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Review Article

Does neuroinflammation drive the relationship between tau hyperphosphorylation and dementia development following traumatic brain injury?

Lyndsey E. Collins-Praino, Frances Corrigan *

Translational Neuropathology Lab, Discipline of Anatomy and Pathology, School of Medicine, University of Adelaide, Adelaide, Australia

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ABSTRACT

A history of traumatic brain injury (TBI) is linked to an increased risk for the later development of dementia. This encompasses a variety of neurodegenerative diseases including Alzheimer's Disease (AD) and chronic traumatic encephalopathy (CTE), with AD linked to history of moderate-severe TBI and CTE to a history of repeated concussion. Of note, both AD and CTE are characterized by the abnormal accumulation of hyperphosphorylated tau aggregates, which are thought to play an important role in the development of neurodegeneration. Hyperphosphorylation of tau leads to destabilization of microtubules, interrupting axonal transport, whilst tau aggregates are associated with synaptic dysfunction. The exact mechanisms via which TBI may promote the later tauopathy and its role in the later development of dementia are yet to be fully determined. Following TBI, it is proposed that axonal injury may provide the initial perturbation of tau, by promoting its dissociation from microtubules, facilitating its phosphorylation and aggregation. Altered tau dynamics may then be exacerbated by the chronic persistent inflammatory response that has been shown to persist for decades following the initial impact. Importantly, immune activation has been shown to play a role in accelerating disease progression in other tauopathies, with pro-inflammatory cytokines, like IL-1β, shown to activate kinases that promote tau hyperphosphorylation. Thus, targeting the inflammatory response in the sub-acute phase following TBI may represent a promising target to halt the alterations in tau dynamics that may precede overt neurodegeneration and later development of dementia.

Contents

* Corresponding author.
E-mail addresses: lyndsey.collins-praino@adelaide.edu.au (L.E. Collins-Praino), frances.corrigan@adelaide.edu.au (F. Corrigan).

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1. Introduction

Traumatic brain injury (TBI) is a major cause of disability and mortality worldwide. In the United States, it is estimated that 1.7 million people sustain a TBI each year (Frieden et al., 2014), with estimates that up to 60 million people worldwide may be affected annually (Feigin et al., 2013). A growing body of research has highlighted that the consequences of TBI may not just be limited to the acute stage, as a history of TBI is linked to the later development of neurodegeneration and dementia. A recent report has highlighted that the dementia related to a history of TBI may be caused by a persistent neuroinflammatory response which does not resolve after the initial impact, which promotes ongoing neuronal loss and synaptic dysfunction (Faden and Loane, 2015). In some individuals, this neuronal loss may eventually lead to a presentation that aligns with Alzheimer's disease (AD) or chronic traumatic encephalopathy (CTE), tauopathies that are characterized by the presence of neurofibrillary tangles (NFTs) and increased levels of oligomeric tau. The exact mechanisms via which TBI promotes tauopathy and its role in the later development of dementia are yet to be fully determined. However, it is likely that the persistent inflammatory response may play a role, as inflammation is known to promote tau phosphorylation and accelerate disease progression in other animal tauopathy models. Understanding the link between TBI, neuroinflammation and accumulation of abnormal species may be a crucial first step for developing timely interventions that may prevent later neurodegeneration.

2. Traumatic brain injury

TBI results from the head impacting with an object or from acceleration/deceleration forces, with the resultant translational and/or rotational forces damaging the blood vessels, axons, nerve cells and glia of the brain in a focal, multifocal or diffuse pattern of involvement (Finnie and Blumbergs, 2002). This primary injury can be either focal, as in skull fractures, intracranial hemorrhages, and contusions, or diffuse, with the acceleration/deceleration forces that result from violent unrestrained head movement, such as in a motor vehicle accident, associated with diffuse axonal injury (DAI) (Abou-Hamden et al., 1997). Whereas this primary injury is not reversible, its delayed consequences and the secondary injury cascade it sets in motion over minutes to days are potentially reversible (Graham et al., 2000), with increasing recognition that some aspects of the secondary injury cascade may even persist for decades after the initial insult (Faden et al., 2016). Injury factors that contribute to this phenomenon include metabolic changes, edema formation, calcium influx, increased oxidative stress, excitotoxicity, inflammation and, ultimately, cell death via necrosis or apoptosis (Saatman et al., 1996).

