD as a neurodegenerative disease are typically categorized into three stages of dementia: mild, moderate, or severe (Kumar et al., 2024). The mild stage is associated with declined execution of functions, slight personality and behavioral alterations, altered sensory perception, and finally a loss in episodic, semantic, and implicit memories (Dickerson & Eichenbaum, 2010). The moderate stage of this progressive disorder entails neuropsychiatric loss of reading and writing skills, incorrect word substitution, aggression, irritability, delusion, and loss of long term memory. Severe stages are characterized by almost a complete loss of speech, a lack of emotion, intense fatigue, and a decline in muscle mass (Siddappaji & Gopal, 2021). Some additional characteristics of AD are psychiatric symptoms such as depression, anxiety, and hallucinations that can occur through any of these stages (Cloak et al., 2024).

II. Neuropathology

As a primary precursor to AD it is necessary to understand its associated Aβ pathology. AD is typically characterized by two major molecular alterations: extra amyloid-beta (Aβ) deposits and interneuronal filaments of the tau protein (Gulisano et al., 2021). This Aβ is formed through processing of the membrane protein known as amyloid β protein precursor (APP) (Bamford et al., 2020). Next, β-secretase is able to shed the ectodomain of APP, which leads to the cleavage of the protein precursor (Hartmann, 2013). As a result, extracellular deposits of amyloid-beta peptides form, and are typically prone to aggregation. Further, dominant missense mutations of the APP gene may contribute as early-onset cues, ultimately leading to the formation of longer, more aggregation prone forms of the protein (Itoh et al., 2022).

Further evidence supporting the significance of Aβ aggregation in AD pathogenesis comes from various studies using mouse models. In AD, Aβ plaques are distributed in different regions of the brain, correlating to the stages of the disease (Hampel et al., 2021). Through mouse models, it was noticed that initially, plaques are deposited within the neocortex, which is highly responsible for higher order brain functions such as sensory perception and cognition (De Sousa et al., 2023). As the disease progresses, plaques may be spread to the hippocampus and other parts of the brain depending on the severity of the disease (Targa Dias Anastacio et al., 2022). While these plaques can be seen in various other conditions, it is apparent that this pattern of prevalence in these particular two brain regions are specific to AD (Hampel et al., 2021).

Following the formation and aggregation of amyloid β protein and its associated plaques, tau plays a subsequent role. More specifically, the aggregation of the amyloid β protein has been observed to induce further pathological changes associated with tau such as hyperphosphorylation and its aggregation (Gulisano et al., 2018). In AD, when tau is hyperphosphorylated as a response to Aβ aggregation, intracellular aggregates may form paired helical filaments (PHF), which are also components that are unique to AD (Rawat et al., 2022). When tau detaches from microtubules it forms the tangles known as NTFs. While this is a characteristic of prominent tauopathies, in AD specifically, the patterns of NFTs are a characteristic specific to AD. Additionally, another component of AD pathology that differentiates AD from other tauopathies is that it follows a distinct pattern of NFT spread (Sinsky et al., 2021).

Specifically, this unique pattern of distribution known as Braak staging, characterizes different progressive stages of Alzheimer's disease based on the NFTs and their associated spread into the memory circuit (Nelson et al., 2009). Stages I and II are limited to transentorhinal regions of the brain, whereas stages III and IV differentiate involvement in the limbic regions such as the hippocampus. Finally, stages V and VI characterize neocortical involvement with tau NFTs. These stages are significant to AD pathology, because they are currently the most tell-tale sign of AD pathology that can be diagnosed in autopsy (Braak et al., 2006).

III. Tau Specific Characteristics of AD

In various tauopathies, a differentiating characteristic of their unique disease pathology is the distribution of specific isoforms (Cherry et al., 2021). However, in AD, all six isoforms are present in PHFs and NFTs, but the relative amount of specific isoforms and the modifications that they undergo may differ depending on the state of the disease's pathology (Kolarova et al., 2012). Specifically in AD, all isoforms of tau are hyperphosphorylated, reducing their affinity for microtubules. This also accounts for the impaired neurotransmission, memory retention, and formation (Rawat et al., 2022). Furthermore, while in some neurodegenerative diseases such as progressive supranuclear palsy, there is an observed difference between the ratios of the 3R and 4R isoforms, in AD, both isoforms aggregate to form the neurofibrillary tangles (Buchholz & Zempel, 2024).

