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Chronic Traumatic Encephalopathy-Integration of Canonical Traumatic Brain Injury Secondary Injury Mechanisms with Tau Pathology

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Abstract

In recent years, a new neurodegenerative tauopathy labeled Chronic Traumatic Encephalopathy (CTE), has been identified that is believed to be primarily a sequela of repeated mild traumatic brain injury (TBI), often referred to as concussion, that occurs in athletes participating in contact sports (e.g. boxing, football, football, rugby, soccer, ice hockey) or in military combatants, especially after blast-induced injuries. Since the identification of CTE, and its neuropathological finding of deposits of hyperphosphorylated tau protein, mechanistic attention has been on lumping the disorder together with various other non-traumatic neurodegenerative tauopathies. Indeed, brains from suspected CTE cases that have come to autopsy have been confirmed to have deposits of hyperphosphorylated tau in locations that make its anatomical distribution distinct for other tauopathies. The fact that these individuals experienced repetitive TBI episodes during their athletic or military careers suggests that the secondary injury mechanisms that have been extensively characterized in acute TBI preclinical models, and in TBI patients, including glutamate excitotoxicity, intracellular calcium overload, mitochondrial dysfunction, free radical-induced oxidative damage and neuroinflammation, may contribute to the brain damage associated with CTE. Thus, the current review begins with an in depth analysis of what is known about the tau protein and its functions and dysfunctions followed by a discussion of the major TBI secondary injury mechanisms, and how the latter have been shown to contribute to tau pathology. The value of this review is that it might lead to improved neuroprotective strategies for either prophylactically attenuating the development of CTE or slowing its progression.

Graphical abstract

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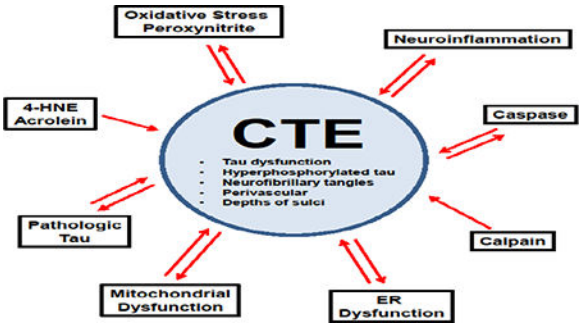

Keywords

traumatic brain injury; chronic traumatic encephalopathy; tauopathy; concussion; repetitive head injury

1. Introduction

Chronic traumatic encephalopathy (CTE) is classified as a neurodegenerative tauophathy (McKee *et al.*, 2016). In addition to CTE several other tauopathies exist including Alzheimer's disease (AD), frontotemporal dementia (FTD), progressive supra nuclear palsy (PSP), corticobasal degeneration, Pick's disease, and argyrophilic grain disease (Lee and Leugers, 2012). One defining characteristic of tauopathies is hyperphosphorylation of the protein tau. Once hyperphosphorylated, tau assumes a tightly folded confirmation, increasing susceptibility to aggregation, conformational change, filament assembly, polymerization into paired helical filaments, and bundling of paired helical filaments into neurofibrillary tangles and neuropil threads (Mietelska-Porowska *et al.*, 2014).

Clinically, CTE is characterized by cognitive, behavioral, and/or mood dysfunction, with the possible accompaniment of motor symptoms (Montenigro *et al.*, 2014). Unfortunately, the current incidence and prevalence of CTE is unknown (Kiernan *et al.*, 2015) because although CTE can be suspected clinically, a definitive diagnosis can only be made post-mortem (McKee *et al.,* 2016). Recently, a consensus meeting was held to define the neuropathological criteria of CTE, and concluded that a CTE diagnosis should be based upon identification of an irregular pattern of abnormally hyperphosphorylated tau accumulations in astrocytes and neurons located around small blood vessels and at the depths of cortical sulci (McKee *et al.,* 2016). Additional non-specific, but supportive features of CTE, include hippocampal tangles, neurofibrillary tangles in the subcortical nuclei, and TAR DNA-binding protein 43 (TDP-43) reactivity in the temporal cortex, hippocampus and amygdala (McKee *et al.,* 2016). However, in reaching the consensus, definition other neuropathologic characteristics of CTE were not addressed including gliosis, inflammation, hemosiderin deposition, and the presence of comorbid pathologies such as Aβ and α-synuclein deposition (McKee *et al.,* 2016). Although the neuropathologic criteria for CTE have now been defined, identification of CTE as a unique entity remains controversial for several reasons including reliance on retrospective case reports subject to selection bias for identification of cases (Maroon *et al.,* 2015), as well a lack of prospective and epidemiologic studies (McCrory *et al.,* 2013). Indeed, the clinical diagnostic criteria of CTE vs. other

neurodegenerative disorders (e.g. AD) for which the history of one or more traumatic brain injuries is an established risk factor is still being intensely debated.

Nevertheless, to date, CTE pathology has only been identified in individuals with a history of traumatic brain injury (TBI) (McKee *et al.,* 2016). CTE pathology has been observed in the brains of military personnel who have sustained blast injuries, and in athletes who participate in sports where the risk of sustaining repetitive head injuries is high including boxing, football, soccer, hockey and rugby (Goldstein *et al.,* 2012; Kiernan *et al.,* 2015; McKee *et al.,* 2009; McKee and Robinson, 2014; McKee *et al.,* 2013; Omalu *et al.,* 2011b; Omalu *et al.,* 2006; Omalu *et al.,* 2005). Although there are several tauopathies, the pathoanatomic location of tau deposition in CTE makes it distinct from the others (Kiernan *et al.,* 2015; McKee *et al.,* 2016). However, the neuronal tau found in CTE does share a similar profile in regard to isoform ratio and phosphorylation state as the tau in AD (Kiernan *et al.,* 2015; McKee *et al.,* 2014; Schmidt *et al.*, 2001). CTE and AD share other similarities; brain injury also increases the risk of developing AD (Guo *et al.,* 2000; Nemetz *et al.,* 1999; Plassman *et al.,* 2000). In fact both pathologic tau (Ikonomovic *et al.,* 2004; Johnson *et al.,* 2012; Uryu *et al.,* 2007) and Aβ deposition (Johnson *et al.,* 2012; Reynolds *et al.,* 2005; Reynolds *et al.,* 2006) are seen following a single severe TBI.

Although advancements have been made in defining the core neuropathological features of CTE, much about CTE is still unknown. Similar to brain injury itself, CTE is heterogeneous both in its supporting neuropathological features (McKee *et al.,* 2016) and in its clinical presentation. Clinically, CTE is suspected of having at least two subtypes, a younger onset subtype predominated by behavior and mood symptoms but with minimal cognitive or motor impairment, and an older onset subtype characterized by cognitive impairment and motor dysfunction (Stern *et al.,* 2013). However, up to four clinical subtypes have been proposed (Montenigro *et al.*, 2014).

The pathophysiologic processes which lead to the development of CTE, the main characteristic of which is pathologic tau deposition, are not well understood. Although repetitive TBI has been singled out as a major etiologic factor in CTE and brain injury is considered necessary for its development (McKee *et al.,* 2016), individuals who have experienced repetitive TBI do not always go on to develop CTE (Hazrati *et al.,* 2013; McKee *et al.,* 2013; Omalu *et al.,* 2011a). Additional factors hypothesized to contribute to CTE include environment, genetics and injury characteristics, e.g. age at injury, type and severity of injury, number of hits, duration between injuries, etc. (Ojo *et al.,* 2016) Although animal models are being utilized to further characterize CTE and repetitive TBI, many have failed to recapitulate the tau pathology seen in CTE or have required the use of transgenic mice already predisposed to develop tau pathology (Ojo *et al.,* 2016). Therefore, there is much still to be elucidated regarding the progression of CTE following injury. However, despite the paucity of information regarding how CTE tau pathology progresses over time, the tau protein itself and processes that contribute to its dysfunction have been well characterized in the literature, thanks in large part to AD, FTD and TBI models in which tauopathy is a.commonly occurring pathology.

In this review, which focuses on CTE, we attempt to integrate what is known about canonical post-traumatic neurodegenerative processes and the tau protein in order to identify mechanisms which could possibly lead to, or contribute to, chronic tau dysfunction following TBI that might serve as pharmacological neuroprotective targets. We have chosen to direct our attention to CTE because, by definition it is associated with the previous occurrence of repetitive, and possibly singular TBI even though, a history of TBI is known to be a risk factor for other neurodegenerative disorders that are involve the same secondary post-TBI degenerative mechanisms. Thus, throughout the rest of this review, we consistently mention what is known about the interaction of post-TBI secondary injury processes such as mitochondrial dysfunction oxidative stress, intracellular calcium overload, etc., with the pathogenesis of other neurodegenerative disorders as AD, that involve tauopathies that appear to be somewhat pathologically distinct from CTE. While this review is mainly directed at CTE, our literature review has revealed a rich interaction between acute post-TBI secondary injury mechanisms and tauopathy development in general.

2. The Tau Protein – Functions and Dysfunctions

2.1 Functions

There are several detailed reviews that cover structure, function, and post-translational modification of the tau protein (Fontaine *et al.*, 2015; Lee and Leugers, 2012; Morris *et al.*, 2011). Tau is encoded for by the MAPT gene found on chromosome 17, a gene that is mutated in several tauopathies including FTD (Ferrari *et al.*, 2011) and PSP (Im *et al.*, 2015). In humans, alternative splicing generates six isoforms of tau containing either three (3R) or four (4R) microtubule binding repeats (Goedert and Jakes, 1990), leading to formation of isoforms with differing characteristics (Lee and Leugers, 2012). Additional heterogeneity exists in the n-terminal region as well (Goedert and Jakes, 1990). As stated previously, the neuronal tau of CTE has a similar isoform ratio and phosphorylation state as the tau of AD (Kiernan *et al.*, 2015; McKee *et al.*, 2014; Schmidt *et al.*, 2001). AD is reported to have a 2:1 ratio of 4R:3R tau (Chen *et al.*, 2010b; Conrad *et al.*, 2007; Ginsberg *et al.*, 2006), a shift from the equal 4R:3R ratio found in healthy adult brains (Goedert and Jakes, 1990; Kosik *et al.*, 1989).

The most well-known function of tau is its ability to bind microtubules, which promotes microtubule assembly and stabilization (Fontaine *et al.*, 2015; Lee and Leugers, 2012; Morris *et al.*, 2011). However, tau has several other functions, including axonal transport (Cuchillo-Ibanez *et al.*, 2008; Lee and Leugers, 2012; Morris *et al.*, 2011), regulation of actin and neurite outgrowth (Lee and Leugers, 2012; Morris *et al.*, 2011), and regulation of signaling pathways (Morris *et al.*, 2011). Tau can associate with heat shock proteins, chaperone proteins involved in the tau degradation pathway (Fontaine *et al.*, 2015; Lee and Leugers, 2012), and although tau is primarily found associated with the cytoskeleton of axons, it can also localize to the nucleus, as well as interact with the plasma membrane and post-synaptic density (Fontaine *et al.*, 2015; Lee and Leugers, 2012; Morris *et al.*, 2011).

The binding of tau to microtubules can be regulated by the tau phosphorylation state, and phosphorylation of tau within the microtubule binding sites decreases the ability of tau to bind microtubules (Fontaine *et al.*, 2015). Similarly, several of the tau mutations utilized in

transgenic tau mice, such as P301L and P301S, function to decrease binding of tau to microtubules and can lead to decreases in microtubule assembly (Fontaine *et al.*, 2015; Hasegawa *et al.*, 1998; Iovino *et al.*, 2014). Several protein kinases and phosphatases regulate tau phosphorylation, and thus its ability to interact with microtubules (Fontaine *et al.*, 2015; Martin *et al.*, 2013; Morris *et al.*, 2011).

2.2 Dysfunctions

One characteristic feature of tauopathies, such as CTE and AD, is tau hyperphosphorylation, where phosphorylation of tau at specific residues occurs as an ordered process, leading to tau aggregation (Alonso *et al.*, 2001; Fontaine *et al.*, 2015; Jeganathan *et al.*, 2008; Morris *et al.*, 2011) and oligomer formation (Tepper *et al.*, 2014). In addition to tauopathies, TBI is also capable of inducing tau hyperphosphorylation (Ikonomovic *et al.*, 2004; Uryu *et al.*, 2007; Yang *et al.*, 2016).

In addition to phosphorylation other post-translational modifications to tau occur such as acetylation, glycosylation, sumolyation, ubiquitination, polyamination, oxidation, nitration, isomerization and truncation (Fontaine *et al.*, 2015; Morris *et al.*, 2011). Many of these post-translational modifications have been implicated in the formation of pathologic tau. For example, oxidation of tau induces cross-linkages and aggregation (Reynolds *et al.*, 2005) and nitration of tau decreases microtubule binding and assembly (Reynolds *et al.*, 2005). Isomerization of pThr231 tau to the cis isoform attenuates tau dephosphorylation, decreases microtubule binding, and promotes aggregation (Wang and Zhang, 2015), and proteolytic cleavage of tau by calpain or caspase (Liu *et al.*, 2011) can result in formation of truncated tau species which are prone to aggregation (Fontaine *et al.*, 2015).

The mechanisms regarding tau toxicity in neurodegenerative disease remain controversial (Morris *et al.*, 2011), with both loss of function and gain of function theories being proposed (Trojanowski and Lee, 2005). However, although hyperphosphorylated tau results in decreased binding of tau to microtubules, several studies indicate that knock-down of tau results in normal behavioral phenotypes, synaptic transmission and microtubule stability, without compensatory increases in other microtubule-binding proteins, such as MAP1 or MAP2, suggesting that tau toxicity may not be a direct result of loss of function (Morris *et al.*, 2011). Rather, the toxicity associated with pathologic tau may in part be due to tau mislocalization and/or dysfunctional axonal transport. The majority of tau is localized to axons (Morris *et al.*, 2011); however, tau hyperphosphorylation results in redistribution of tau from the axon to the somatodendritic compartment, an effect which is sufficient to impair synaptic function (Hoover *et al.*, 2010), and several studies have shown that pathologic tau isoforms impair fast axonal transport (Lee and Leugers, 2012).

Evidence has also accumulated suggesting that tau oligomers, i.e. pre-filamentous tau aggregates, are more toxic than filamentous or monomeric tau (Spires-Jones *et al.*, 2011). For example, injection of human tau oligomers into mouse brains results in impaired memory consolidation, as well as synaptic and mitochondrial dysfunction, whereas administration of tau monomers or fibrils does not (Lasagna-Reeves *et al.*, 2011), while repression of human tau in transgenic mice results in attenuation of neuronal loss and cognitive impairment despite continued increases in neurofibrillary tangle formation

(Santacruz *et al.*, 2005). Similarly, in a drosophila model of tauopathy, neurodegeneration can still be seen in the absence of neurofibrillary tangle formation (Wittmann *et al.*, 2001). Interestingly, It has been hypothesized that one reason oligomeric tau is able to accumulate in tauopathies is due to the fact that both oligomeric tau and cleaved forms of tau, which have an increased propensity for aggregation compared to full-length tau, are preferentially degraded via autophagy (Chesser *et al.*, 2013), a pathway reported to be defective in tauopathies (Piras *et al.*, 2016) and TBI (Sarkar *et al.*, 2014). Although proteasome dysfunction, the mechanism which preferentially degrades monomeric tau, has also been reported to occur following TBI due to mechanisms such as oxidative stress (Bader and Grune, 2006; Weih *et al.*, 2001; Yao *et al.*, 2008), monomeric full-length tau has a decreased propensity to aggregate compared to cleaved tau (Chesser *et al.*, 2013) and is less toxic than oligomeric tau (Spires-Jones *et al.*, 2011).

Tau is considered to have prion-like properties (Alonso *et al.*, 2016; Medina and Avila, 2014), which likely contribute to intracellular, intraregional, and trans-synaptic spread of pathologic tau (Liu *et al.*, 2012; Medina and Avila, 2014). Tau can be secreted from neurons in its naked form or within exosomes or membrane vesicles (Chai *et al.*, 2012; Medina and Avila, 2014; Saman *et al.*, 2012; Simon *et al.*, 2012). In healthy neurons the release of tau is induced by neuronal activity, however, neuronal activity is altered following TBI (Carron *et al.*, 2016) and in tauopathy brains (Pooler *et al.*, 2013), likely resulting in abnormal tau release (Pooler *et al.*, 2013). Additionally, both c-terminal proteolytic cleavage of tau and tau overexpression are capable of enhancing tau secretion (Medina and Avila, 2014; Plouffe *et al.*, 2012; Simon *et al.*, 2012). *In-vitro,* extracellular tau is known to be toxic (Gomez-Ramos *et al.*, 2006; Medina and Avila, 2014), through a mechanism which may involve increases in intracellular calcium levels via tau stimulation of muscarinic receptors (Gomez-Ramos *et al.*, 2008), and in further support of the toxic oligomeric theory, only extracellular tau aggregates, not tau monomers, are taken up by cells (Alonso *et al.*, 2016; Frost *et al.*, 2009; Wu *et al.*, 2013). Once tau is secreted, the extracellular tau has the ability to enhance tau pathology. For example, transplanting TBI induced tau oligomers into naive brains of hTau transgenic mice results in oligomeric spread of tau and accelerated cognitive impairment (Gerson *et al.*, 2016), secreted tau fibrils are capable of inducing transcellular misfolding and tau aggregation (Kfoury *et al.*, 2012), and hyperphosphorylated tau is capable of forming filaments and tangles with non-phosphorylated tau (Alonso *et al.*, 1996). Therefore, it is possible that in non-familial tauopathies, such as CTE, an initial event, such as repetitive TBI, triggers a misfolding cascade which can then be transmitted in a prion-like manner (Morales *et al.*, 2015).