TBI can be classified into three categories based on the immediate effects after the injury: mild, moderate or severe TBI, typically based on the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974). Mild TBI leads to unconsciousness of less than 30 min and GCS of 13 and above, while moderate and severe TBI may result in unconsciousness of more than 30 min, GCS of 9–12 for moderate and below 8 for severe, comatose state and even disability (Teasdale and Jennett, 1974). Although concussion and mTBI have been used interchangeably, it has been suggested that concussion is its own entity, reflecting a brain injury induced by biomechanical forces resulting in the initiation of a complex pathophysiological cascade that, importantly, does not necessarily lead to a loss of consciousness and does not cause abnormalities on standard structural imaging (McCrory et al., 2013).

3. Link between TBI and dementia

A growing body of epidemiological evidence has suggested that TBI may increase the risk of dementia (Mortimer et al., 1991; Guo et al., 2000; Fleminger et al., 2003; Wang et al., 2012; Lee et al., 2013; Nordstrom et al., 2014), with suggestions that a dose-dependent relationship might exist, in which risk of dementia increases with TBI severity (Plassman et al., 2000). It should be noted, however, that even a single mild TBI may increase long-term dementia risk (Lee et al., 2013). A recent retrospective study by Gardner and colleagues (2014) looked at the link between TBI and dementia development in 164,661 individuals over the age of 55, with a history of TBI or non-brain trauma, over a follow-up period of 5–7 years, and found that prior moderate or severe TBI can increase the risk of dementia with a minimum hazard ratio of 1.3 (Gardner et al., 2014). In accordance with these results, a retrospective study of patients in the National Insurance Database within Taiwan found 2.66% of TBI patients developed dementia compared to 1.53% of non-TBI patients within a 5 year follow-up period, representing a 1.68 fold higher risk (Wang et al., 2012). A previous history of TBI may also lower age of dementia onset, with Nordstrom et al. finding a strong association between TBI and onset of dementia before 65 years of age in a cohort study of Swedish men conscripted for military service, although it should be noted that the number of cases of young onset dementia were quite low (Nordstrom et al., 2014). In accordance with this, age of onset of cognitive impairment in older adults was found to be reduced in those with a past history of TBI compared to those without (Li et al., 2016). Nonetheless, it is important to note that many of these studies are retrospective and thus may be influenced by difficulties with recall and lack of baseline cognitive functioning measurements, and indeed not all studies have reported a link between TBI and later dementia risk (Crane et al., 2016). As such, additional studies and meta-analyses investigating this link are critically needed.

Furthermore, the type of dementia associated with TBI is less clear and may depend on the type of insult involved. Although it remains to be systematically studied, in recent years, there has been growing support for the hypothesis that a single moderate or severe TBI increases the risk of developing late-onset Alzheimer's disease (AD), while repetitive mild TBI is associated with an elevated risk of chronic traumatic encephalopathy (CTE), although the reason behind this has not yet been biologically explained (Smith et al., 2013; Washington et al., 2016). Both AD and CTE share common features in widespread neuronal loss associated with the deposition of tau, but also significant differences as summarized in Table 1. The link between moderate-severe TBI and AD has been supported by two key meta-analyses of case-control studies by Mortimer et al. (1991) and Fleminger et al. (2003), which found significant associations between moderate-severe TBI and AD, reporting pooled odds ratios of 1.82 (95% confidence interval (CI) 1.26-2.67) and 1.58 (95% CI 1.21-2.06), respectively. Conversely, CTE has been linked to a history of repeated concussion, as seen in veterans of military service, professional NFL players and rugby players, amongst others (McKee et al., 2009). Nonetheless, the strongest links are between TBI and dementia, which describes brain atrophy as a result of ongoing neuronal loss with associated cognitive decline, (Faden and Loane, 2015), rather than a specific type like AD or CTE, and may reflect the heterogeneity of the initial impact and its interaction with genetic and lifestyle risk factors. Importantly, TBI is known to drive the accumulation of pathological proteins including tau aggregates (Johnson et al., 2012) that may facilitate the later development of dementia. (Johnson et al., 2012)

Table 1
Comparison of the pathological features and presentation of Alzheimer's Disease and Chronic Traumatic Encephalopathy.