Although the ratio of 4R and 3R isoforms are less significant to AD than other neurodegenerative diseases, it can still serve as an important marker of the disease's pathology (Holper et al., 2022). With the proper associated technology, changes in the ratios of tau isoforms or modifications occurring post-translationally to the protein tau have recently been observed to be a promising biomarker for AD and other similar diseases (Bellier et al., 2023). These observed changes in cerebrospinal fluid or blood can serve as biomarkers for AD diagnosis and tracking progression (Salvado et al., 2023). Thus, understanding the molecular mechanisms of various neurodegenerative diseases and their associated pathological characteristics is a promising development aimed towards developing targeted therapies and potentially counteracting disease progression (Zhang et al., 2022).

IV. PTMs and Cellular Response

Observing the molecular mechanisms, it is apparent that PTMs of tau isoforms are crucial to the progression and pathogenesis of AD (Guo et al., 2020). Knowing that all isoforms of tau in AD are hyperphosphorylated, it is important to recognize phosphorylation as a PTM. In AD, phosphorylation occurs at polar amino acid sites such as threonine, serine, and tyrosine residues. More specifically, the sites include Ser202, Thr205, Ser396, Ser404, and Ser422 (Kimura et al., 2014). Responsible for phosphorylation, the enzymes glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase (CDK5), and microtubule affinity-regulating kinase

(MARK) are prominent PTM regulators in AD pathogenesis. For example, GSK-3β is a major kinase that is responsible for phosphorylating tau at numerous of its associated sites (Fukiyama et al., 2023). Overactivation of this enzyme specifically is associated with abnormal tau phosphorylation. Since the activity of GSK-3β is regulated by phosphorylation, it is inhibited by phosphorylation at Ser9, yet activated at Tyr216 (Sayas & Avila, 2021). CDK5 is typically regulated by its regulatory subunit p25. When p25 accumulates, tau is abnormally phosphorylated and contributes to the hyperactivation of CDK5 (Kimura et al., 2014). Mark kinases specifically affect microtubule dynamics by phosphorylating sites that are critical for proper microtubule binding (Timm et al., 2008). However, again, the increased activity of this kinase contributes to hyperphosphorylation, and ultimately disrupts microtubule stability, therefore mechanisms of neuronal transport (Gong & Iqbal, 2009).

Aside from hyperphosphorylation, two other PTM that are often associated with AD are acetylation and glycosylation (Zhong et al., 2023). In acetylation, histone acetyltransferases (HATs) are responsible for adding an acetyl group to the lysine residue of a protein. This PTM is known to cause the loss of function of tau protein (Park et al., 2022). Furthermore, acetylated tau is more prone to aggregation in the form of paired helical filaments and NFTs (Cohen et al., 2011). Because increased levels of acetylated tau are prominently associated with neurotoxicity and cognitive deficits, interestingly, modulations of the mechanisms that both activate and inhibit acetyltransferases are being explored as a therapeutic strategy for AD (Min et al., 2016). Next, the glycosylation addition of sugar molecules to N-linked amino acid terminals affect the solubility of tau, influencing its ability to form aggregates (Alquezar et al., 2020). Therefore, the combined effects of these enzymes are critical in AD pathogenesis through promoting the aggregation of hyperphosphorylated tau isoforms, ultimately contributing to cellular and cognitive decline.

Chronic Traumatic Encephalopathy (CTE)

Chronic Traumatic Encephalopathy (CTE) is characterized as a progressive neurodegenerative disease resulting from repeated head trauma (Inserra et al., 2019). The most common groups diagnosed with CTE are athletes, most commonly American football players (Safinia et al., 2016). According to post-mortem studies of American football players' brains, researchers identified signs of CTE in 87% of the 202 subjects studied (Boston University, 2017). This finding is pertinent because CTE is associated with concussion and other brain injuries that fall under the classification of traumatic brain injury (TBI) (Graham & Sharp, 2019).