3. Traumatic Brain Injury - Pathophysiological Mechanisms

Although the specific mechanisms by which repetitive TBI can lead to CTE or by which a single severe TBI can lead to AD are still being elucidated, much of the pathology that occurs in tauopathies is paralleled in TBI. TBIs range from mild to severe, with at least 2.5 million TBIs occurring in the United States annually (Faul M, 2010), the majority of which are classified as mild (Holm *et al.*, 2005). However, these numbers are underestimates because mild TBIs often go unreported, especially in sports and military communities (Jordan, 2013; Marion *et al.*, 2011), populations which are at additional risk for sustaining

repeat injuries. In fact, it is estimated that sports-related TBIs alone occur at a rate of 3.8 million annually (Langlois *et al.*, 2006).

3.1 Primary Injury Mechanisms

TBI consists of a primary injury followed by a secondary injury cascade. The primary injury occurs immediately and is caused by external forces, such as a direct impact, rapid acceleration/deceleration, or blast a wave. Primary injury can result in contusion, hemorrhage, ischemia, shearing and straining of axons and blood vessels, and diffuse axonal injury from the mechanical insult (Maas *et al.*, 2008; McAllister, 2011; Weber, 2012). Of important relevance to CTE, which consists of tau pathology located at the depths of cortical sulci and around blood vessels, are deceleration/acceleration and blast forces (McKee *et al.*, 2016). Deceleration/acceleration forces are particularly damaging to long white matter tracts and the grey-white matter junctions of the cerebral cortex (McAllister, 2011), and blast injury has been reported to damage perivascular neural tissue due to transmission of pressure waves throughout the cerebral vasculature (McAllister, 2011).

3.2 Secondary Injury Mechanisms

Cellular strain and deformation caused by the primary injury results in membrane depolarization, mechanoporation of membranes, ionic imbalances, and neurotransmitter release, resulting in initiation of the secondary injury cascade, a process which occurs hours to weeks following injury (Maas *et al.*, 2008; McAllister, 2011), and is heavily influenced by alterations in calcium homeostasis (Weber, 2012).

3.2.1 Intracellular Calcium Overload, Oxidative Damage and Mitochondrial Dysfunction—Activation of calcium channels by high levels of extracellular glutamate following injury, along with activation of voltage-gated calcium channels and membrane leakage lead to large increases in intracellular calcium (Weber, 2012). As essential regulators or calcium homeostasis (Rizzuto *et al.*, 2000; Rizzuto *et al.*, 1999) mitochondria buffer the increases in intracellular calcium following TBI (Lifshitz *et al.*, 2003; Xiong *et al.*, 1997). Increases in mitochondrial calcium lead to decreased respiration and increased generation of reactive oxygen and nitrogen species (ROS/RNS) (Fiskum, 2000; Sullivan *et al.*, 2005). Following TBI, as the electron transport chain becomes impaired, single electrons leak from complex I, generating superoxide radicals ($O_2^{\bullet -}$), which rapidly react the nitric oxide ($NO^{\bullet}$) generated by calcium activated mitochondrial nitric oxide synthase (mtNOS), forming peroxynitrite (PN) anion ($ONOO^-$) (Bringold *et al.*, 2000; Radi *et al.*, 2002). Protonation of $ONOO^-$ results in peroxynitrious acid (ONOOH) which decomposes into nitrogen dioxide ($NO^{\bullet}_2$) and hydroxyl (OH•) radicals. Alternatively, $ONOO^-$ can react with carbon dioxide to form nitrosoperoxocarbonate ($ONOOCO_2^-$) which decomposes into the radicals $NO^{\bullet}_2$ and ($CO^{\bullet -}_3$) (Bains and Hall, 2012; Hall *et al.*, 2010). PN is demonstratively increased following TBI (Deng *et al.*, 2007; Hall *et al.*, 2004; Hall *et al.*, 2012; Singh *et al.*, 2007) and because of its unique diffusion radius, mitochondrial derived PN is capable of damaging multiple cellular structures (Hall *et al.*, 2010).

The highly reactive PN-derived radicals, $NO^{\bullet}_2$, OH•, $CO^{\bullet -}_3$, initiate lipid peroxidation (LP) of polyunsaturated fatty acids, such as arachidonic acid, which are highly enriched in

neurons and cellular and organelle membranes, forming lipid peroxyl radicals (Bains and Hall, 2012; Hall *et al.*, 2010). LP propagates throughout the membrane as lipid peroxyl radicals react with adjacent polyunsaturated acids, and although lipid peroxidation is considered to be a self-propagating process, it is also catalyzed by the presence of iron, particularly in the acidic tissues of TBI (Hall *et al.*, 2010). Following TBI, decreases in pH cause iron to be released from the iron storage proteins, ferritin and transferritin, and additional iron is released from the hemoglobin deposited during hemorrhages and microbleeds (Hall *et al.*, 2010). Therefore, similar to tau deposition in CTE, iron-catalyzed LP may be enhanced near the vasculature following TBI. LP terminates with formation of neurotoxic aldehydes, such as 4-hydroxynonenal (4-HNE) and 2-propenal (acrolein). Both LP and its derivatives, 4-HNE and acrolein, are well known to be increased following TBI (Bayir *et al.*, 2007; Hall *et al.*, 2004; Mustafa *et al.*, 2010; Mustafa *et al.*, 2011; Singh *et al.*, 2013) (Cebak *et al.*, 2016; Hill *et al.*, Submitted).

The neurotoxic aldehydes, 4-HNE and acrolein, covalently bind proteins via the amino acids lysine, histidine, or cysteine, resulting in enzyme inhibition and protein dysfunction (Hall *et al.*, 2010; Petersen and Doorn, 2004; Stevens and Maier, 2008). In addition to protein dysfunction, neurotoxic aldehydes, ROS/RNS and lipid peroxyl radicals are capable of inducing DNA damage to both nuclear and mitochondrial DNA (Dalleau *et al.*, 2013; Hall *et al.*, 2010). As a major site of PN formation, mitochondria are particularly susceptible to attack by LP-derived neurotoxic aldehydes. Binding of 4-HNE and acrolein to mitochondria results in extensive mitochondrial dysfunction through impairment of mitochondrial respiration and enhanced generation of ROS/RNS (Singh *et al.*, 2013; Vaishnav *et al.*, 2010) (Cebak *et al.*, 2016; Hill *et al.*, Submitted; Miller *et al.*, 2013; Picklo *et al.*, 1999; Picklo and Montine, 2001). Following TBI, the mitochondrial dysfunction induced by LP-derived neurotoxic aldehydes and increased intra-mitochondrial calcium concentrations leads to formation of the mitochondrial permeability transition pore (mPTP) (Bringold *et al.*, 2000; Hansson *et al.*, 2008; Sullivan *et al.*, 2005). Opening of the mPTP results in collapse of the mitochondrial membrane potential, loss of ATP production, mitochondrial swelling, rupture of the outer mitochondrial membrane and release of calcium and cytochrome c into the cytosol (Galluzzi *et al.*, 2009; Sullivan *et al.*, 2005).

3.2.2 Calcium-Mediated Proteolytic Degradation—Extrusion of calcium back into the cytosol leads to neurodegeneration, necrosis, and activation of the calcium-dependent cysteine protease, calpain, which is capable of breaking down a variety of cytoskeletal proteins including MAP2, spectrin and tau (Galluzzi *et al.,* 2009; Kampfl *et al.,* 1997; Sullivan *et al.,* 2005; Wang, 2000). In fact, calpain-cleaved αII-spectrin breakdown products are frequently used to assess post-TBI axonal damage and neuroprotection following TBI (Bains *et al.,* 2013; Deng-Bryant *et al.,* 2008; Deng *et al.,* 2007; Mbye *et al.,* 2009; Miller *et al.,* 2014; Mustafa *et al.,* 2011; Saatman *et al.,* 1996). Similarly, mitochondrial release of cytochrome c leads to activation of the protease caspase-3 and induction of apoptosis (Galluzzi *et al.,* 2009; Sullivan *et al.,* 2005; Wang, 2000).

One effect of cytoskeletal degradation following TBI is impairment of axonal transport. Following injury, axonal transport of amyloid precursor protein (APP), the precursor to Aβ, a pathologic protein found in the tauopathy, AD, and some cases of CTE, is impaired and

results in accumulations of APP in axonal varicosities and bulbs of damaged neurons; as such, the accumulation of APP following TBI is often used as a marker for traumatic axonal injury (Chauhan, 2014). In addition to cytoskeletal degradation, protein accumulation following TBI can also occur due to proteasomal dysfunction (Yao *et al.,* 2008). In particular, the proteasome is responsible for the degradation of oxidatively damaged proteins, however, it is also subject to oxidative stress-induced impairment itself (Bader and Grune, 2006; Weih *et al.,* 2001; Yao *et al.,* 2008). In addition to protein accumulation following injury, impairment of axonal transport also leads to somatodendritic accumulation of organelles, such as the mitochondria (Kilinc *et al.,* 2008), although, impairment of mitochondrial dynamics following TBI is complex and includes additional processes such as alterations in fission and fusion (Fischer *et al.,* 2016).

Following injury, the endoplasmic reticulum (ER) also functions to regulate calcium homeostasis (Weber, 2012). Increases in ER stress are reported to occur in both single (Begum *et al.,* 2014; Krajewska *et al.,* 2011; Larner *et al.,* 2004; Logsdon *et al.,* 2014) and repetitive TBI (Lucke-Wold *et al.*, 2016). In fact, calcium release from the ER has been hypothesized to be toxic to neurons and white matter tracts (Weber, 2012). In addition to regulation of intracellular calcium stores, the ER is involved in protein folding and quality control of misfolded proteins and protein aggregates through a process termed, the unfolded protein response (UPR) (Hoozemans and Scheper, 2012). Therefore, in addition to calcium-induced pathology, ER stress can also lead to several additional aspects of cellular dysfunction, including inhibition of protein synthesis (Doutheil *et al.*, 1997), apoptosis (Nakagawa *et al.*, 2000), accumulation of protein aggregates (Hoozemans and Scheper, 2012), and activation of the tau kinase, GSK-3β (Song *et al.*, 2002).

3.2.3 Neuroinflammation—Another important contributory factor to the pathology that occurs following TBI is inflammation. Inflammation has been observed acutely following TBI in both severe and mild injury, an effect which is amplified in mild TBI by repeated injury (Collins-Praino and Corrigan, 2016). Following injury, resident immune cells, such as astrocytes and microglia, are activated by damaged tissue and cellular debris (Collins-Praino and Corrigan, 2016; Karve *et al.*, 2016), but can also be activated by other mechanisms such as ROS/RNS (Collins-Praino and Corrigan, 2016). Additionally, peripheral immune cells are recruited to the site of injury (Collins-Praino and Corrigan, 2016; Karve *et al.*, 2016). Immune cells are capable of releasing both pro-inflammatory and pro-survival cytokines and chemokines; therefore, they are capable of serving both destructive and reparative roles following injury (Collins-Praino and Corrigan, 2016; Karve *et al.*, 2016). For example, the microglial phenotype M1 is neurotoxic, while the microglial phenotype M2 is neuroprotective (Karve *et al.*, 2016). Chronic microglial activation has been observed following both human and experimental TBI and has been linked to chronic neurodegeneration (Faden and Loane, 2015). In fact, the neurotoxic M1 phenotype has been shown to persist longer than the M2 phenotype following TBI (Collins-Praino and Corrigan, 2016; Kumar *et al.*, 2016; Wang *et al.*, 2013a) Furthermore, some studies have demonstrated that persistent neuroinflammation can occur decades following severe TBI or repetitive concussion (Collins-Praino and Corrigan, 2016; Coughlin *et al.*, 2015; Ramlackhansingh *et al.*, 2011). Physiologically, one explanation for the persistence of neuroinflammation

following repetitive TBI focuses on microglial priming. Microglial priming is a process in which microglia develop exaggerated immune responses and decreased activation thresholds following an insult such as TBI; therefore, neuroinflammation can be chronically exacerbated upon additional TBIs or systemic inflammation (Collins-Praino and Corrigan, 2016).

3.2.4 Tau Phosphorylation—In direct relation to CTE, TBI also results in increased levels of total and phosphorylated tau. In human TBI, injury severity is correlated with increased tau phosphorylation, increased activity of the tau kinase GSK-3β, and decreased activity of the tau phosphatase, PP2A, (Yang *et al.*, 2016). Tau pathology has been reported following cases of single severe TBI (Ikonomovic *et al.*, 2004; Johnson *et al.*, 2012; Uryu *et al.*, 2007), in patients whom have died within six months of sustaining a concussion (McKee *et al.*, 2014), and in young military veterans with a history of blast exposure (McKee and Robinson, 2014). Therefore, there is not only increasing interest in investigating the development of CTE-like tau pathology in animal models of single and repetitive TBI, but also in the development of tau as a biomarker for TBI *(Section 5. Tau – A Biomarker for TBI)*. Figure 1 hypothesizes the possible contribution of single, or perhaps multiple, pathophysiological mechanisms to the development of CTE.

4. The Role of Tau in Cellular Dysfunction

The process in which acute TBI pathology develops into the chronic tau pathology seen in the tauopathies CTE and AD remains to be established, however, the mechanisms that can initiate formation of pathologic tau as well as the mechanisms by which tau can induce cellular dysfunction parallel many of the secondary injury mechanisms of TBI, including damage by ROS/RNS and LP-derived neurotoxic aldehydes, mitochondrial dysfunction, ER stress, calpain and caspase activation, and inflammation.

4.1 Oxidative Stress

Oxidative stress is elevated in several tauopathies (Alavi Naini and Soussi-Yanicostas, 2015; Castellani *et al.,* 1995; Litvan, 2004; Martinez *et al.,* 2008a). It is well known that in the tauopathy AD, Aβ is capable of inducing oxidative stress, a process which is hypothesized to be upstream of the formation of pathologic tau (Giraldo *et al.*, 2014). Several studies confirm both the ability of oxidative stress to induce tau pathology and the ability of pathologic tau to induce oxidative stress, suggesting the possibility that in tauopathies such as CTE a self-propagating cycle of pathologic tau formation and oxidative stress occurs and leads to cellular dysfunction and neurodegeneration.

In-vitro, oxidative stress can induce both increases in tau aggregation and phosphorylation. Exposing tau isolated from bovine brain to iron-catalyzed oxidation results in dimerization, polymerization and formation of tau filaments (Troncoso *et al.,* 1993), and in primary rat cortical neurons, oxidative stress (Fe^{2+}/H_2O_2) increases tau phosphorylation by increasing activity of the tau kinase, GSK-3β, an effect which is attenuated by the GSK-3β inhibitor, lithium (Lovell *et al.,* 2004). Interestingly, lithium also has the ability to attenuate tau pathology *in-vivo* by decreasing GSK-3β dependent tau phosphorylation and aggregation in transgenic tau mice (Perez *et al.,* 2003). Additional *in-vitro* studies indicate that tau

phosphorylation is also induced by chronic oxidative stress. Inhibiting glutathione synthase in neuroblastoma cells induces a mild, chronic oxidative stress, which increases the activity of the tau kinase, JNK, decreases the activity of the tau phosphatase, PP2A, and results in increases in tau phosphorylation and tau aggregation (Su *et al.*, 2010). Although these studies indicate oxidative stress has the ability to induce tau phosphorylation *in-vitro*, oxidative stress induced tau dephosphorylation has also been reported (Davis *et al.*, 1997; Galas *et al.*, 2006; Olivieri *et al.*, 2001; Zambrano *et al.*, 2004). However, dephosphorylation of tau following oxidative stress exposure seems to be limited to acute administration of H_2O_2.

In-vivo experiments also link tau phosphorylation to oxidative stress exposure. Transgenic mice deficient for the mitochondrial antioxidant enzyme, SOD2, have increases in mitochondrial-induced oxidative stress, which result in increased tau phosphorylation, an effect which is attenuated by antioxidant administration (Melov *et al.*, 2007). Additionally, transgenic mice overexpressing the mutated form of human tau, P301S, show markers of oxidative stress such as, increased mitochondrial protein carbonyls and decreased SOD2, months prior to the appearance of tau hyperphosphorylation and tangle formation (Dumont *et al.*, 2011).

While oxidative stress has a demonstrated ability to induce tau pathology, several studies show that tau itself has the ability to induce oxidative stress. *In-vitro,* overexpressing tau impairs trafficking of peroxisomes, organelles responsible for H_2O_2 detoxification and results in increased susceptibility to H_2O_2-induced oxidative stress (Alavi Naini and Soussi-Yanicostas, 2015; Stamer *et al.*, 2002). Tauopathy animal models also suggest the ability of tau to induce oxidative stress. Cultured neurons obtained from transgenic rats expressing a truncated form of human tau analogous to that found in AD have increased levels of ROS and are more susceptible to oxidative stress, effects which are likely the result of decreased numbers of mitochondria and abnormal mitochondrial distribution (Alavi Naini and Soussi-Yanicostas, 2015; Cente *et al.*, 2006). Furthermore, transgenic mice overexpressing mutant human tau, P301L, also show increased generation of ROS, another consequence of mitochondrial dysfunction (Alavi Naini and Soussi-Yanicostas, 2015; David *et al.*, 2005).

In summary, oxidative stress is well-established to occur in neurodegenerative tauopathies, and there are several mechanisms by which oxidative stress can induce tau phosphorylation and aggregation and by which pathologic tau can induce oxidative stress (Figure 2). Therefore, a primary event capable of inducing either oxidative stress or tau dysfunction, such as TBI, could set off a chronic and self-propagating cyclical cascade of oxidative stress and pathologic tau formation.

4.2 Peroxynitrite

Oxidative stress is often used as a broad term which encompasses a multitude of reactive species, one specific reactive species being PN. The PN derived radical, $NO•_2$, is capable of nitrating tyrosine at the 3 position, thus forming 3-NT, a specific marker of PN-induced cellular damage (Hall *et al.*, 2010). 3-NT modified tau has been identified in a variety of tauopathies, including AD, frontotemporal dementia, and Pick's disease (Horiguchi *et al.*, 2003; Smith *et al.*, 1997).