	Alzheimer's disease	Chronic traumatic encephalopathy
Pattern of tau deposition	First observed in the transentorhinal region (stages I and II), spreads to the limbic regions in stages III and IV and then extends uniformly throughout the neocortex. More uniform cortical distribution than seen with CTE, with involvement particularly of layers V and VI of the cortex (Braak and Braak, 1991)	Initially, NFTs are seen in the superficial cortical layers (layers II and III), at the base of sulci and surrounding blood vessels. These NFTs extend through the cerebral cortex, starting with patchy involvement (Stage 1) to widespread pathology affecting most of the cortex (Stage IV), with involvement of other regions such as the hippocampus and entorhinal cortex in later stage disease (Stage III and IV) (Stein et al., 2014)
Amyloid beta plaques	Initially involves the isocortex, spreading to additional allocortical deposits in regions like the hippocampus, then the subcortical nuclei, the upper brainstem and, eventually, the pons (Thal et al., 2002)	Not a consistent feature reported in ~50% of cases, with the incidence of neuritic Aβ plaques increasing with increasing severity of tauopathy (Stein et al., 2015b)
TDP-43	Detected in 25–50% of cases (Wilson et al., 2011)	Abnormal TDP-43 inclusions are a consistent feature of CTE and occur in over one-half of stage I cases and in all of stage IV cases (Stein et al., 2014)
Pattern of brain atrophy	Marked atrophy of the medial temporal lobe, including the hippocampus, entorhinal cortex and amygdala; eventual involvement of other cortical areas, including the parietal and frontal lobes (Probst et al., 1999)	Atrophy is pronounced in the frontal, temporal and medial lobes. Atrophy of white matter, particularly corpus callosum, with thinning of hypothalamic floor (McKee et al., 2016)
Symptoms	Memory loss, disorientation, impaired judgment, loss of motivation, mood and personality changes, increased anxiety (Scheltens et al., 2016)	Memory loss, confusion, impaired judgement, loss of impulse control, aggression, depression, anxiety, suicidality (Stein et al., 2015a)

4. Role of tau in dementia

Tau was first discovered as a microtubule associated protein (MAP) capable of stimulating tubulin assembly in the brain (Weingarten et al., 1975). In recent years, a growing number of studies have recognized the critical role that tau plays in dementia. CTE, for example, is characterized by a unique pattern of abnormally phosphorylated tau (ptau) deposition, with neurofibrillary tangles (NFTs) aggregating in the superficial cortical layers of the brain, particularly at the base of the sulci and surrounding blood vessels (McKee et al., 2009). The accumulation of abnormal tau is associated with the eventual development of cerebral atrophy, enlargement of the lateral and third ventricles, thinning of white matter pathways, such as the corpus callosum, scarring of the cerebellum, and degeneration of neurons in areas such as the cerebral cortex (Corsellis et al., 1973).

Conversely, in AD, intracellular NFTs have been shown to preferentially distribute in layers V and VI of the cerebral cortex (Hof et al., 1992). These NFTs, which tend to be smaller than those seen in CTE, spread through the brain following a stereotyped pattern of six stages (Braak and Braak, 1991) Tau pathology in AD has been shown to lead to a disruption of synaptic function (Gomez-Isla et al., 1997; Spires-Jones and Hyman, 2014). Levels of tau, particularly of soluble tau oligomers, are increased early in AD, before NFTs and clinical symptoms appear (van Helmond et al., 2010). Furthermore, tau pathology may correlate better with cognitive impairment than amyloid plaques (Nelson et al., 2012; Rolstad et al., 2015). CSF levels of tau phosphorylated at 231 ($ptau_{231}$) found that levels were higher in patients with mild cognitive impairment, and that increased levels of $ptau_{231}$ were predictive of conversion to AD in patients with mild cognitive impairment (Buerger et al., 2002). Furthermore, an a small study of 22 patients with AD, number of NFTs within the CA1 region of the hippocampus and entorhinal cortex were significantly associated with cognitive status assessed via a mini-mental state exam, whereas Aβ burden had no additional predictive value beyond its interactions with NFTs (Giannakopoulos et al., 2003). A more recent study by Ossenkoppele and colleagues (2016) reported that tau pathology, as measured by the novel PET tracer ^{18}F-AV1451, was found predominantly in brain areas that are critical for cognitive functions affected in AD and strongly co-localized with hypo-metabolic regions (Ossenkoppele et al., 2016). In contrast, amyloid-β (Aβ) pathology, as measured by the PET tracer ^{11}C-PiB PET, was ubiquitously present throughout the brain, in both clinically relevant areas associated with a patient's presentation and non-relevant areas (Ossenkoppele et al., 2016). For example, in patients presenting with predominantly amnestic symptoms, Aβ was found both within the medial temporal lobe, as would be expected, but also in the frontal cortex, a region not associated with the patient's symptoms (Ossenkoppele et al., 2016). Hence, tau pathology appears to play a significant role in the development of cognitive impairment associated with dementia.