I. Clinical Presentations

The clinical presentation of CTE involves a variety of cognitive, behavioral, and motor symptoms. As specified by various medical research centers, CTE is a progressive neurodegenerative disease characterized by neuronal death, therefore these symptoms ultimately contribute to a gradual decline in cognitive, motor, and functional skills (Gandy et al., 2014). As CTE continues to worsen over time, increased neuronal death contributes to the shortened life spans of affected individuals (Lakhan & Kirchgessner et al., 2012). Individuals with CTE may experience memory impairment that is characterized by issues with short term memory impairment. However, due to the disease's progressive nature, these may progress to more severe deficits. Other cognitive symptoms may be classified as executive dysfunctions that impair problem solving and attention deficits compromising the retention of focus in affected individuals (McKee et al., 2013).

Another common presentation of CTE are mood disorders and physical symptoms. In addition to behavioral changes, affected individuals may experience depression, apathy, emotional instability, and aggression. Furthermore, behavioral changes may also be characterized as difficulties with impulsivity, irritability, and potentially socially inappropriate behavior depending on the severity of the disease's pathology (Antonius et al., 2014). Individuals may experience symptoms similar to Parkinson's disease. This consists of tremors, rigidity, and bradykinesia (slowed movements). Problems with balance, coordination leading to unsteadiness may also be prominent in CTE cases (Montenigro et al., 2015).

II. Neuropathology

In accordance with the ionic imbalance experienced as a primary response of TBI, the sudden increase of calcium ions within neurons activates various calcium dependent kinases, which catalyze the phosphorylation of various proteins (Atkins et al., 2006). The specific kinase pertinent to the onset of CTE pathology is the calcium dependent kinase known as Glycogen Synthase Kinase-3β (GSK-3β) . GSK-3β is directly responsible for catalyzing the phosphorylation specifically of the protein tau (Fukiyama et al., 2023). Researchers have concluded that the molecular modifications of the protein tau are one of the major prominent pathological characteristics of the onset of CTE (Halicki et al., 2023).

The pathology of CTE is often described through four stages, known for their progressive symptoms (Inserra & DeVrieze, 2019). Interestingly, many parallels may be drawn between the stages of AD and CTE. Stage I of CTE is characterized by mild cognitive impairment of memory and attention span in addition to slight behavioral changes. Stage II is classified through more extensive pathology in the frontal cortex (Castellani et al., 2016). The tau pathology tends to spread in a prion-like manner, spreading to the superficial layers of the cortex (Alyenbaawi et al., 2020). Stage III is characterized as widespread tau pathology throughout the entire frontal-temporal cortices. This includes the hippocampus, amygdala, and entorhinal cortex. Stage IV is defined as severe tau pathology that affects the majority of neural regions spanning to the brainstem and spinal cord. Furthermore, extensive cortical atrophy and white matter changes are evident (McKee et al., 2015). Focusing on the molecular response of TBIs, concussions contribute to a complex molecular runaway inflammatory cascade upon initial injury (Veenith et al., 2009). To simplify this cascade, the first responses that typically occur immediately following TBI are mechanical damage and cellular disruption.

III. Mechanical Damage and Cellular Disruption from TBI

Concussive hits automatically lead to axonal shearing, a process by which axons are shredded and torn. This results in the immediate compromise of the structural integrity of the neuron, therefore impairing efficient neurotransmission (Bruggeman et al., 2021). Additionally, these injuries may also immediately disrupt the cell membrane, contributing to an immediate ionic imbalance between calcium and potassium ebbing through the neuron. This imbalance also affects the ability of the neuron to generate an action potential, or in other words, the electrical conduction of a neural signal is compromised (Grider er al., 2023).

These early molecular mechanisms serve as primary responses to TBI, which then initiate an additional signaling cascade of secondary responses including the disruption of the blood-brain barrier, and the release of neurotoxic substances. In its normal function, the blood-brain barrier (BBB) is a semi-permeable vascular membrane that tightly regulates molecular movement between the blood and the brain (Chodobski et al., 2012). When this system is disrupted as a result of TBI, the permeability of the BBB increases, which consequently impairs the barrier's ability to protect the brain's central neurons. This

consequence of TBI potentially increases the possibility of neurotoxic substances entering the brain without regulation (Archie et al., 2021). Furthermore, upon injury, the primary response of an ionic imbalance triggers an unnecessary release of glutamate in the brain, which ultimately triggers apoptosis (Krishnamurthy & Laskowitz, 2016). Thus, due to disruption of the BBB, the brain is more prone to the cell death that may result from the random influx of glutamate in the brain (Boyko et al., 2023).