Peroxynitrite is capable of inducing tau dysfunction through both oxidation and nitration mechanisms (Reynolds *et al.*, 2005; Reynolds *et al.*, 2006). *In-vitro,* cysteine oxidation of tau by PN results in formation of disulfide crosslinks, tau oligomerization, and decreased microtubule assembly (Landino *et al.*, 2004). PN can also promote tau oligomerization through addition of tyrosyl radicals which results in formation of 3,3′-dityrosine irreversible crosslinks and stabilization of insoluble tau filament aggregates characteristic of late stage paired helical filaments (PHF) (Reynolds *et al.*, 2005; Reynolds *et al.*, 2006). Furthermore, although PN-derived $NO•_2$ nitration of tau has been shown to inhibit tau polymerization (Reynolds *et al.*, 2005), 3-NT modification of tau does result in disrupted binding of tau to microtubules and inhibition of tubulin assembly (Reynolds *et al.,* 2006; Zhang *et al.,* 2005).

Peroxynitrite has also been shown to modify tau *in-vivo.* Injection of the PN donor, SIN-1, into rat hippocampus results in both nitration and hyperphosphorylation of tau, and increased activation of the tau kinases, GSK-3β and p38 MAPK, processes are attenuated by pre-administration of the PN scavenger, uric acid (Zhang *et al.,* 2006). SIN-1 administration increased levels of nitrated p85, a regulator of GSK-3β, suggesting that PN is capable of inducing tau hyperphosphorylation by nitration of upstream proteins in tau phosphorylation cascade (Zhang *et al.,* 2006). Furthermore, SIN-1 also led to a decrease in proteasome activity, which combined with the fact that the nitrated form of tau is less susceptible to proteasomal degradation, resulted in an increase in tau aggregation (Zhang *et al.,* 2006).

In summary, there are several mechanisms by which the reactive species, PN, can induce tau pathology, including oxidation, nitration, and induction of tau hyperphosphorylation, processes which lead to accumulation of toxic tau aggregates and/or destabilization of microtubules. PN is generated following TBI; therefore it is possible that the PN formed acutely following TBI initiates tau dysfunction, while other mechanisms of PN generation, such as continued mitochondrial dysfunction, contribute to chronic PN-induced tau dysfunction as suggested in Figure 3.

4.3 Lipid Peroxidation-Derived Neurotoxic Aldehydes

Lipid peroxidation-derived aldehydes have been found to be elevated in the brains of several tauopathies (Butterfield *et al.,* 2010; Lovell *et al.,* 2001; Markesbery and Lovell, 1998; Martinez *et al.,* 2008a; Martinez *et al.,* 2008b; Montine *et al.,* 1997; Muntane *et al.,* 2006; Odetti *et al.,* 2000; Sayre *et al.,* 1997). In fact, in PSP, a tauopathy with paired helical filament morphology distinct from AD, significant increases in 4-HNE are correlated with tau aggregation, suggesting that accumulation of 4-HNE may contribute to impairment of tau degradation (Odetti *et al.*, 2000).

The LP-derived aldehydes 4-HNE and acrolein are both capable of inducing tau pathology. *In-vitro*, administration of 4-HNE to cultured rat hippocampal neurons results in direct binding of 4-HNE to tau, preventing dephosphorylation of tau by alkaline phosphatases (Mattson *et al.*, 1997). Acrolein, a more potent neurotoxic aldehyde than HNE (Vaishnav *et al.*, 2010), also induces hyperphosphorylation of tau, both in neuroblastoma cells and in cultured cortical mouse neurons, an effect which can be attenuated by inhibiting the tau kinases, GSK-3β and p38 MAPK (Gomez-Ramos *et al.*, 2003).

In addition to inducing tau hyperphosphorylation, 4-HNE and acrolein are also capable of promoting tau aggregation. In P19 neuroglial cultures, 4-HNE addition results in cytotoxicity and formation of high molecular weight tau species characteristic of neurofibrillary tangles (Montine *et al.*, 1996). However, the effect of 4-HNE on tau aggregation is greatest for tau which has already been hyperphosphorylated. *In-vitro,* administration of 4-HNE promotes assembly of phosphorylated tau, but not native tau, into neurofibrillary tangle-like fibrillary polymers (Perez *et al.*, 2000). Phosphorylation of tau is also required in order for 4-HNE to induce conformational changes to tau, such as the Alz50 epitope conformational change characteristic of early AD (Liu *et al.*, 2005; Takeda *et al.*, 2000). Therefore, 4-HNE may play a role in NFT formation by stabilizing pathologic tau confirmations (Liu *et al.*, 2005). However, 4-HNE does not further enhance aldehydic modification of paired helical filaments, suggesting that paired helical filaments are either already extensively modified by aldehydes or that they are in a confirmation which prevents further aldehyde modifications (Liu *et al.*, 2005). Acrolein also promotes tau aggregation in a concentration-dependent manner, with the fastest aggregation rates occurring in pseudophosphorylated tau, further suggesting that hyperphosphorylation of tau increases its susceptibility to aldehyde-induced aggregation (Kuhla *et al.*, 2007).

While LP-derived aldehydes have a demonstrated ability to induce tau pathology, tau itself can enhance formation of LP-derived aldehydes. For example, in brain homogenates derived from transgenic mice overexpressing mutant human tau, P301L, ferric iron-induced LP results in increased formation of the LP-derived aldehyde, malondialdehyde, compared to wild-type mice (David *et al.*, 2005).

In summary, LP-derived aldehydes are known to be present in human tauopathies, and LP-derived aldehydes, such as 4-HNE and acrolein, are capable of inducing tau phosphorylation and promoting and stabilizing tau aggregation, in particular the aggregation of hyperphosphorylated tau. Therefore, it is possible that following TBI, increases in 4-HNE and acrolein and increases in hyperphosphorylated tau work synergistically to promote tau aggregation, while other mechanisms of 4-HNE and acrolein generation, such as continued mitochondrial dysfunction and tau-induced LP, contribute to a chronic, self-promoting and cyclic cascade of LP and pathologic tau formation (Figure 4).

4.4 Mitochondrial Dysfunction

Alterations in mitochondrial function are known to occur in the tauopathies, AD and FTD (Baloyannis, 2006; David *et al.*, 2005), and in normal aging (Swerdlow, 2011). Several studies indicate that mitochondrial dysfunction is capable of inducing tau dysfunction, and that tau itself is capable of inducing mitochondrial dysfunction.

Impairment of oxidative phosphorylation can lead to tau dysfunction and pathologic tau formation both *in-vitro* and *in-vivo*. For example, in primary rat striatal rat neurons, inhibition of complex-I, inhibition of complex-II, or uncoupling of oxidative phosphorylation leads to decreased ATP production, cellular death and retrograde transport of tau and mitochondria from the axons to the soma (Escobar-Khondiker *et al.*, 2007). In fact, complex-I inhibited neurons contain somal mitochondria which associate with tau at the outer mitochondrial membrane (Escobar-Khondiker *et al.*, 2007). *In-vivo,* inhibition of

complex-I can also induce tau pathology. Chronically infusing the complex-I inhibitor, rotenone, into rats results in cell death, motor dysfunction, and increases in cytosolic tau, phosphorylated tau, and neuronal, glial, and oligodendrocytic tau fibrils (Hoglinger *et al.*, 2005). Furthermore, increased levels of the PN marker, 3-NT, and ubiquitin, a marker for defective protein degradation, are found within cells containing pathologic tau (Hoglinger *et al.*, 2005). Mitochondrial dysfunction is known to lead to PN formation (Bringold *et al.*, 2000; Radi *et al.*, 2002) and can indirectly reduce proteosomal activity (Hoglinger *et al.*, 2005). Therefore, it is possible that complex-I induced mitochondrial dysfunction can lead to formation of pathologic tau through a combination of mechanisms including mitochondrial and tau redistribution, generation of reactive nitrogen species, and impairment of proteosomal degradation pathways.

Pathologic tau has also been observed in transgenic mice lacking the mitochondrial antioxidant enzyme SOD2. Mitochondrial SOD2 catalyzes the dismutation of superoxide ($O_2^{\bullet -}$), formed when single electrons leak from complex I of the electron transport chain (Brand *et al.*, 2004), to the less reactive oxygen species, H_2O_2 (Flynn and Melov, 2013). Thus, SOD2 is an essential enzyme without which the undismutated O2•- wil react with mitochondrial NO• to form the reactive nitrogen species PN. . However, pharmacological administration of the catalytic antioxidant EUK-189 is able to attenuate tau phosphorylation in SOD2 deficient mice (Melov *et al.*, 2007), confirming that mitochondrial generated $O_2^{\bullet -}$ or downstream PN (formed upon reaction of mitochondrial $O_2^{\bullet -}$ and NO•) is capable of driving tau phosphorylation (Melov *et al.*, 2007). Additional evidence supports the theory that mitochondrial dysfunction can induce tau phosphorylation. In transgenic mice overexpressing the human tau mutation, P301S, mitochondrial abnormalities, including carbonyl modification of mitochondrial proteins and decreases in mitochondrial enzyme activities, precede tau hyperphosphorylation and tangle formation by at least three months (Dumont *et al.*, 2011). However, while it is likely that the mitochondrial abnormalities contributed to pathologic tau development, it is also likely that the overexpression of mutated human tau itself induces mitochondrial abnormalities.

Multiple studies provide evidence that tau can induce mitochondrial dysfunction. Mitochondria are synthesized in neuronal cell bodies and then transported throughout the neuron along microtubules by the anterograde motor protein, kinesin (Chang *et al.,* 2006; Morris and Hollenbeck, 1995), while damaged mitochondria are transported toward the soma by the retrograde motor protein, dynein (Miller and Sheetz, 2004). Therefore, neuronal health relies extensively on proper axonal transport of mitochondria. In CTE, fast axonal transport along microtubules is impaired, with decreases being seen both in kinesin and dynein (Kokjohn *et al.,* 2013). Tau is primarily found in axons, functioning to stabilize microtubules (Maccioni and Cambiazo, 1995); however, tau also serves to regulate the attachment and detachment of motor proteins (Trinczek *et al.,* 1999). Therefore, it has been hypothesized that overexpression of tau or accumulation of pathologic tau can impair axonal transport of mitochondria to the synapse, resulting in decreased synaptic ATP, calcium dysregulation and neurodegeneration (Sheng and Cai, 2012). However, it should be noted that in addition to mitochondria, tau-induced impairment of axonal transport affects additional organelles, vesicles, and proteins, and that each likely contributes to their own downstream pathologies. For example, tau overexpression can inhibit trafficking of

peroxisomes, neurofilaments, Golgi-derived vesicles, the ER, and amyloid precursor protein (APP) (Darios *et al.,* 2005; Ebneth *et al.,* 1998; Stamer *et al.*, 2002), the precursor to Aβ, a pathologic species found in the tauopathy AD and in a subset CTE cases.

In regard specifically to axonal transport of mitochondria, several mechanisms by which tau-induced impairment of axonal transport have been reported. *In-vitro,* overexpression of tau in neuroblastoma cells leads to preferential impairment of anterograde mitochondrial transport, resulting in mitochondria that are clustered near nuclei but absent in neurites (Ebneth *et al.*, 1998). The degree to which tau overexpression interferes with mitochondrial transport is influenced by the number of microtubule binding domain repeats. For instance, overexpression of either 3R or 4R tau leads to redistribution of mitochondria from axons to the soma (Stoothoff *et al.*, 2009); however, 4R tau, the isoform expressed to a greater degree in AD and CTE (McKee *et al.*, 2014; Schmidt *et al.*, 2001) has the greatest effect on redistribution (Stoothoff *et al.*, 2009). The N-terminus of tau has also been shown to be sufficient for inhibiting anterograde transport (LaPointe *et al.*, 2009). In fact, filamentous tau, which contains an exposed N-terminus, inhibits kinesin-dependent fast axonal transport, whereas monomeric tau confirmations with unexposed N-terminal regions do not (LaPointe *et al.*, 2009). Hyperphosphorylation of tau at AD-specific sites also results in decreased mitochondrial transport due to extension of the N-terminal projection domain and expansion of inter-microtubule distances (Shahpasand *et al.*, 2012). Additional studies confirm the ability of phosphorylated tau impair anterograde transport. Inhibition of anterograde transport by filamentous tau is dependent upon on activation of the tau kinase, GSK-3β (LaPointe *et al.*, 2009). In PC12 cells, ceramide-induced CDK5-dependent tau phosphorylation results in dissociation of phosphorylated tau from the microtubules, clustering of mitochondria and ER near the centrosome, and cell death, effects which are attenuated by preventing tau phosphorylation (Darios *et al.*, 2005).

Tau-induced impairment of mitochondrial transport likely has pathologic implications beyond decreased delivery of mitochondria to the synapse. For example, the clustering of mitochondria and ER near the centrosome in PC12 cells results in an increase in mitochondria-ER associations, neurotoxic transfer of Ca^{2+} from the ER to the mitochondria, and induction of apoptosis (Darios *et al.*, 2005). Pathologic mitochondria-ER associations have also been observed in the soma of spinal motor neurons in transgenic mice overexpressing the human tau mutation, P301L (Perreault *et al.*, 2009), and correlate with accumulation of hyperphosphorylated tau at the surface of the rough ER (rER) (Perreault *et al.*, 2009). In fact, hyperphosphorylated tau is found on the surface of rER in the tauopathy, AD (Perreault *et al.*, 2009). Because mitochondria-ER associations require the ER to be absent ribosomes, it is possible that tau is capable of inducing mitochondria-ER associations by displacing ribosomes from the ER surface (Perreault *et al.*, 2009).

In addition to impairment of mitochondrial transport and alterations in mitochondrial-ER dynamics, other tau-induced mitochondrial impairments have been reported such as abnormal morphology. For example, neurons from transgenic mice overexpressing the human tau mutation, P301L, have decreased numbers of mitochondria and mitochondria which have abnormally swollen morphology (Yoshiyama *et al.*, 2007).

Tau-induced decreases in oxidative phosphorylation capacity have also been reported. The mitochondria from P301L mice have reductions in complex I (David *et al.*, 2005; Rhein *et al.*, 2009) and complex V (ATP synthase) protein and activity levels (David *et al.*, 2005). Additionally, aged P301L mice have decreases in ATP production and increases in ROS due to decreases in complex-I driven respiration (David *et al.*, 2005). Importantly, reductions in complex V (ATP synthase) have also been seen in the human tauopathy, FTD (David *et al.*, 2005).

Although many studies that investigate the effect of tau on mitochondrial function rely on mutated forms of human tau, the mutant tau constructs, such as P301, do induce tau hyperphosphorylation. Therefore, the mutant tau constructs are representative of non-genetic, hyperphosphorylated tau disease states. However, the possibility exists that mutated tau isoforms cause greater mitochondrial dysfunction than wild type tau. For example, stable overexpression of human mutant tau, P301L, into SY5Y cells results in complex I impairment, decreased ATP production, increased susceptibility to oxidative stress, abnormal morphology, and fission-fusion dysfunction (Schulz *et al.*, 2012); however, overexpression of wild-type 4R human tau results in increases in complex I activity, normal morphology and normal fission-fusion dynamics (Schulz *et al.*, 2012).

Tau oligomers, which have been implicated as the species responsible for tau-induced neurotoxicity (Spires-Jones *et al.*, 2011), are also capable of inducing mitochondrial dysfunction. Injections of full-length human tau oligomers, but not tau fibrils or monomers, into mouse hippocampi induce memory impairment, neurodegeneration, loss of synaptic proteins, and mitochondrial dysfunction (Lasagna-Reeves *et al.*, 2011). Specifically, the tau oligomers co-localized with mitochondria, decreasing complex I protein levels, and activating the intrinsic apoptotic protease, caspase-9 (Lasagna-Reeves *et al.*, 2011). However, complex V protein levels were not altered, suggesting that complex I dysfunction occurs prior to tau-induced complex V dysfunction and ATP depletion (Lasagna-Reeves *et al.*, 2011).

Truncated tau fragments are also capable of inducing mitochondrial dysfunction. In immortalized cortical neurons, Asp421 tau, a mutant mimicking C-terminus caspase-3 cleavage of tau at Asp421, induces mitochondrial fragmentation, decreases mitochondrial calcium buffering capacity, and increases production of mitochondrial ROS (Quintanilla *et al.*, 2009), effects which are attenuated by administration of the calcineurin inhibitors cyclosporine A (CsA) or FK506, suggesting that the calcium-dependent phosphatase, calcineurin, plays a role in caspase-cleaved tau induction of mitochondrial dysfunction (Quintanilla *et al.*, 2009). Tau is a known calcineurin substrate; therefore, it is possible that caspase-cleaved tau interacts differentially with calcineurin, increasing its activity level toward substrates which effect mitochondrial fragmentation (Quintanilla *et al.*, 2009). Interestingly, both CsA and FK506 are neuroprotective in experimental TBI (Kilbaugh *et al.*, 2011; Kulbe *et al.*, 2016; Marmarou and Povlishock, 2006; Mbye *et al.*, 2009; Mbye *et al.*, 2008; Reeves *et al.*, 2007; Sullivan *et al.*, 2011), and CsA has been shown to attenuate levels of cleaved tau in the hippocampus of rats following severe controlled cortical impact injury (CCI) (Gabbita *et al.*, 2005).