Tau is primarily a neuronal protein encoded by a single gene located on the long arm of chromosome 17 (position 17q21) (Neve et al., 1986). This single gene can result in six major isoforms in the adult human CNS due to alternative splicing of its mRNA (Goedert et al., 1989). Tau contains a microtubule (MT)-binding domain in the carboxy-terminal (C-terminal) of the protein, which is composed of repeats of a highly conserved tubulin-binding motif (Lee et al., 1989). The six isoforms differ from one another in terms of the number of tubulin-binding repeats that they contain in this region (as well as by the presence or absence of one or two 29-amino acid long inserts at the acidic N-terminal region of the protein) (Ballatore et al., 2007). The microtubule-binding domain contains four imperfect repeat domains (31–32 residues each), encoded by exons 9–12. Alternative splicing of exon 10 leads to isoforms with either three (3R) or four (4R) repeats (Andreadis, 2012). While the proportion of isoforms expressed can vary during development, normally, the ratio of 3R to 4R is 1:1 in the adult brain, although this may shift in certain disease states (e.g. frontotemporal dementias (FTDs) (Goedert and Spillantini, 2011).

The normal function of tau is to promote elongation and stabilization of microtubules (MTs), with this dependent on its phosphorylation state. The ability of tau to bind to the MTs is regulated predominantly by phosphorylation at a number of serine/threonine binding sites on either side of the MT-binding domain (Mazanetz and Fischer, 2007). While in a low or non-phosphorylated state, tau stably binds to the microtubule; conversely, ptau has lower affinity for the MTs, leading to it becoming detached (Lindwall and Cole, 1984; Hanger et al., 2009). Tau phosphorylation is complex, as tau contains 80 potential serine/threonine and 5 potential tyrosine sites on its longest isoform (Tau_{441}), with phosphorylation occurring at least 30 of them (Mendoza et al., 2013). It is thought that frequent cycles of

binding and detachment of tau from the MTs are needed to allow effective axonal transport (Terwel et al., 2002), which is important for movement of signaling molecules, trophic factors and other essential cellular constituents, including organelles (Ballatore et al., 2007). The phosphorylation state of tau is thus highly dependent on the actions of kinases and phosphatases. Numerous tau kinases have been described, with protein kinase A (PKA), protein kinase C (PKC), glycogen synthetase kinase-3β (GSK-3β), casein-kinase 1 (CK1), the microtubule-affinity-regulating kinase (MARK), mitogen-activated protein kinase (MAPK), calcium/calmodulin-dependent protein kinase II (CAMKII) and cyclin-dependent kinase 5 (CDK5) receiving particular attention (Wang et al., 2013b). While several serine/threonine protein phosphatases (i.e. PP1, cdk2, and cdk5 (Drewes et al., 1992; Baumann et al., 1993; Hanger et al., 2009)), along with PP2A, PP2B and PP5, have all been shown to dephosphorylate tau (Wang et al., 2013b), PP2A appears to be the principal tau phosphatase *in vivo*, accounting for approximately 70% of human brain phosphatase activity (Liu et al., 2005).