In accordance with the ionic imbalance experienced as a primary response of TBI, the sudden increase of calcium ions within neurons activates various calcium dependent kinases, which catalyze the phosphorylation of various proteins (Atkins et al., 2006). The specific kinase pertinent to the onset of CTE pathology is the calcium dependent kinase known as Glycogen Synthase Kinase-3β (GSK-3β). GSK-3β is directly responsible for catalyzing the phosphorylation specifically of the protein tau (Rawat et al., 2022). Researchers have concluded that the molecular modifications of the protein tau are the most prominent pathological characteristics of the onset of CTE (Cherry et al., 2021).

IV. PTMs and Isoforms

In CTE, there is an observed predominance of 4R tau isoforms. While both 4R and 3R isoforms undergo hyperphosphorylation, the predominance of 4R isoforms is a significant classification of CTE specifically (Cherry et al., 2021). The NFTs formed in CTE additionally are composed of 4R and 3R isoforms, typically found around small blood vessels and at the depths of subpial regions (McKee et al., 2015). The accumulation of these isoforms and 4R predominance is responsible for contributing to microtubule destabilization and cellular toxicity to both neurons and glial cells (Mietelska-Porowska et al., 2014).

Upon the initial translation of the protein tau, it must undergo specific post translational modifications (PTMs) (Haj-Yahya & Lashuel, 2018). One specific PTM of the protein tau is phosphorylation. When GSK-3β is activated, tau protein may be phosphorylated at many different sites all with different regulatory functions (Nadel et al., 2023). However, when GSK-3β is overactivated by the excessive amount of calcium ions absorbed as a result of TBI, tau protein may become hyperphosphorylated at multiple sites, counteracting the regulatory nature of the PTM in its normal state (Bartolome et al., 2022). Repeated TBI continues the overactivation of GSK-3β, therefore continuing the cycle of hyperphosphorylated tau being produced as a result of the PTM (Cheng et al., 2021).

Aside from the abnormal PTMs of the protein tau, another common molecular change resulting from repeated TBI is neuroinflammation. When the brain initially experiences trauma, microglia and astrocytes are released as an initial immune response (Davidson et al., 2023). When GSK-3β is activated, tau protein may be phosphorylated at many different sites all with different regulatory functions (Sayas & Avila, 2021). However, when GSK-3β is overactivated by the excessive amount of calcium ions absorbed as a result of TBI, tau protein may become hyperphosphorylated at multiple sites, counteracting the regulatory nature of the PTM in its normal state (Bartolome et al., 2022). Repeated TBI continues the overactivation of GSK-3β, therefore continuing the cycle of hyperphosphorylated tau being produced as a result of the PTM (Sayas & Avila, 2021).

When tau is hyperphosphorylated, it detaches from microtubules and forms abnormal tau aggregates known as neurofibrillary tangles (NFTs) (Gong & Iqbal, 2008). Hyperphosphorylation as a PTM negatively affects both the normal functioning of the protein tau and proper functioning of the neuron itself (Zhong et al., 2023). When tau detaches from microtubules, it is unable to maintain the structural integrity of the neuron, therefore impairing axonal transmission.

As a result, the protein tau begins to aggregate in the neuron (Robbins et al., 2021). These abnormal aggregates are also known as NFTs, which continuously impairs intracellular transport to the point of cell death. This process is only further reinforced and repeated through further TBI (Avila, 2010). This process perpetuates a neurodegenerative cycle of neuroinflammation and abnormal cellular responses.

Conclusion

Understanding the molecular mechanisms of Alzheimer's Disease and Chronic Traumatic Encephalopathy–specifically associated with abnormal tau aggregation and cellular response–holds significant promise for advancing the field of neurobiology, specifically preventative and treatment methods. Identifying the unifying molecular characteristics of these tauopathies can lead to the development of broad preventative measures, offering a proactive approach to reducing disease incidence. Simultaneously, exploring the molecular differences among these conditions allows for the observation of differential treatment strategies that can be precisely targeted to the specific pathologies involved. Furthermore, the distinct molecular features of each tauopathy can serve as reliable biomarkers, facilitating earlier and more accurate diagnoses. While research has previously been conducted following this approach, emphasis should be placed on exploring the differences between tauopathies in order to begin identifying distinct treatment methods for unique tauopathies. The dual approach of recognizing both shared and unique aspects of tauopathies underscores the potential for further comprehensive medical research and strategies.

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