In addition to C-terminal cleavage, truncated tau fragments can also be generated by N-terminal processing. Although this process is not well understood, caspases, such as caspase-6 have the ability to cleave tau at the N-terminus (Horowitz *et al.*, 2004), and N-terminal tau fragments have been reported to induce mitochondrial dysfunction. For example, addition of the NH_2-26-44 tau fragment to cerebellar granule neuron homogenates results in decreases in cytochrome oxidase (COX) activity, adenine nucleotide translocator (ANT) activity, and ANT-dependent impairment of oxidative phosphorylation (Atlante *et al.*, 2008). Importantly, N-terminal tau fragments have been identified in AD and other tauopathies (Amadoro *et al.*, 2010). In fact, in AD, a 20-22kD NH_2-tau fragment is highly enriched in synaptosomes, localizing with synaptic mitochondria, and correlating with synaptic and mitochondrial dysfunction (Amadoro *et al.*, 2010). Synapses have high metabolic demands, met by enrichment of synaptic mitochondria (Khatri and Man, 2013; MacAskill *et al.*, 2010). Not only are synaptic mitochondria essential for proper neurotransmission (Sheng and Cai, 2012) and synaptic plasticity (Cheng *et al.*, 2010; MacAskill *et al.*, 2010; Sheng and Cai, 2012), but their dysfunction is implicated in neurodegeneration (Cheng *et al.*, 2010; Sheng and Cai, 2012). Therefore, localization of the 20-22kD NH_2-tau with synaptic mitochondria has important implications for synaptic health, especially considering the fact that 20-22kD NH_2-tau is capable of inducing mitochondrial dysfunction. *In vitro*, the 20-22kD NH_2-tau fragment induces abnormal mitochondrial morphology, increases mitochondrial fragmentation, decreases mitochondrial fusion, enhances redistribution of mitochondria to the soma, decreases mitochondrial protein and mtDNA copy number, and enhances mitophagy, effects which correlate with *in-vitro* synaptic pathology and oxidative stress (Amadoro *et al.*, 2014).

In addition to truncated tau species, phosphorylated tau has also been implicated in alteration of mitochondrial fission-fusion dynamics. Specifically, in the tauopathy AD, phosphorylated tau interacts with Drp1, a mitochondrial fission GTPase, and is associated with increases in GTPase activity indicative of mitochondrial fission, suggesting that phosphorylated tau may enhance mitochondrial fragmentation through interaction with Drp1 (Manczak and Reddy, 2012).

In summary, mitochondrial dysfunction is known to occur in human tauopathies, and there are several mechanisms by which mitochondrial dysfunction can induce tau pathology and by which pathologic tau species can induce mitochondrial dysfunction. Therefore, a primary event capable of inducing mitochondrial dysfunction or formation of pathologic tau species, such as TBI, could set off a self-propagating, cyclical cascade of mitochondrial dysfunction and pathologic tau formation, which work synergistically to induce cellular damage. In fact, in transgenic mice expressing mutations which induce both mitochondrial dysfunction and tau pathology, neurodegeneration and oxidative stress are increased over either mutation alone (Kulic *et al.*, 2011). Furthermore, in addition to a self-propagating, cyclical cascade of mitochondrial-tau dysfunction, because mitochondrial impairment results in production of species capable of inducing damage to mitochondrial DNA (mtDNA), which encodes for electron transport chain proteins (Dalleau *et al.*, 2013; Hall *et al.*, 2010), mitochondrial dysfunction is capable of enhancing and perpetuating its own chronic damage. In fact, accumulations in mtDNA damage have been hypothesized to contribute to both aging and neurodegenerative disease (Keogh and Chinnery, 2015).

4.5 Endoplasmic Reticulum Stress

ER stress has been documented in several tauopathies, including AD, FTD, and CTE, and correlates with tau hyperphosphorylation (Hoozemans and Scheper, 2012; Hoozemans *et al.*, 2009; Lucke-Wold *et al.*, 2016; Nijholt *et al.*, 2012). ER dysfunction has been reported to occur both upstream and downstream of pathologic tau formation (Ho *et al.*, 2012). Upstream of tau, pharmacological induction of ER stress increases tau phosphorylation both *in-vitro* and *in-vivo* (Fu *et al.*, 2010; Ho *et al.*, 2012; Lin *et al.*, 2014). One mechanism by which ER stress can increase tau phosphorylation is through activation of the tau kinase, GSK-3β (Fu *et al.*, 2010; Lin *et al.*, 2014). However, pathologic tau species can also induce ER dysfunction. The ER is responsible for protein folding and degradation; therefore, ER stress results in the build-up of misfolded and unfolded proteins, inhibition of ER-associated degradation (ERAD), initiation of the Unfolded Protein Response (UPR), and decreased protein synthesis (Abisambra *et al.*, 2013; Radford *et al.*, 2015).

Tau is capable of activating the UPR *in-vitro.* Pharmacologic induction of tau phosphorylation in primary rat cortical neurons results in UPR activation (Ho *et al.*, 2012). Similarly, stable expression of tau in HEK cells activates the UPR and is accompanied by increased ubiquitin levels suggestive of ERAD impairment (Abisambra *et al.*, 2013). *In-vivo,* the UPR is known to be increased in both transgenic tau animal models and human tauopathies (Abisambra *et al.*, 2013; Hoozemans and Scheper, 2012; Hoozemans *et al.*, 2009; Nijholt *et al.*, 2012; Radford *et al.*, 2015). It has been hypothesized that the increased UPR seen in tauopathies is the result of tau-induced ERAD impairment (Abisambra *et al.*, 2013). For example, transgenic mice overexpressing human mutant tau, P301L, show ERAD impairment concomitant with associations between tau and the ERAD hetereocomplex (Abisambra *et al.*, 2013). However, activation of UPR in tauopathies may also be due to the buildup of misfolded tau proteins (Radford *et al.*, 2015). UPR activation has also been suggested to play a direct role in neurotoxicity. In fact, pharmacologic inhibition of the UPR in P301L mice decreases tau phosphorylation, neurodegeneration, and behavioral impairment (Radford *et al.*, 2015).

An additional mechanism by which tau induced ER dysfunction can contribute to cellular dysfunction is inhibition of protein synthesis. Microsomes are vesicle-like fragments which contain ER and ribsosomes. In brain microsomes isolated from the tauopathy, AD, oligomeric tau associates more strongly with ribosomes than in control brains, suggesting that pathologic tau may have an effect on RNA translation (Meier *et al.*, 2016). In fact, *in-vitro,* wild type, mutant, and oligomeric tau are all able to reduce RNA translation (Meier *et al.*, 2016), and in primary neurons cultured from transgenic mice overexpressing human mutant tau, P301L, there are both decreases in RNA translation and protein levels (Meier *et al.*, 2016). Specifically, there are marked decreases in the protein PSD-95, a post-synaptic protein important in learning and memory (Meier *et al.*, 2016).

Soluble tau oligomers and truncated tau forms have been specifically implicated in tau induced ER dysfunction. Depleting soluble tau both in cell culture and in P301L mice reduces UPR activation and inhibition of ERAD, suggesting soluble tau oligomers rather than insoluble tau aggregates are responsible for tau-induced ER dysfunction (Abisambra *et al.*, 2013). In regards to truncated tau isoforms, inducing ER stress in immortalized cortical

neurons expressing Asp-421 truncated tau, which mimics caspase-3 cleavage, results in increased cellular toxicity and caspase-3 activation compared to cells expressing full length tau (Matthews-Roberson *et al.*, 2008). In fact, ER stress itself has the capability of inducing the caspase-3 activation (Morishima *et al.*, 2002; Song *et al.*, 2002) which leads to tau truncation.

In summary, ER stress is known to occur in several tauopathies, including CTE, and there are several mechanisms by which ER stress can induce tau pathology and by which pathologic tau species can induce ER dysfunction. Therefore, as summarized in Figure 5, a primary event capable inducing ER stress or tau pathology, such as TBI, could set off a chronic and self-propagating cascade of ER dysfunction and pathologic tau formation, which results in protein accumulation, decreased protein synthesis, and cellular dysfunction.

4.6 Calpain Activated Proteolysis

Tau is a known substrate of the calcium-dependent cysteine protease, calpain (Johnson *et al.*, 1989; Litersky *et al.*, 1993; Yang and Ksiezak-Reding, 1995). Calpain cleavage of tau results in the formation of a 35kD tau fragment (Liu *et al.,* 2011) and a 17kD tau fragment, purported to be between 10-17kD (Garg *et al.,* 2011; Park and Ferreira, 2005). Increased calpain activity and depletion of the endogenous calpain inhibitor, calpastatin, have been found in the tauopathy, AD, (Grynspan *et al.,* 1997; Rao *et al.,* 2008; Saito *et al.,* 1993; Tsuji *et al.*, 1998) and the presence of the 17kD tau fragment correlates with increases in calpain activity in a variety of tauophathies, including AD, FTD and dementia pugilistic (i.e. CTE) (Ferreira and Bigio, 2011).

The 17kD tau fragment has a decreased association with the microtubules and accumulates in the perikarya (Canu *et al.,* 1998). *In-vitro,* glutamate and thapsigargin induced increases in calcium have been shown to induce formation of calpain-cleaved 17kD tau (Garg *et al.*, 2011). The 17kD tau fragment has been reported for form prior to increases in tau phosphorylation (Park and Ferreira, 2005), and is suspected of being neurotoxic (Park and Ferreira, 2005; Park *et al.,* 2007; Sinjoanu *et al.,* 2008). For example, *in-vitro,* Aβ induces calpain activation in cultured hippocampal neurons, leading to formation of 17kD tau and neurodegeneration, affects which are attenuated by inhibiting calpain activation (Park and Ferreira, 2005; Park *et al.,* 2007; Sinjoanu *et al.,* 2008). However, other studies have shown that 17kD tau does not induce toxicity *in-vitro* and is equally expressed in the brains of AD and healthy controls, suggesting that 17kD tau is a marker for calpain activation but does not have a direct role in neurotoxicity (Garg *et al.,* 2011).

In addition to cleaving tau, calpain has also been identified as an upstream activator of extracellular-regulated kinase (ERK) (Veeranna *et al.,* 2004), which is capable of phosphorylating tau (Fang *et al.,* 2010; Qi *et al.,* 2016), In fact, increases in active ERK expression are associated with early tau deposition in neurons and glia in several tauopathies (Ferrer *et al.,* 2001).

Despite controversy surrounding the role of the calpain generated 17kD tau fragment in neurotoxicity, both increases in calpain and 17kD tau have been identified in human tauopathies. Due to increases in intracellular calcium levels, calpain is highly activated

following TBI (Deng *et al.*, 2007; Thompson *et al.*, 2006); therefore it is possible that TBI initiates formation of calpain-cleaved 17kD tau, whereas chronic generation of 17kD tau could be the result of calpain activation by calcium derived from chronically dysfunctional calcium buffering organelles suspected of having self-propagating, cyclic interactions with pathologic tau, such as the mitochondria and ER (Figure 6).

4.7 Caspase Activated Proteolysis

Tau is a known substrate of the caspase proteases (Fasulo *et al.*, 2000; Park *et al.*, 2007), which are well known for their role in apoptosis. The most well characterized caspase cleavage site on tau is Asp421, located on the c-terminus end. Multiple caspases, including caspase 3, can cleave tau at Asp421 (Gamblin *et al.*, 2003), which results in a tau fragment of 50kD (Chung *et al.*, 2001; Park *et al.*, 2007). However, tau can also undergo n-terminal processing by caspases, such as caspase-6 (Horowitz *et al.*, 2004). Caspase cleaved tau is found in several tauopathies (Guillozet-Bongaarts *et al.*, 2007; Newman *et al.*, 2005), and is inversely correlated with cognitive function in the tauopathy, AD (Rissman *et al.*, 2004), with formation of Asp421 truncated tau considered to occur relatively early in the disease process (Guillozet-Bongaarts *et al.*, 2005; Rissman *et al.*, 2004). It is hypothesized that accumulation of Asp421 truncated is the result of dysregulation of autophagy, a process known to occur in the tauopathy, AD (Nixon, 2006). In fact, in immortalized cortical neurons, stably expressed Asp421 truncated tau is preferentially degraded by autophagy, while full length tau is dependent on proteasomal degradation (Dolan and Johnson, 2010).

Several lines of evidence suggest that Asp421 truncated tau is pathologic. *In-vitro*, the c-terminus of tau is responsible for inhibiting polymerization of tau, suggesting that Asp421 truncated tau has enhanced polymerization properties (Berry *et al.*, 2003). In fact, Asp421 truncated tau assembles into filaments at a faster rate and to a higher degree than full length tau (Gamblin *et al.*, 2003; Rissman *et al.*, 2004). Furthermore, full length tau undergoes enhanced filament formation in the presence of Asp421 truncated tau, suggesting that Asp421 truncated tau may be able to seed filament formation of other tau species (Rissman *et al.*, 2004). *In-vitro,* overexpression of Asp421 truncated tau, representative of caspase-3 cleaved tau, results in increased apoptosis (Chung *et al.*, 2001; Fasulo *et al.*, 2000). Caspase-3 is an executioner caspase in the apoptotic cascade; therefore, the fact that caspase-3 cleaved tau is capable of enhancing apoptosis suggests that caspase-3 and Asp421 truncated tau may be involved in a chronic, self-propagating apoptotic cascade (Fasulo *et al.*, 2000). Additionally, as previously discussed, caspase cleaved tau fragments are also capable of inducing mitochondrial dysfunction (Quintanilla *et al.*, 2009) and ER stress (Matthews-Roberson *et al.*, 2008).

Evidence suggests that non-truncated tau forms can also initiate caspase activation and tau truncation. For example, overexpressing human mutant tau P301L in mice results in apoptosis, caspase-3 activation, and appearance of caspase truncated tau (de Calignon *et al.*, 2010; Ramalho *et al.*, 2008). Similarly, overexpression of human 4R tau results in caspase activation, although total numbers of caspase bearing neurons are low (de Calignon *et al.*, 2010). Therefore, it is possible that, *in-vivo,* full-length pathologic tau, particularly soluble pre-tangle tau species, are capable of activating caspase-3, which results in formation of

distinct truncated tau species. In fact, suppression of tau in P301L mice decreases caspase activation despite the continued presence of neurofibrillary tangles (de Calignon *et al.*, 2010).

Although formation of caspase truncated tau is considered to occur early in the disease process (Guillozet-Bongaarts *et al.*, 2005; Rissman *et al.*, 2004), Asp421 truncated tau is still capable of inducing tau phosphorylation and conformational change (de Calignon *et al.*, 2010) and can be the subject of phosphorylation and conformation change itself (Rissman *et al.*, 2004). However, similar to human studies, transgenic animal models of tauopathy suggest that formation of caspase truncated tau occurs prior to tau aggregation and correlates with cognitive decline. In fact, in P301L mice, caspase cleavage of tau proceeds neurofibrillary tangle formation (de Calignon *et al.*, 2010; Ramalho *et al.*, 2008), and is coincident with the beginnings of cognitive impairment (Ramalho *et al.*, 2008). Furthermore, animal models confirm *in-vitro* findings that caspase truncated tau can seed filament formation of full length tau (Gamblin *et al.*, 2003; Rissman *et al.*, 2004). For example, virally overexpressing Asp421 tau in wild type mice results in formation of tau aggregates which contain both Asp421 truncated and full length tau (de Calignon *et al.*, 2010).

As illustrated in Figure 7, tau is a substrate for the apoptotic caspase proteases and caspase truncated tau is present in human tauopathies. Additionally, caspase cleaved can induce cellular dysfunction. Apoptosis and caspase activation occurs following TBI; therefore, it is possible that TBI-induced caspase activation can initiate formation of caspase cleaved tau, whereas long-term generation of caspase truncated tau could be the result of chronic caspase activation due to chronic mitochondrial dysfunction or ER stress, organelles suspected of having self-propagating, cyclic interactions with pathologic tau. In fact, in P301L mice, activated executioner caspases can be found in neurons containing late stage neurofibrillary tangles, despite the absence of apoptosis (Spires-Jones *et al.*, 2008). Furthermore, because caspase truncated tau is capable of activating caspase-3, impairing mitochondrial function, and enhancing ER stress, it is possible that caspase truncated tau itself can self-propagate its formation.

4.8 Neuroinflammation

Neuroinflammation occurs in multiple tauopathies including CTE, AD, PSP, Pick's disease, and corticobasal degeneration (Daneshvar *et al.*, 2015; Ishizawa and Dickson, 2001; Sasaki *et al.*, 2008; Zilka *et al.*, 2009a). Astrocytes and microglia make up two of the most important cells of the CNS innate immune system. Astrocytes containing pathologic tau have been identified in several tauopathies, including CTE (Kahlson and Colodner, 2015; McKee *et al.*, 2016). Similarly, microglia are activated in CTE and other tauopathies (Cherry *et al.*, 2016; Faden and Loane, 2015; Ishizawa and Dickson, 2001; Saing *et al.*, 2012; Sasaki *et al.*, 2008; Zilka *et al.*, 2009a). Evidence suggests that neuroinflammation can both induce tau pathology and be induced by pathologic tau species.

Under physiologic conditions astrocytes contain limited amounts of tau protein, and tau is not considered to be a major component of the astrocyte cytoskeleton (Kahlson and Colodner, 2015). However, in CTE and other tauopathies, hyperphosphorylated tau is present in astrocytes (Kahlson and Colodner, 2015; McKee *et al.*, 2016). Although astrocytic

tau pathology is not well defined in CTE, supporting neuropathological criteria for the diagnosis of CTE includes p-tau positive thorned astrocytes located at the glial limitans in the subpial and periventricular regions (McKee *et al.*, 2016). Additionally, the astrocytic tau of CTE is known to be composed mainly of the 4R subtype (McKee and Robinson, 2014).

Although the phenotypes of the astrocytes containing hyperphosphorylated tau vary between tauopathies, thorned astrocytes, such as those characteristic of CTE, morphologically resemble reactive astrocytes and therefore may be indicative of a neuroinflammatory response similar to gliosis (Kahlson and Colodner, 2015), a process known to occur following TBI (Burda *et al.*, 2016). The presence of hyperphosphorylated tau within astrocytes is hypothesized to have several consequences for astrocytic function (Kahlson and Colodner, 2015). Astrocytes assist in maintenance of the blood-brain barrier; therefore, it is possible that astrocytic tau pathology can lead to blood-brain barrier dysfunction (Kahlson and Colodner, 2015). For example, overexpressing human tau in the astrocytes of mice results in mild blood-brain barrier disruption in areas of extensive astrocytic tau pathology (Forman *et al.*, 2005). In addition to maintenance of the blood-brain barrier, astrocytes remove excessive extracellular glutamate; therefore, it is possible that astrocytic tau pathology can lead to impairment of extracellular glutamate removal, resulting in neuronal excitotoxicity and synaptic dysfunction (Kahlson and Colodner, 2015). In fact, overexpressing either human wild-type or mutant P301L tau in the astrocytes of mice results in a decrease in astrocyte glutamate transporter expression and activity which correlates with behavioral impairment (Dabir *et al.*, 2006). Furthermore, overexpressing tau in astrocytes leads to astrocyte degeneration both *in-vitro* and *in-vivo* (Higuchi *et al.*, 2002; Yoshiyama *et al.*, 2003), and overexpressing human tau in the astrocytes of mice results in neuronal degeneration in regions associated with astrocytic tau pathology (Forman *et al.*, 2005), indicating astrocytic tau pathology may play a direct role in both astrocytic and neuronal cell death (Kahlson and Colodner, 2015).

Although several tauopathies contain astrocytic tau pathology, evidence suggests that astrocytes do not phagocytise pathologic tau species. In the tauopathies, AD and FTD, tau oligomers are found to be surrounded by active astrocytes, but are not co-localized with astrocytes, suggesting the occurrence of an inflammatory response, but that astrocytes do not internalize tau oligomers (Nilson *et al.*, 2016). Conversely, in AD, FTD, and transgenic mice overexpressing human tau (hTau), tau oligomers are found co-localized with active microglia, suggesting active phagocytosis of tau oligomers by microglia (Nilson *et al.*, 2016). In fact, microglia themselves have been implicated in the anatomic spread of tau pathology (Nilson *et al.*, 2016). As shown in Figure 8, microglia are capable of both phagocytosis and exocytosis; therefore, microglial-dependent propagation of tau through phagocytosis and exocytosis may explain non-synaptic spread of tau throughout the brain (Asai *et al.*, 2015). The depletion of microglia has been shown to reduce the propagation of tau *in-vivo*, both in an adenovirus model of rapid tau propagation and in transgenic mice overexpressing human mutant tau, P301S (Asai *et al.*, 2015). Furthermore, transplanting microglia obtained from the brains of transgenic mice overexpressing human tau (hTau) and null for the microglial receptor, CX3R1, to the brains of wild-type mice results in increases in phosphorylated tau within the wild-type brains (Maphis *et al.*, 2015b).

The neuronal-microglial chemokine-chemokine receptor signaling pathway, CX3CL1-CX3CR1 has been implicated in both neurodegeneration and neuroprotection following CNS injury (Bhaskar *et al.*, 2010). CX3CL1-CX3CR1 signaling is known to be altered following TBI (Poniatowski *et al.*, 2016), and may play a role in the development of tau pathology. In fact, tau overexpression is capable of increasing CX3CL1 levels, whereas CXCR1 depletion is capable of enhancing microglial activation and tau pathology. Transgenic mice overexpressing human tau (hTau) show increased levels of the neuronally-derived ligand, CX3CL1 (Bhaskar *et al.*, 2010). Knocking out the microglial receptor, CXC3R1, in hTau mice results in increases in microglial activation which are correlated with cognitive impairment (Bhaskar *et al.*, 2010; Maphis *et al.*, 2015b) In fact, hTau/CX3R1$^{-/-}$ mice show earlier tau pathology than hTau/CX3R1$^{+/+}$ mice (Maphis *et al.*, 2015b).

Alteration in the CX3CLI-CX3CR1 signaling pathway has been shown to enhance tau phosphorylation upon systemic administration of lipopolysaccharide (LPS), a compound capable of activating microglia through the TLR4 receptor (Bhaskar *et al.*, 2010). LPS-induced activation of microglia increases tau phosphorylation in wild-type and hTau mice (Bhaskar *et al.*, 2010). However, the effect is enhanced in CX3R1$^{-/-}$ mice, further enhanced in hTau/CX3R1$^{-/-}$ mice, and is dependent on neuronal activation of the tau kinase, p38 MAPK, and release of the microglial derived cytokine, IL-1β (Bhaskar *et al.*, 2010).

In hTau/CX3R1$^{-/-}$ mice, microglial activation occurs prior to the appearance of tau pathology and correlates with its anatomic spread (Maphis *et al.,* 2015b), suggesting that microglia activation enhances formation of pathologic tau. Additionally, studies suggest that microglial-induced neural toxicity is dependent on the presence of tau. Culturing neurons with LPS-activated CX3R1$^{-/-}$ microglia results in increased neurodegeneration; however this effect is attenuated in tau$^{-/-}$ neurons (Maphis *et al.,* 2015a). Similarly, LPS activation of microglia in CX3R1$^{-/-}$ mice results in caspase-3 activation which is localized to p-tau positive neurons of the dentate gyrus, an effect which is attenuated in tau$^{-/-}$ mice (Maphis *et al.,* 2015a). In non LPS-stimulated CX3R1-/- mice, a reduction in microglial activation and neuronal caspase-3 is also seen in tau$^{-/-}$ mice compared to tau$^{+/+}$ mice (Maphis *et al.,* 2015a), an effect which correlates with attenuation of behavioral impairment (Maphis *et al.,* 2015a).

In addition to the CX3CLI-CX3CR1 signaling studies, several additional lines of evidence suggest that activation of microglia, as well as secretion of pro-inflammatory cytokines contribute to tau pathology. In fact, in the tauopathy AD, microglial expression of IL-1β is correlated with neuronal tau hyperphosphorylation (Sheng *et al.,* 2001). *In-vitro,* activation of microglia with LPS results in microglial secretion of IL-β, neuronal activation of the tau kinase, p38 MAPK, increases in neuronal tau phosphorylation, and decreases in the synaptic protein, synaptophysin (Li *et al.,* 2003). In primary hippocampal neurons, the pro-inflammatory cytokine IL-6 has been shown to increase tau phosphorylation, an effect which is attenuated by inhibiting the tau kinase, cdk5 (Quintanilla *et al.,* 2004). Additionally, exposing SY5Y or N-tera2 cells to media conditioned by LPS and IFNγ-activated human microglia results in increased production and release of tau (Lee *et al.,* 2015). In fact, direct treatment of SY5Y or N-tera2 cells with the inflammatory cytokines, IL-1β or IL-6 was sufficient to increase levels of tau mRNA and protein expression (Lee *et al.,* 2015).

In-vivo, systemic administration of the microglial activator, LPS, results in increased tau phosphorylation acutely in the hippocampus of mice though activators of cdk5 and GSK-3β activation (Roe *et al.,* 2011). In regards to cytokine expression, implantation of IL-1β beads into rat cerebral cortex, in simulation of chronic IL-1β exposure, results in increased mRNA expression of tau and p38 MAPK and increased tau phosphorylation (Sheng *et al.*, 2001; Sheng *et al.,* 2000). Similarly, adenovirus expression of the cytokine IFN-γ, a master regulator of inflammation, in two different mouse models of P301L tau overexpression results in increased phosphorylation of soluble tau through activation of the tau kinase, GSK-3β, however, INF-γ induction of tau phosphorylation did not result in increased tangle pathology or behavioral deficits (Li *et al.*, 2015).

Although activation of microglia has been shown to increase tau phosphorylation, the ability of activated microglia to induce tau aggregation or tangle formation is less clear. For example, in rTg4510 mice overexpressing human mutant tau P301L, injection of LPS directly into the anterior cortex and hippocampus, results in ipsilateral and contralateral microglia activation and increases in tau phosphorylation one week following injection; however, pre-tangle and mature tangle formation was not increased (Lee *et al.,* 2010). Interestingly, in this model activated microglia also did not co-localize with p-tau positive neurons (Lee *et al.,* 2010). Conversely, *in-vitro,* activated microglia are capable of inducing tau aggregation through a mechanism involving production of ROS and the cytokine, TNF. Co-culturing primary hippocampal neurons with microglia pre-activated with LPS and IFN-γ results in aggregation of tau in neurites as determined by FRET imaging, whereas tau aggregation is not seen in neurons cultured in the absence of activated microglia (Gorlovoy *et al.,* 2009). Similarly, direct administration of the cytokine, TNF, to neuronal cultures results in formation of tau aggregates and increases in neuronal ROS production (Gorlovoy *et al.,* 2009). In fact, TNF-induced tau aggregation is attenuated by the scavenging of ROS, suggesting that microglial-induced tau aggregation may be due to microglial secretion of TNF and activation of ROS generating neuronal NADPH oxidase (Gorlovoy *et al.*, 2009).

In addition to activated microglia being shown to induce tau pathology, tau has been shown to activate microglia. *In-vitro,* transfection of microglia with Tau40, the longest isoform of human tau, results in increases in microglia activation, migration, phagocytosis, and cytokine secretion (Wang *et al.*, 2013b). Additionally, in pure microglial cultures, Tau40 induces accumulation of endogenous phosphorylated tau at the cell membrane, enhances secretion of non-phosphorylated tau, and alters expression of tau phosphatases and kinases (Wang *et al.*, 2013b). *In-vivo,* overexpression of human mutant tau, P301L, results in increased expression of chemokines and innate immune system components (Li *et al.*, 2015) and activated microglia accumulate near p-tau positive neurons (Sasaki *et al.*, 2008). Similarly, in transgenic rats expressing truncated human tau, reactive microglia are associated with neurofibrillary tangles and axonal degeneration (Zilka *et al.*, 2009b).

Upon further examination, many of the transgenic tau animal models suggest a cyclic relationship between microglial activation and formation of tau pathology. For example, the overexpression of human mutant tau, P301S, in mice is sufficient to increase microglial activation; however, microglial activation, synapse loss and impaired synaptic function all precede filamentous tau formation (Yoshiyama *et al.*, 2007).

It is currently unclear whether neuroinflammation in CTE and other tauopathies is detrimental or protective. In P301S mice, the immunosuppressant, FK506, is able to attenuate neuroinflammation, neurodegeneration and tau pathology (Yoshiyama *et al.*, 2007). Similarly, minocycline, a tetracycline class antibiotic with neuroinflammatory properties, is able to reduce astrocyte activation, the production of inflammatory cytokines, and decrease tau phosphorylation in the cortex of transgenic mice overexpressing human tau (hTau) (Garwood *et al.,* 2010). Importantly, both FK506 and minocycline have been shown to be neuroprotective in TBI (Miyauchi *et al.,* 2013; Singleton *et al.,* 2001; Vink and Nimmo, 2009).

An additional pathway implicated in inflammation, the cholinergic pathway, is known to be impaired in TBI and neurodegenerative disease. In TBI there are deficits in cholinergic transmission and chronic loss of cholinergic neurons (Shin and Dixon, 2015), and recent evidence has demonstrated the occurrence of tau pathology in the cholinergic neurons of the nucleus basalis of Meynert in CTE brains (Mufson *et al.,* 2016). The neurotransmitter, acetylcholine (Ach), is purported to have anti-inflammatory properties and the cholinergic pathway has been implicated in regulation of the immune system (Yoshiyama *et al.,* 2012). In fact, chronic administration of a centrally acting anti-cholinergic to mice overexpressing human mutant tau, P301S, results in increases in tau phosphorylation and insolubility, activation of tau kinases, neurodegeneration, and microglial activation (Yoshiyama *et al.,* 2012). Furthermore, anti-cholinergic administration enhances the effects of LPS-induced microglial activation in P301S mice (Yoshiyama *et al.,* 2012).

Therefore, if neuroinflammation is a detrimental process, acetylcholine esterase inhibitors (AChEI), which have long been used for symptomatic treatment of cognitive impairment in neurodegenerative tauopathies but are also purported to have anti-inflammatory properties due to their ability to upregulate cholinergic pathways (Yoshiyama *et al.,* 2010), should be neuroprotective in animal models of tauopathy. If fact, in transgenic mice overexpressing human mutant tau, P301S, chronic treatment with the AChEI, donepezil, results in decreased astrocyte and microglial activation, decreased tau phosphorylation and insolubility, and decreased synaptic and neuronal loss (Yoshiyama *et al.,* 2010). Furthermore, in P301S mice, donepezil is able to attenuate LPS-induced microglial activation and reduce brain levels of IL-1β and COX-2, suggesting that the neuroprotective effects of AChEI are due to attenuation of neuroinflammation. (Yoshiyama *et al.,* 2010).

Although inhibition of neuroinflammation has been shown to be protective in some tauopathy models, neuroinflammation may also serve a protective role against the development of tau pathology and cognitive dysfunction through promotion of cellular and debris clearance mechanisms. For example, in transgenic mice overexpressing human mutant tau, P301S, LPS-induced activation of microglial also been shown to decrease phosphorylated tau and improve cognitive function through the promotion of authophagy (Qin *et al.,* 2016).

Microglia themselves are also responsible for the clearance of damaged neurons, aberrant synapses and demyelinated axons (Sanchez-Mejias *et al.,* 2016). Therefore, degeneration of microglia leads to neuronal degeneration in areas absent immune surveillance (Sanchez-

Mejias *et al.,* 2016). In the temporal cortex of the tauopathy, AD, dystrophic (degenerating, fragmented, senescent, etc.) microglia are co-localized with degenerating neurons positive for tau (Streit *et al.,* 2009). Similarly, degenerating microglia are found in the hippocampus of AD, a region in which phosphorylated tau preferentially accumulates over Aβ plaques (Sanchez-Mejias *et al.,* 2016). Although the appearance of dystrophic microglia, a phenomenon known to increase with aging, precedes the spreading of tau pathology in AD, suggesting that loss of microglial neuroprotection as one ages can lead to neurodegeneration (Streit *et al.,* 2009), additional evidence suggests that soluble phosphorylated tau is capable of inducing microglial degeneration. For example, *in-vitro,* both phagocytosis of extracellular soluble p-tau and phagocytosis of apoptotic SY5Y cells containing intracellular soluble p-tau induces microglial toxicity, an effect which can be attenuated by immuno-depletion of p-tau (Sanchez-Mejias *et al.,* 2016).

In summary, CTE and TBI share common neuroinflammatory processes such as astrogliosis and activation of microglia. In fact, chronic neuroinflammation occurs in tauopathies and TBI. In CTE, tau positive astrocytes have been hypothesized to have several detrimental consequences, including blood-brain barrier dysfunction, extracellular glutamate dysregulation, and induction of neurodegeneration. In addition to astrocytes, the activation of microglia and the release of inflammatory cytokines have been implicated in induction of tau pathology and neurodegeneration. However, pathologic tau, itself, is capable of inducing both activation and degeneration of microglia, with degeneration of microglia capable of inducing neurodegeneration. Therefore, it is possible that following an initial insult capable of activating microglia and inducing pathologic tau formation, such as TBI, that microglia and tau interact to induce a feedforward cycle of neuroinflammation, pathologic tau formation, and neurodegeneration (Figure 8). In fact, chronic neuroinflammation is found both in tauopathies and decades following TBI.

5. Tau - A Biomarker for TBI

Stretching, shearing and degeneration of axons following TBI causes tau to be released from microtubules, increasing the levels of tau in biofluids. For this reason, there is growing interest in using cerebral spinal fluid (CSF), plasma, or serum tau as a biomarker for TBI, including mild TBI and sports-related head injury (Kulbe and Geddes, 2015). Furthermore, CSF tau already holds diagnostic potential in the tauopathy, AD (Blennow *et al.*, 2010).

Increased levels of serum tau have been found in various models of animal TBI. For example, on the severe end of the spectrum, the cleaved form of tau (c-tau) is acutely elevated 6h post-injury in the serum of rats receiving a severe CCI. However, tissue levels of c-tau remained elevated beyond 6h and were significantly increased for at least 7 days post-injury, both in the hippocampus and the cortex (Gabbita *et al.*, 2005).

More diffuse models of injury, such as mild blast TBI, mild rotational TBI and repetitive closed head injury have shown post-injury increases in serum tau to be sustained for longer periods of time. Following a single, low-intensity blast TBI in mice, serum tau is significantly elevated two hours and one day following injury (Ahmed *et al.*, 2015). However, non-significant elevations in serum tau were sustained for at least one month

following injury (Ahmed *et al.*, 2015); a time course which parallels findings in mice receiving a mild blast-injury in which phosphorylated and cleaved forms of neuronal tau were increased 24h and one month post-injury (Huber *et al.*, 2013). Therefore, increases in serum tau following blast TBI are likely to be representative of pathophysiological changes to tau in the brain tissue. Additionally, in rats receiving a mild TBI produced by rotational acceleration forces, serum tau is significantly elevated for at least 14d post-injury (Rostami *et al.*, 2012), and in mice receiving repetitive closed head injuries, serum levels of total tau and phosphorylated tau are significantly elevated one day to one month post-injury, findings which again parallel increases in cortical phosphorylated tau (Yang *et al.*, 2015).

In human TBI, increases in serum tau correlate with injury severity (Wang *et al.*, 2016) and peak two days post-injury (Wang *et al.*, 2016). However, in severe TBI, levels of CSF tau continue to rise beyond two days, peaking between five and 15 days post-injury (Franz *et al.*, 2003). In addition to full-length tau, cleaved tau isoforms have also been found in CSF following severe TBI (Zemlan *et al.*, 2002; Zemlan *et al.*, 1999). Importantly, several studies show that following severe TBI, levels of tau in the serum, cerebrospinal fluid, and brain extracellular fluid correlate with outcomes up to one year post-injury (Liliang *et al.*, 2010; Magnoni *et al.*, 2012; Ost *et al.*, 2006; Wang *et al.*, 2016; Zemlan *et al.*, 2002), suggesting that in severe TBI, acute increases in peripheral tau may be related to pathologic processes that contribute to mortality and morbidity.

The ability of tau to serve as a biomarker for mild TBI in human patients is less clear. Although serum tau is known to be elevated following pediatric mild TBI (Guzel *et al.*, 2010), the clinical utility of serum tau as a biomarker for mild TBI has been questioned. For example, serum tau is unable to distinguish between mild TBI with or without intracranial lesion (Guzel *et al.*, 2010; Kavalci *et al.*, 2007), and serum levels of c-tau are unable to predict the development of post-concussive symptoms following mild TBI (Bazarian *et al.*, 2006; Ma *et al.*, 2008).

Despite the less than promising results in regard to the value of peripheral tau as a biomarker for mild TBI, various tau isoforms have been found to be elevated in the plasma, serum, or CSF of groups at risk for sustaining multiple head injuries, such as athletes and military personnel. In fact, in male athletes, participation in collision sports is associated with elevated levels of plasma tau (Di Battista *et al.*, 2016). In boxing, total tau levels are increased in the CSF for up to ten days and in the plasma for up to six days following a match, with significantly increased levels being seen in the CSF of players sustaining more hits to the head (Neselius *et al.*, 2012; Neselius *et al.*, 2013; Zetterberg *et al.*, 2006). In hockey, total tau is elevated in the serum of concussed players for up to six days following injury and correlates with duration of post-concussive symptoms (Shahim *et al.*, 2014). Similarly, caspase cleaved tau (c-tau), a fragment itself capable of perpetuating tau pathology, is elevated in the serum of hockey players post-concussion, and the tau fragment, Tau-A, correlates with the number of days it takes concussed players to return to play (Shahim *et al.*, 2016). Tau-A is generated by cleavage of tau by ADAM-10 (Shahim *et al.*, 2016), a metalloproteinase which has been shown to be elevated in animal models of TBI (Warren *et al.*, 2012).

In addition to acute and sub-chronic time points, increases in peripheral tau have been shown to be sustained chronically in both athletes and military personnel. Compared to controls, the serum of symptomatic retired NFL players contains a significantly increased number of tau positive exosomes, which correlate with cognitive impairment (Stern *et al.*, 2016). Exosomes are stable cell exocytosed nanovesicles, the content of which is representative of the cell of origin (Stern *et al.*, 2016). Furthermore, plasma levels of total tau are significantly increased in military personnel sustaining three or more TBIs and levels correlate with post-concussive symptoms, despite the majority of participants having sustained TBIs at least 18 months prior (Olivera *et al.*, 2015).

Therefore, these studies suggest that in addition to severe TBI, concussions, sub-concussive hits, and repetitive mild head injuries are sufficient enough to cause acute dissociations of tau from the microtubules, and that repeat injuries can lead to sustained increases in peripheral tau. Furthermore, the correlation that tau positive exosomes and sustained plasma tau levels have with chronic symptoms suggests that increases in peripheral tau may indeed be representative of brain pathology.

6. TBI, Tau, and CTE - The Animal Models

6.1 Experimental TBI-induced Tau pathology

Animal models have been used extensively to model TBI and are able to recapitulate several aspects of human TBI neuropathology and behavioral impairment (Xiong *et al.*, 2013). Currently, animal models are being used to elucidate the effects of single or repetitive TBI on acute and chronic tau pathology. Ojo et al. (Ojo *et al.*, 2016) has extensively covered methodologies, pathologies, and the benefits and challenges of using animals to study repetitive TBI and CTE. A multitude of factors are purported to influence CTE development including injury type, injury severity, impact number, impact frequency, age at injury, time elapsed since injury, genetics, gender, and environment (Ojo *et al.*, 2016). Therefore, examining the relationship between TBI and CTE in animals is challenging; a difficulty which is evidenced throughout the literature. For example, while some animal models of repetitive TBI induce significant increases in tau phosphorylation, others have either found no significant tau pathology or tau pathology in only single animals (Ojo *et al.*, 2016). Furthermore, despite increases in phosphorylated and total tau following injury, most studies fail to recapitulate other pathologic characteristic of CTE such as tangle formation, glial tau, perivascular tau deposition, and deposition of tau at the depths of sulci, a characteristic which would be practically impossible to model in the lissencephalic rodent brain (Ojo *et al.*, 2016).

The anatomic and physiologic differences between humans and rodents (mice being the most common animal used in studies of tau) further complicate matters. Anatomically, human brains contain higher ratios of white to grey matter, higher ratios of glia to neurons, sulci, gyri, longer myelinated axons, and a denser vascular supply (Ojo *et al.*, 2016). The ratio of 3R to 4R tau also differs in rodents and in humans. Healthy adult brains express equal ratios of 3R and 4R tau (Goedert and Jakes, 1990; Ojo *et al.*, 2016), whereas rats and mice express 4R tau, an isoform which is preferentially phosphorylated and prone to aggregation, to a much higher degree than 3R tau (Hanes *et al.*, 2009; McMillan *et al.*, 2008;

Ojo *et al.*, 2016). Additionally, animal models of CTE often depend on the use of transgenic mice. For example, many of the transgenic mice used to study pathologic tau utilize FTD-17 mutations, such as P301L, which preferentially favor 4R splicing (Ojo *et al.*, 2013; Ojo *et al.*, 2016). Transgenic tau mice also overexpress tau compared to wild type mice, and are predisposed to the development of tau pathology (Ojo *et al.*, 2016). In fact, in some CTE studies, transgenic tau mice are aged and already display tau pathology prior to injury (Ojo *et al.*, 2013; Ojo *et al.*, 2016).

Despite the difficulty in using animals to investigate the relationship between TBI, tau and CTE, important observations have been made. Several pathologic tau isoforms have been observed in experimental animal models of TBI, including increases in total tau, phosphorylated tau, cleaved tau, tau oligomers, tau aggregates and other pathologic tau confirmations. However, animal models of TBI are diverse, ranging from mild to severe, focal to diffuse, and single to repetitive, which can affect the time course and type of tau pathology seen following injury.

Several different models of TBI, including controlled cortical impact injury (CCI), fluid percussion injury (FPI), and blast injury have shown tau to be increased acutely following injury. CCI, a focal model of injury which includes aspects of contusion, hemorrhage and diffuse injury (Hall *et al.*, 2005), results in severity-dependent increases in cleaved tau (c-tau), with severe injury inducing significant increases in c-tau beginning at 6h in the cortex and 48h in the hippocampus, increases which are sustained for at least seven days following injury and which are attenuated by the neuroprotective drug CsA (Gabbita *et al.*, 2005). Similarly, following a moderate FPI, a mixed model of focal and diffuse injury (Thompson *et al.*, 2005), oligomeric and phosphorylated tau are increased acutely: 4h, 24h and 2 weeks post-injury (Gerson *et al.*, 2016; Hawkins *et al.*, 2013). Mild blast TBI, which encompasses both the blast wave and rotational acceleration-deceleration forces and results in diffuse injury, transient axonal injury, and vascular pathology (Courtney and Courtney, 2015; Kovacs *et al.*, 2014), has also been shown to increase tau acutely following injury. For example, mild blast TBI increases phosphorylated tau in rat hippocampus 6h post-injury (Perez-Polo *et al.*, 2015), and a repetitive blast injury consisting of three closely spaced blasts results in total tau levels being increased 24h post-injury in mouse cerebellum (Arun *et al.*, 2013).

Chronic tau pathology has also been observed following blast injury. Tau phosphorylation and pathologic tau conformations are increased in rat hippocampus and cortex one month following either a single blast or six blasts spaced 48h apart (Turner *et al.*, 2015). Furthermore, rats exposed to repeat injury showed evidence of perivascular tau pathology, a defining feature of human CTE (Turner *et al.*, 2015). Seventy days following a single blast injury in rats, total tau protein is also increased in several brain regions including the amygdala, prefrontal cortex and hippocampus; an affect which can be attenuated by environmental enrichment (Kovesdi *et al.*, 2011). Tau oligomers have also been observed to develop one month following a single blast TBI (Gerson *et al.*, 2016). In fact, tau oligomers extracted from rat brains one month following a single blast TBI have prion-like characteristics, increasing the spread of tau pathology and accelerating the rate of cognitive decline when injected into brains of transgenic mice overexpressing human tau (Gerson *et*

al., 2016). Tau aggregation also occurs following blast TBI, although in a delayed manner. For example, three months following a single blast injury, rats develop tau aggregates in the prefrontal cortex and hippocampus that were not yet present one-month following injury (Sajja *et al.*, 2015).

Chronic tau pathology has also been detected following closed head injury, another animal model of diffuse TBI. Similar to blast injury, increases in tau phosphorylation and pathologic tau conformations have been found one month following a single closed head injury (Turner *et al.*, 2015). However, other studies have shown a requirement for repeat injuries in order to induce tau pathology following closed head injury. For example, in aged, transgenic mice overexpressing human tau and who already showed signs of tau pathology prior to injury, repeat injury (five injuries space 48h apart) but not single injury, resulted in increases in cortical and hippocampal tau phosphorylation three weeks post-injury (Ojo *et al.*, 2013); however, other characteristic CTE pathologies, such as perivascular tau, neuritic threads and astrocytic tangles, were not seen (Ojo *et al.*, 2013). Similar increases in tau phosphorylation following repetitive closed head injury occur in wild-type mice. For example, exposing mice to four closed head injuries spaced three days apart results in increased tau phosphorylation in the hippocampus and cortex, effects which are sustained for at least seven days and 30 days, respectively (Yang *et al.*, 2015). Additionally, chronic increases in tau phosphorylation following repetitive closed head injury have been observed to occur beyond 30 days. For example, exposing mice to three closed head injuries spaced 24h apart, results in increases in tau phosphorylation in the corpus callosum, cortex, hippocampus and amygdala six months following injury (Luo *et al.*, 2014). Furthermore, evidence suggests that the presence of tau following repetitive closed head injury is linked to the development of pathology following injury. In fact, in a two-hit frontal impact model of closed head injury, knocking out tau attenuates chronic axonal degeneration and learning and memory deficits (Cheng *et al.*, 2014).

Newer models of closed head injury, which also incorporate rotational acceleration-deceleration forces in an attempt to more closely model human concussion, also have demonstrated increases in tau pathology following injury. In a model termed CHIMERA, which stands for Closed-Head Impact Model of Engineered Rotational Acceleration, an impact device is used to deliver a closed head injury to mice while allowing for free rotation of the head upon impact (Namjoshi *et al.*, 2014). In CHIMERA, two impacts spaced 24h apart results in increases in tau phosphorylation over the first 48h following injury (Namjoshi *et al.*, 2014). Chronic increases in tau phosphorylation have also been seen in similar models. For example, in another combined model of closed head injury and rotational acceleration, exposing mice to five injuries spaced 24h apart results in increases in tau phosphorylation for at least 30 days following injury (Kane *et al.*, 2012). Similarly, in a closed head injury model which allows for head mobility and the use of non-anaesthetized mice, tau phosphorylation is increased in the cortex, hippocampus, amygdala and dentate gyrus seven days and one month following single or repetitive (42 injuries) injury (Petraglia *et al.*, 2014). Furthermore, increases in tau phosphorylation were sustained out to six months in repetitive injury mice (Petraglia *et al.*, 2014).

Although less studied in isolation, evidence suggests that rotational acceleration-deceleration forces themselves are capable of inducing tau pathology. In fact, head restraint during blast injury is able to attenuate increases in tau phosphorylation, neuroinflammation, microvascular pathology, neurodegeneration, and learning and memory impairment (Goldstein *et al.*, 2012). In swine models of rotational head injury, PHF-tau is reported to accumulate in neuronal perikarya following injury (Smith *et al.*, 1999). Similarly, a model using air pressure to induce a rotational head injury in mice absent a blast wave, results in increases in tau phosphorylation two and eight weeks post-injury; however, similar to other models, additional aspects of tau pathology such as tau aggregation were not seen (Sabbagh *et al.*, 2016).

6.1.1 Select Mechanisms of Experimental TBI-induced Tau Pathology—Multiple animal models of TBI, including diffuse injury, blast injury, closed head injury and rotational acceleration-deceleration injury, have all demonstrated increases in pathologic tau following injury. These models of injury also result in widespread damage to axons and white matter tracts, suggesting the possibility that diffuse axonal damage and pathologic tau formation are related. In fact, in transgenic mice expressing either human mutant tau, P301S, or the six isoforms of wild type human tau, a mild repetitive impact-acceleration injury induces dose-dependent advanced tau hyperphosphorylation and tangle formation ten weeks following injury (Xu *et al.*, 2015). However, tau pathology only develops in regions of the brain associated with transient axonal injury; specifically, tau pathology develops in the retinal ganglion cells as this model induces transient axonal injury to the optic nerve (Xu *et al.*, 2015). In addition to diffuse axonal injury being capable of inducing tau pathology, dendritic damage has also been implicated in increased tau phosphorylation. For example, in rats, epidural cortical compression rapidly results in mechanical disruption of the dendritic cytoskeleton, resulting in increases in phosphorylated tau, alterations in tau kinase and phosphatase activity levels, and dendritic remodeling, implying rapid changes to cortical circuitry that could have long lasting effects on brain function (Chen *et al.*, 2010a).

Several experimental TBI studies have identified additional mechanisms which also may contribute to pathologic tau formation. Several studies have observed that increases in tau phosphorylation following injury are accompanied by alterations in phosphatase or kinase activity. In FPI, increases in tau phosphorylation twelve weeks post-injury are accompanied by decreases in expression and activity of the tau phosphatase, PP2A, neurodegeneration and cognitive impairment, effects which are attenuated by the administration of the PP2A activator, sodium selenite (Shultz *et al.*, 2015). Similarly, in blast and weight-drop models of TBI, acute increases in tau phosphorylation coincide with decreases in activity of tissue non-specific alkaline phosphatase (TNAP), a phosphatase with greater activity towards phosphorylated tau than PP2A (Arun *et al.*, 2015). Additionally, following CCI in mice, increases in tau phosphorylation, cognitive impairment and hippocampal degeneration are all attenuated by administration of lithium, an inhibitor of the tau kinase, GSK-3β (Yu *et al.*, 2012).

In addition to alterations in tau phosphatase and kinase activity, oxidative stress also has been observed to coincide with tau pathology following experimental TBI. Exposing mice to a single blast results in increases in phosphorylated and cleaved tau 24h post-injury in the

cortex, hippocampus, and cerebellum, increases which are sustained in the hippocampus 30 days post-injury, and which are accompanied acutely by increases in oxidative stress defense mechanisms in the hippocampus and cerebellum, namely increases in the mitochondrial anti-oxidant, SOD2 (Huber *et al.*, 2013). Oxidative stress has also been seen to accompany tau pathology in repetitive models of TBI. In a repetitive blast injury model, exposing mice to six blasts spaced 48h apart results in increases in pathologic tau, apoptosis, and impulsivity, effects which are attenuated by administration of the antioxidant, lipoic acid (Lucke-Wold *et al.*, 2015). Lipoic acid inhibits NOX4, an enzyme increased in CTE brains which is capable of inducing oxidative stress (Lucke-Wold *et al.*, 2015). Additionally, in a repetitive mild closed head injury model, exposing mice to three impacts spaced 24h apart, results in increases in phosphorylated tau, inflammation, and synaptic and cognitive impairment 30 days post-injury, effects which are attenuated by inhibition of monoacylglycerol lipase (MAGL) (Zhang *et al.*, 2015). MAGL metabolizes endocannabinoid 2-arachidonoylgylcerol (2-AG) to prostaglandins and arachidonic acid (Zhang *et al.*, 2015). Therefore, inhibiting MAGL acts to increase 2-AG, a compound known for having anti-inflammatory and neuroprotective properties (Zhang *et al.*, 2015), while also decreasing the 2-AG metabolite, arachidonic acid, which is itself capable of initiating LP (Bains and Hall, 2012; Hall *et al.,* 2010).

Experimental TBI has also been shown to increase toxic forms of tau by impairing the function of the proline isomerase, Pin1. Pin1, converts tau phosphorylated at Thr231 from the cis isomer to the less toxic trans configuration (Kondo *et al.*, 2015). Phosphorylation of Pin1 increases following experimental TBI, leading to decreased Pin1 activation and, therefore, increased levels of the cis isomer (Kondo *et al.,* 2015). Pin1 can also be inhibited through cysteine oxidation (Chen *et al.*, 2015), an event likely to occur under TBI-induced oxidative stress conditions. Formation of the cis isomer of phosphorylated tau (cis p-tau) is reported to be an early pathogenic event in the tauopathy, AD, (Nakamura *et al.,* 2012), and increases in cis p-tau have been identified in CTE (Kondo *et al.*, 2015), and in experimental models of severe TBI, repetitive mild TBI (rmTBI) and blast TBI (Kondo *et al.*, 2015). In fact, six months following rmTBI cis p-tau which developed acutely at the site of injury has spread to additional brain regions (Kondo *et al.*, 2015). Cis p-tau is suspected of being neurotoxic. In fact, in an experimental model of severe TBI, administration of a cis p-tau antibody prevents development and spread of cis p-tau, attenuates disruptions in microtubule and mitochondrial transport, and improves functional and behavioral outcomes (Kondo *et al.,* 2015).

In addition to dysfunction of enzymes and oxidative stress pathways, dysfunctional tau clearance mechanisms have been observed following experimental TBI. A moderate-severe closed head injury in mice results in impairment to the glymphatic pathway for at least one month following injury and correlates with increases in tau phosphorylation (Iliff *et al.*, 2014). The glymphatic pathway is a perivascular network responsible for CSF recirculation and clearance of interstitial proteins such as tau and Aβ (Iliff *et al.*, 2014; Iliff *et al.*, 2012). The glympathic pathway is highly dependent on the protein, perivascular glial aquaporin-4 (AQP4), which is also chronically impaired following experimental TBI (Iliff *et al.,* 2014; Ren *et al.,* 2013). In fact, knock-out of aquaporin-4 results in increases in tau phosphorylation, axonal degeneration, neuroinflammation, and behavioral deficits following

experimental TBI suggesting that chronic glymphatic dysfunction following TBI may contribute to the development of neurodegenerative tauopathies through impairment of tau clearance (Iliff *et al.*, 2014).

6.2 Experimental TBI without Tau Pathology

Although multiple animal models have demonstrated that pathologic tau is increased following acute TBI, pathologic tau can be sustained chronically following TBI, and several possible mechanisms that could lead to tau dysfunction following injury, there have been other animal models which have failed to demonstrate any tau pathology following injury. In fact, even the use of transgenic mice does not always ensure formation of tau pathology following experimental TBI. For example, in a repetitive mild closed head injury in which aged transgenic mice expressing the shortest form of human tau (T44) received a total of 16 injuries over the course of four weeks, only 1 in 9 mice developed neurofibrillary tangles and cerebral atrophy (Yoshiyama *et al.*, 2005). However, except for the individual mouse displaying tau pathology, this model was also unable to induce any cognitive deficits six months post-injury (Yoshiyama *et al.*, 2005).

Several additional examples demonstrate the difficulty of modeling CTE in rodents. In a mouse study that paralleled several clinical and pathological aspects of human TBI, a single mild closed head injury resulted in pathology and behavioral deficits that remained static over time, whereas repeat injury (five injuries spaced 48h apart) resulted in progressive neuroinflammation, white matter degradation, and behavioral impairment over 6-18 months following injury despite no increases in tau phosphorylation (Mouzon *et al.*, 2014). Similarly, in a mouse model combining impact and rotational acceleration, repeating injuries on a daily or weekly basis resulted in increases in astrogliosis and cognitive impairment up to one year following injury, but no increases in tau phosphorylation (Mannix *et al.*, 2013).

A lack of tau pathology following rmTBI has also been seen at more acute time points. For example, in a mouse model of repetitive mild closed head injury, five impacts spaced 24h or 48h apart results in motor and cognitive deficits, axonal degeneration and astrogliosis, particularly in the visual system, ten weeks following injury; however, increases in hyperphosphorylated tau were not seen (Bolton Hall *et al.*, 2016). Similarly, although exposing mice to five injuries spaced 24h apart results in increased hemorrhagic lesions, diffuse axonal injury, neurodegeneration, and astrogliosis 24h post-injury compared to intervals spaced 48h apart, neither injury paradigm results in increased tau phosphorylation (Bolton and Saatman, 2014).

In summary, use of animal models to study CTE and the development of chronic tau pathology following experimental TBI is complicated by a multitude of factors including heterogeneity of human injury, heterogeneity of individuals, and anatomic and physiologic differences between humans and rodents. Although individual studies have failed to recapitulate all aspects of CTE pathology, numerous studies have confirmed the ability of experimental TBI to induce acute and chronic tau pathology, and the ability of repetitive injury to exacerbate that pathology. Furthermore, animal models have confirmed mechanisms suspected of contributing to tau pathology following injury such as tau kinase and phosphatase dysfunction and induction of oxidative stress pathways, and identified

additional mechanisms that possibly contribute to tau dysfunction following injury such as Pin1 inhibition and dysfunction of the glympathic pathway.

7. Conclusions and Possible Neuroprotective Strategies to Prevent or Interrupt the Progression of CTE

Traumatic brain injury results in a secondary injury cascade that includes processes such as calpain and caspase activation, mitochondrial and ER dysfunction, increases in oxidative stress including generation of peroxynitrite which trigger, lipid peroxidation and LP-derived breakdown products, most notably the neurotoxic aldehydes 4-HNE and acrolein, and neuroinflammation. While these post-TBI biochemical and cellular pathophysiological events begin within the first minutes, days and hours post-TBI, there is evidence that some of these events may persist into the chronic injury phase exerting negative effects on recovery months and perhaps years after the single of repetitive TBI episodes and contributing to age-related neurodegenerative diseases. Similar processes occur in neurodegenerative tauopathies and many have been shown to occur upstream, downstream, and in a circular cascade with tau dysfunction (Figure 9). A history of TBI, particularly repetitive, is a risk factor for both CTE and AD; therefore, it is possible that several of the above mentioned pathologies, which occur acutely following TBI, lead to chronic neurodegeneration and tau dysfunction. However, the apparent complexities of the mechanistic link between acute post-traumatic secondary injury processes and their contribution to chronic outcomes is yet to be un-raveled. Nevertheless, since CTE has only been documented in individuals with histories of repetitive, and perhaps even single, TBIs, it is entirely possible that early initiation of neuroprotective treatments that will effectively inhibit the acute, subacute and early chronic secondary injury phases will lessen the development of the tauopathy that is the key neuropathology seen in CTE. While a single neuroprotective approach might be able to significantly attenuate the progressive brain damage in CTE, since a variety of cellular dysfunctions can lead to tau dysfunction, which can in turn lead to several cellular dysfunctions, it is likely that a multi-mechanistic neuroprotective combinational approach to CTE prevention and interruption will be needed.

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Definitions

2-AG	2-arachidonoylglycerol
3-NT	3-nitrotyrosine
4-HNE	4-hydroxynonenal
Ach	acetylcholine
AChEI	acetylcholine esterase inhibitor
AD	Alzheimer's disease
ADAM-10	A disintegrin and metalloproteinase domain-containing protein 10
ANT	adenine nucleotide translocator
APP	amyloid precursor protein
AQP4	aquaporin-4
CCI	controlled cortical impact injury
CDK5	cyclin-dependent kinase 5
CHIMERA	closed-head impact model of engineered rotational acceleration
COX	cytochrome oxidase
CsA	cyclosporine A
c-tau	cleaved tau
CTE	chronic traumatic encephalopathy
CX3CL1	C-X3-C motif ligand 1 / fractalkine
CX3CR1	CX3C chemokine receptor / fractalkine receptor
DRP1	dynamin-related protein
ERAD	ER-associated degradation
ERK	extracellular-regulated kinase
FPI	fluid percussion injury
FRET	fluorescence resonance energy transfer
FTD	frontotemporal dementia
GSK-3β	glycogen synthase kinase-3β

hTau	human tau
IFN	interferon
IL	interleukin
JNK	c-Jun-terminal kinase
LP	lipid peroxidation
LPS	lipopolysaccharide
MAGL	monoacylglycerol lipase
MAP	microtubule-associated protein
MAPK	mitogen-activated protein kinase
MAPT	microtubule-associated protein tau
mPTP	mitochondrial permeability transition pore
mtNOS	mitochondrial nitric oxide synthase
NADPH	nicotinamide adenine dinucleotide phosphate
NFT	neurofibrillary tangle
NOX4	NADPH oxidase 4 gene
PHF	paired helical filament
PIN1	peptidyl-prolyl cis-trans isomerase NIMA-interacting 1
PN	peroxynitrite
PP2A	protein phosphatase 2
PSD-95	postsynaptic density 95
PSP	progressive supranuclear palsy
p-tau	phosphorylated tau
rmTBI	repetitive mild TBI
RNS	reactive nitrogen species
ROS	reactive oxygen species
SOD2	mitochondrial superoxide dismutase 2, manganese-dependent superoxide dismutase
TNAP	tissue non-specific alkaline phosphatase
TBI	traumatic brain injury

TDP-43	transactive response DNA-binding protein
TLR4	toll-like receptor 4
UPR	unfolded protein response

Highlights

- Chronic traumatic encephalopathy (CTE) is a recently described neurodegenerative tauopathy that is a chronic sequela of traumatic brain injury (TBI).
- CTE occurs predominantly after repeated episodes of mild TBI in athletes involved in contact sports or in military combatants exposed to single or repetitive explosive blast-injuries.
- This review discusses the possible involvement of the well characterized post-TBI pathophysiological mechanisms in the pathogenesis of tau protein deposition that is distinctly characteristic of CTE.
- The analysis of the possible interactions of TBI secondary injury with CTE tauopathy has suggested several neuroprotective approaches that might serve, either singly or in combination, to limit the development of CTE.

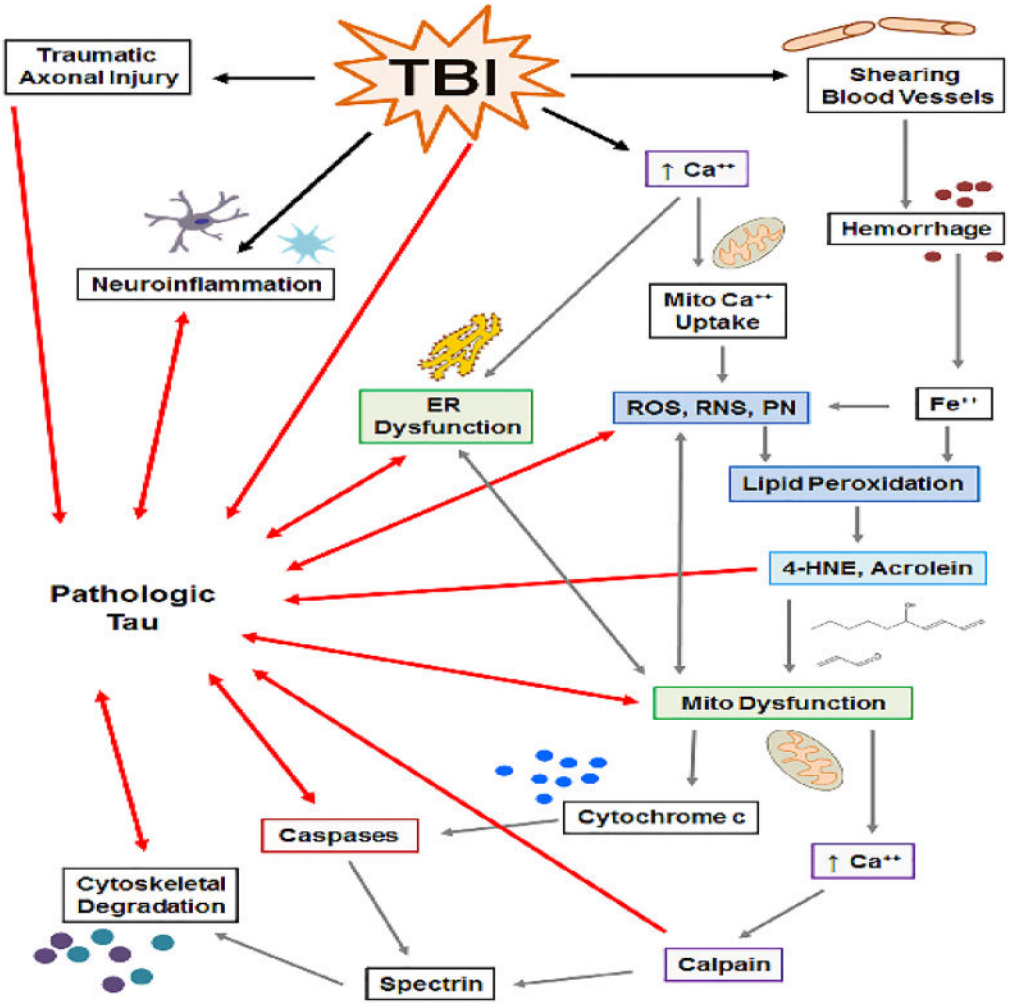

Figure 1. Interplay between TBI pathophysiology and mechanisms of pathologic tau formation demonstrating several cyclic relationships between the two

TBI induces traumatic axonal injury (TAI), neuroinflammation, increases in intracellular Ca^{++}, shearing of blood vessels, and tau hyperphosphorylation. TAI causes microtubule detachment of tau and tau mislocalization. Ca^{++} uptake by the endoplasmic reticulum (ER) and mitochondria leads to organelle dysfunction, including increases in ROS, RNS, and peroxynitrite (PN), initiation of lipid peroxidation (LP), and 4-HNE and acrolein formation. Hemorrhage-derived Fe^{++} catalyzes formation of reactive species and LP. 4-HNE and acrolein bind mitochondrial proteins, exacerbating dysfunction and generation of reactive species. Dysfunctional mitochondria enhance ER dysfunction, release cytochrome c, which activates caspases, and extrude Ca^{++} into the cytosol, which activates calpain. Calpain cleaves cytoskeletal proteins (e.g. spectrin) resulting in cytoskeletal degradation. Neuroinflammation, ER dysfunction, ROS/RNS/PN, mitochondrial dysfunction, caspase/calpain activation, and cytoskeletal degradation contribute to formation of pathologic tau (e.g. post-translational modification, conformational change, aggregation, etc.). In return, pathologic tau contributes to neuroinflammation, ER dysfunction, generation of ROS/RNS/PN, mitochondrial dysfunction, caspase activation and cytoskeletal degeneration.

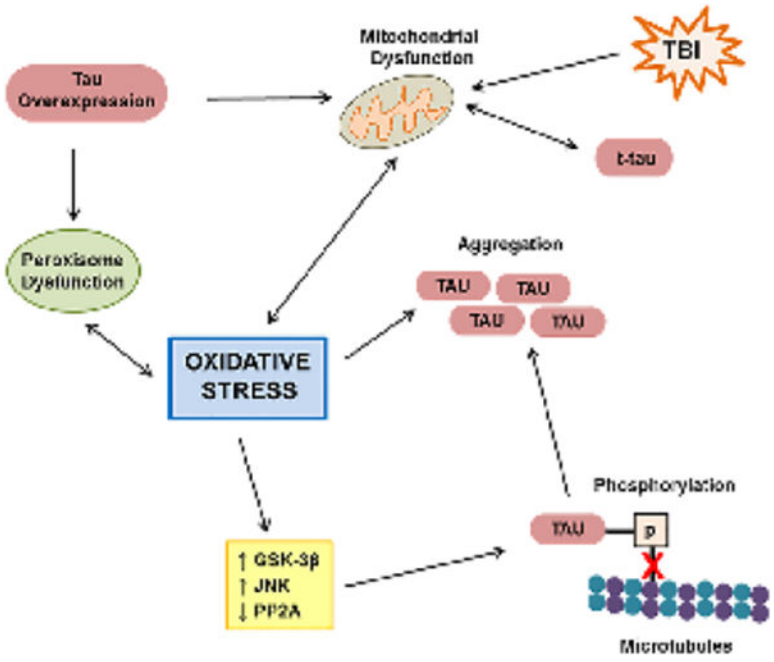

Figure 2. Select pathways demonstrating the role of oxidative stress in formation of tau pathology

TBI induces mitochondrial dysfunction, resulting in increased oxidative stress, which in turn, exacerbates mitochondrial dysfunction. Proteases downstream of mitochondrial dysfunction cleave tau, forming truncated tau (t-tau), which in turn, exacerbates mitochondrial dysfunction. Experimental tau overexpression induces mitochondrial and peroxisome dysfunction. Peroxisome dysfunction exacerbates oxidative stress and is enhanced by oxidative stress. Oxidative stress increases tau kinases activity (GSK-3β, JNK) and decreases tau phosphatase activity (PP2A), resulting in hyperphosphorylation of tau, which decreases tau binding of microtubules (red X), leading to tau aggregation, which is enhanced by oxidative stress itself.

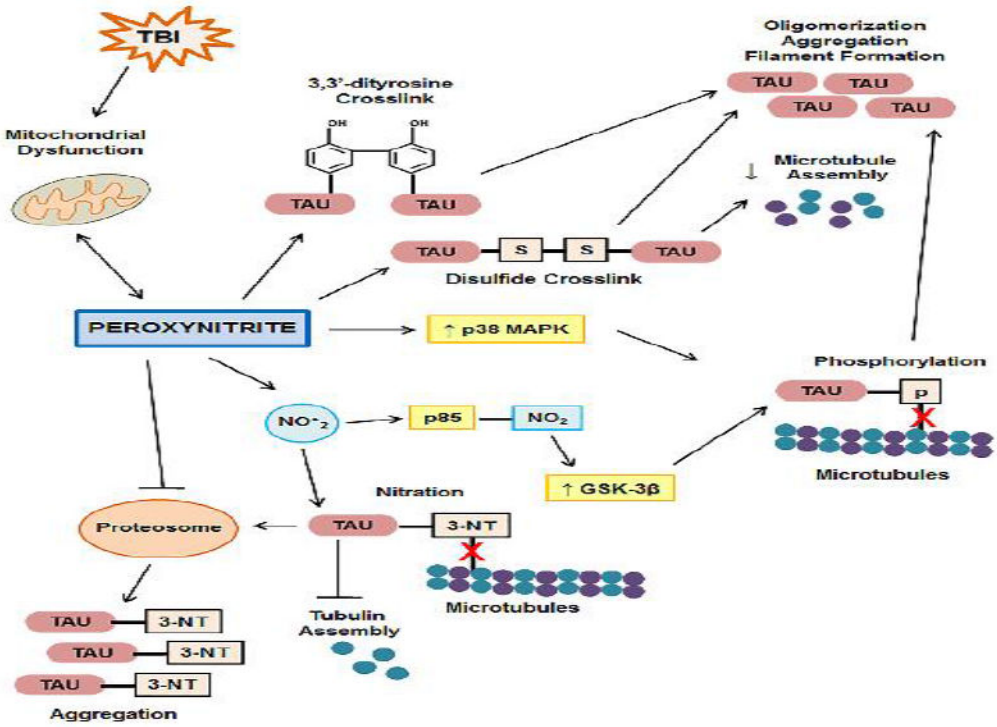

Figure 3. Mechanisms by which peroxynitrite leads to formation of tau pathology

TBI-induced mitochondrial dysfunction generates peroxynitrite (PN), which in turn, exacerbates mitochondrial dysfunction. PN nitrates or oxidizes tau forming 3,3′-dityrosine or disulfide crosslinks, respectively. Crosslinked tau induces tau oligomerization, aggregation and filament formation. Disulfide crosslinked tau also decreases microtubule assembly. PN increases the tau kinase, p38 MAPK. PN-derived $NO•_2$ increases the tau kinase, GSK-3β, through nitration of the GSK-3β upstream regulator, p85. Increased tau kinase activity results tau hyperphosphorylation which decreases binding of tau to microtubules (red X). $NO•_2$ directly nitrates tau at the 3 position of tyrosine, generating tau-3NT. Tau-NT has decreased microtubule binding properties (red X) and inhibits tubulin assembly. Tau-3NT is preferentially degraded by the proteasome, an organelle that's function is inhibited by PN, resulting in build-up and aggregation of tau-NT.

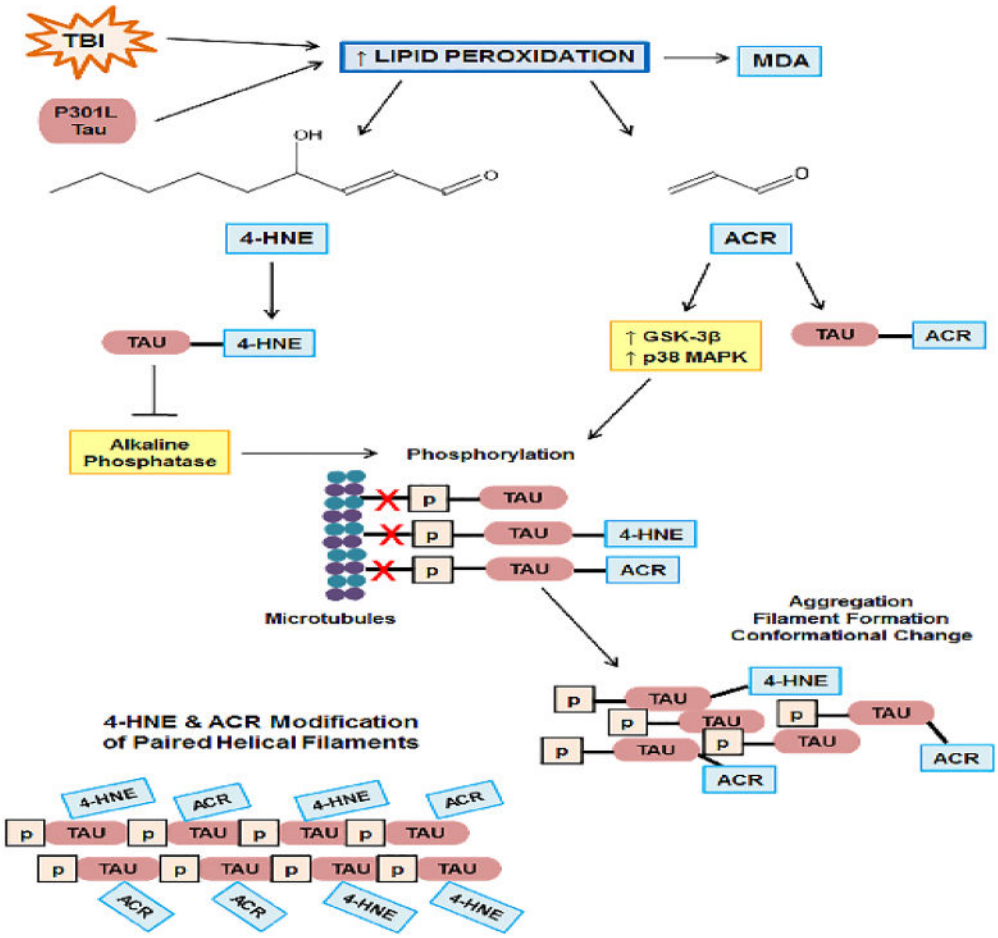

Figure 4. The role of 4-hydroxynonenal (4-HNE) and acrolein (ACR) in formation of tau pathology

TBI induces lipid peroxidation (LP). Overexpression of P301L mutant also increases LP as measured by the LP-derived, malondialdeyde (MDA). LP results in the formation of the neurotoxic aldehydes, 4-HNE and ACR, which covalently bind proteins, including tau, causing protein dysfunction. ACR increases activity of the tau kinases, GSK-3β and p38 MAPK, and 4-HNE-modified tau inhibits alkaline phosphatase, resulting in hyperphosphorylation of tau, 4-HNE modified-tau, and ACR modified-tau, which decreases binding of tau to the microtubules (red X), leading to conformational changes, aggregation, and filament formation. Paired helical tau filaments are extensively modified by 4-HNE and ACR.

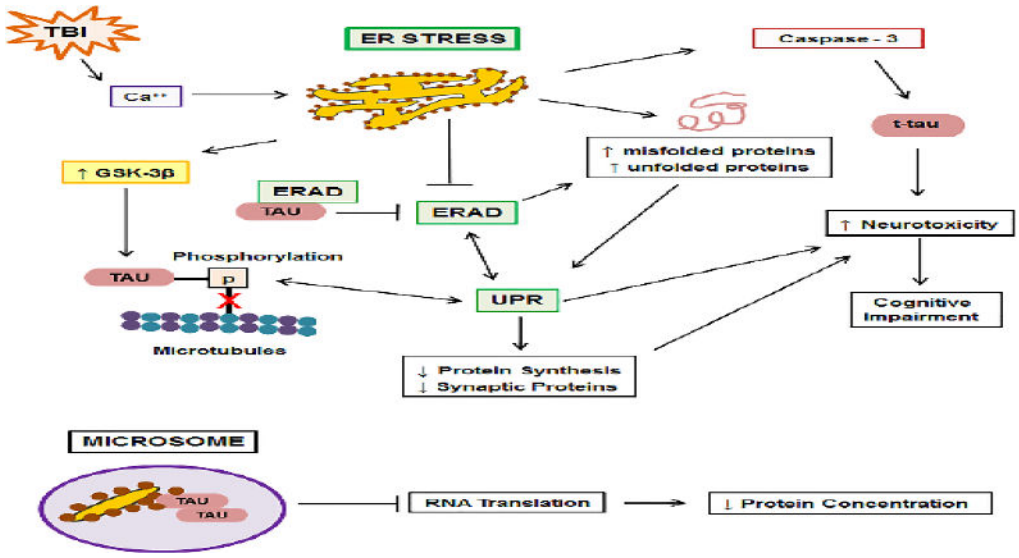

Figure 5. Mechanisms by which endoplasmic reticulum (ER) stress and dysfunction can lead to formation of tau pathology

Following TBI increases in intracellular Ca^{++}, derived extracellularly or from dysfunctional mitochondria, induce ER stress. ER stress increases activity of the tau kinase, GSK-3β, resulting in tau hyperphosphorylation, which decreases binding of tau to microtubules (red X). ER stress results in the buildup of misfolded and unfolded proteins, including tau, both directly and through inhibition of ER-associated degradation (ERAD). Tau itself inhibits ERAD through associations with the ERAD heterocomplex. ERAD and buildup of misfolded and unfolded proteins activate the unfolded protein response (UPR), which in turn, activates ERAD. The UPR results in increases in tau phosphorylation, which in turn, activate the UPR. UPR activation increases neurotoxicity and behavioral impairment and decreases synthesis of proteins, including synaptic proteins. ER stress activates the protease, caspase-3, resulting in tau truncation (t-tau) and increased neurotoxicity. Alzheimer's disease-derived microsomes contain ER fragments and ribosomes which strongly associate with oligomeric tau, resulting in decreased RNA translation and decreased protein concentrations.

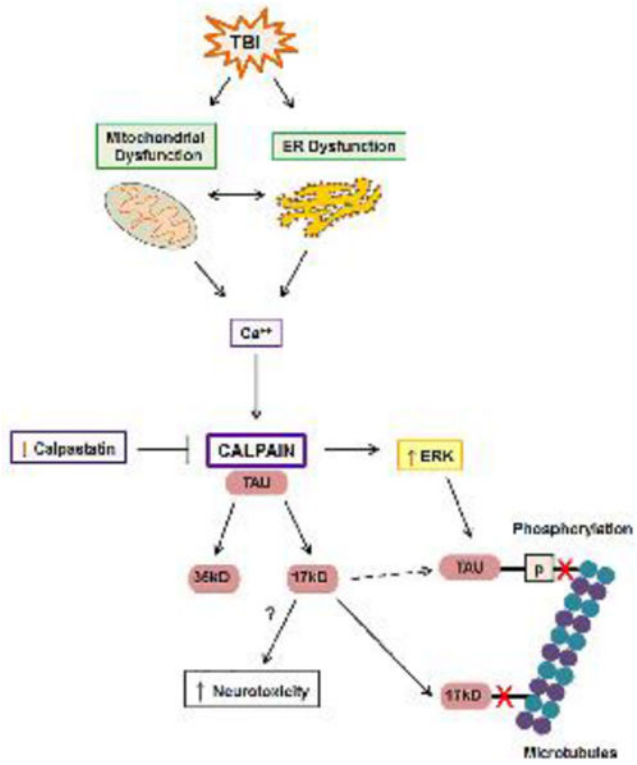

Figure 6. The role of calpain in the formation of pathologic tau

TBI-induced increases in intracellular Ca^{++} derived extracellularly or from dysfunctional mitochondria and ER, activate the protease calpain. The endogenous calpain inhibitor, calpastatin, is decreased in tauopathies such as Alzheimer's disease. Calpain cleaves tau into 35kD and 17kD fragments. The 17kD tau fragment forms prior to increases in tau phosphorylation and may directly enhance tau phosphorylation (dotted arrow). Calpain induces activation of the tau kinase, ERK, resulting in hyperphosphorylation of tau, which decreases binding of tau to microtubules. 17kD has a decreased affinity for microtubule binding (red X) and may be neurotoxic.

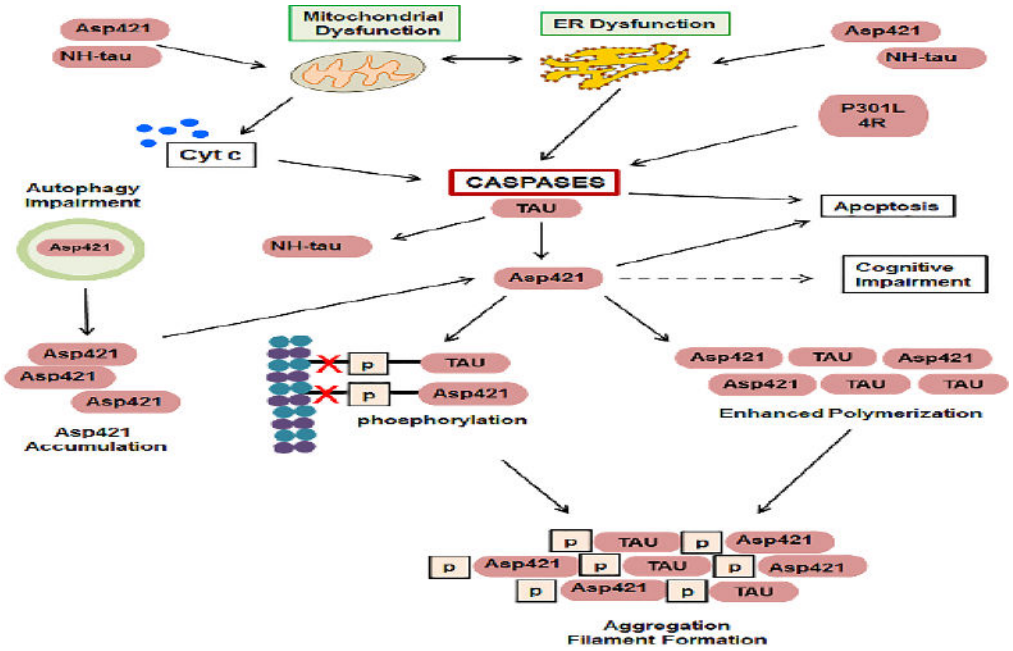

Figure 7. Mechanisms in which caspases play a central role in the formation of pathologic tau

Following TBI, caspases are activated downstream of ER dysfunction and mitochondrial release of cytochrome c. Overexpression of P301L tau or 4R also induce caspases activation. Caspases, including caspase-3, cleave tau at Asp421, but N-terminal caspase-cleavage also occurs (NH-tau). Caspases-cleaved tau can further exacerbate mitochondrial and ER dysfunction. Asp421 is preferentially degraded by autophagy, therefore, impairment to autophagy results in accumulation of Asp421 tau. Asp 421 tau leads to enhanced tau polymerization and phosphorylation, resulting in decreased binding of tau to microtubules (red X) and increased aggregation and filament formation. Caspase activation and Asp421 expression lead to apoptosis. Asp421 precedes cognitive impairment.

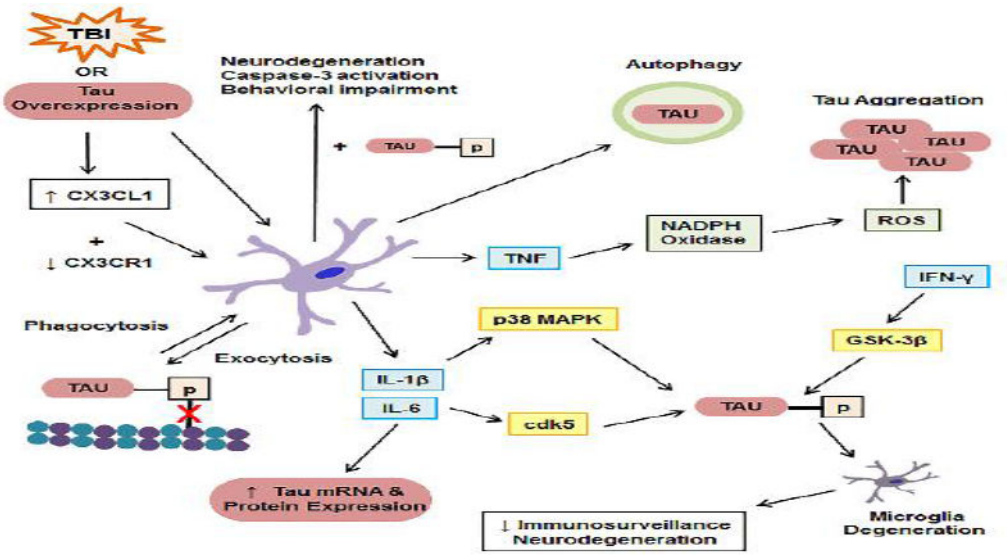

Figure 8. Proposed role for microglia in the formation of pathologic tau

TBI and experimental tau overexpression activate microglia. Microglia can be activated through decreases in the microglia receptor, CX3CR1, and increases in the neuronally-derived ligand, CX3CL1, which is elevated following TBI and experimental tau overexpression. Microglial secretion of IL-6 increases tau mRNA and protein expression. Microglial secretion of IL-1β and IL-6 increases tau kinase activity (p38 MAPK and cdk5), as does the presence of the cytokine IFN-γ (GSK-3β), resulting in tau hyperphosphorylation, which decreases binding of tau to microtubules (red X), and microglial phagocytosis of hyperphosphorylated tau. Microglia spread tau in a prion-like manner through phagocytosis and exocytosis. Hyperphosphorylated tau induces microglia degeneration, resulting in decreased immunosurveillance and increased neurodegeneration. The microglia-derived cytokine, TNF, activates NADPH Oxidase, increasing ROS and formation of tau aggregates. The presence of phosphorylated tau enhances the effect of activated microglia on neurodegeneration, caspase-3 activation, and behavioral impairment. Activated microglia induce autophagy, resulting in autophagic degradation of tau.

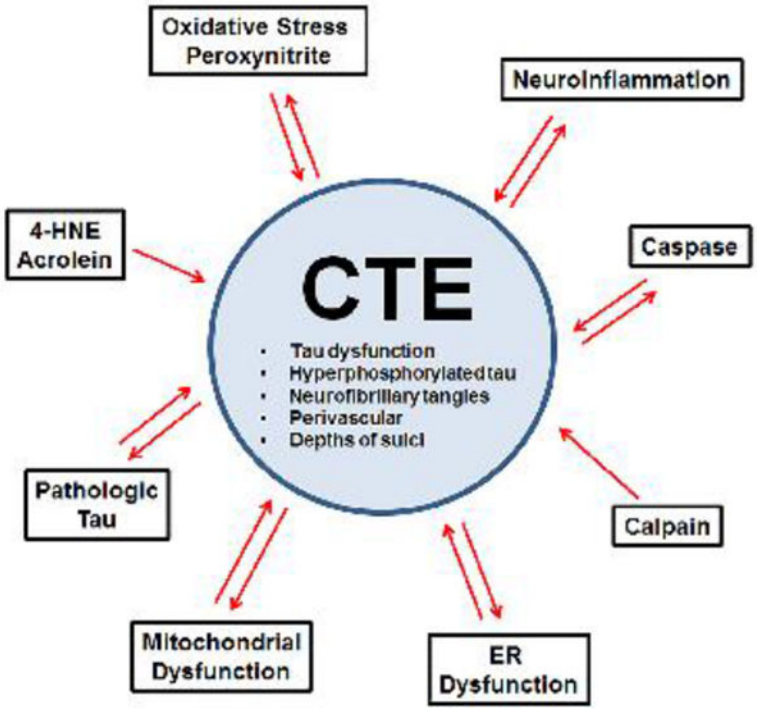

Figure 9. Simplified schematic demonstrating proposed pathological mechanisms that can contribute to CTE development and pathologic mechanisms that can be exacerbated by CTE

Examples of pathologic tau include hyperphosphorylation, nitration, oxidation, aggregation, filament formation, etc. For simplicity, relationships between pathologic mechanisms are not included in this figure, but are detailed elsewhere (Fig 1– 8).