In tauopathies, such as AD and CTE, tau becomes hyperphosphorylated, allowing its abnormal aggregation and leading to toxicity, both due to a loss of its normal function, as well as gain of new pathological functions (Medina et al., 2016). While tau in the healthy brain contains 2–3 mol of phosphate per mole of the protein (Ksiezak-Reding et al., 1992; Kopke et al., 1993), this phosphorylation level is increased 3–4 fold in AD (Kopke et al., 1993). Hyperphosphorylation promotes the detachment of tau from MTs, which destabilizes the MTs, thus inhibiting axonal transport between the soma and synapse, eventually leading to neuronal injury (Bunker et al., 2004). Indeed, treatment with microtubule stabilization drugs has been shown to be beneficial in a number of pre-clinical models of tauopathy (Zhang et al., 2005; Brunden et al., 2010; Zhang et al., 2012). For example, treatment with Epothilone D was able to improve microtubule density and axonal integrity, with an associated improvement in spatial memory on the Barnes Maze, in PS19 mice (Zhang et al., 2012). Following detachment from MTs, tau may mislocalize from the axon to the somatodendritic compartment, where it may contribute to synaptic dysfunction (Hoover et al., 2010; Koleske, 2013). As such, one potential causative factor for the link between tau hyperphosphorylation and cognitive impairment may be destabilization of MTs and impaired axonal transport.

Detachment of tau from microtubules also increases the amount of soluble tau present in the neuron, which makes it prone to self-aggregation and polymerization, leading to the formation of tau oligomers (Maeda et al., 2007). These oligomers combine and further aggregate to form paired helical filaments (PHFs), which then assemble to form NFTs, as seen in AD and CTE. Recent evidence suggests that it is tau oligomers, and not NFTs, that are toxic in AD and other neurodegenerative conditions (Lasagna-Reeves et al., 2011, 2012; Maeda et al., 2007; Patterson et al., 2011). Indeed, oligomers of recombinant full-length human tau protein led to synaptic and mitochondrial dysfunction and impaired memory consolidation when injected subcortically in wild-type mice, while tau fibrils and monomers did not result in impairment (Lasagna-Reeves et al., 2011). Evidence also suggests that tau oligomers may act as templates for the misfolding of native tau, thereby seeding the spread of the toxic forms of the protein (Gerson and Kayed, 2013).

It is now well known, from a variety of study models, that tau has the ability to transfer between cells both *in vitro* and *in vivo* (Wu et al., 2016). There is strong evidence that this transfer may occur via the release of tau extracellularly from neurons. Tau is present in the cerebrospinal fluid (CSF) and interstitial fluid (ISF) of both tau transgenic mouse lines and AD brains (Kurz et al., 1998; Barten et al., 2011). Additionally, tau has been shown to be released from primary cultures of cortical neurons in response to activity (Pooler et al., 2013). Once tau is released, it can be internalized by neighboring recipient cells, where is can lead to the generation of more pathological tau (Michel et al., 2014; Yamada et al., 2014). Pathological tau can then be passed on to additional recipients, leading to the abnormal propagation of tau throughout the brain (Wu et al., 2016). In support of this, researchers have recently reported the ability of tau oligomers to enter and exit cells, propagating from disease-affected regions to unaffected areas, leading to the spread of pathology throughout the brain (Lasagna-Reeves et al., 2012; Gerson and Kayed, 2013). While the exact mechanisms that may lead to tau release from cells are not yet known, Wu and colleagues (2016) used novel optogenetic and chemogenetic techniques to demonstrate that increasing neuronal activity may enhance tau release and spread (Wu et al., 2016). In an *in vitro* model system, primary neurons from a wild-type mouse transfected with channelrhopsin (ChR2) and fluorescently-tagged hTau expressing viral vectors showed an increase of 250% of tau in the media following 30 min of stimulation with a blue light with a wavelength of 473 nm (Wu et al., 2016). *In vivo*, stimulation with both an optogenetic (CHR2 depolarization by blue light with a wavelength of 473 nm) and chemogenetic (designer receptor exclusively activated by designer drug, or DREADD) approach resulted in an increase in tau pathology in the stimulated hippocampus or entorhinal cortex compared to the non-stimulated side (Wu et al., 2016). Interestingly, this tau does not form higher aggregates, even when cultured for >20 days, suggesting that the tau that is released is likely to be soluble, and, perhaps, oligomeric (Pooler et al., 2013; Yamada et al., 2014; Wu et al., 2016). The release of tau in response to neuronal activity may be particularly relevant in AD, as cells in the AD brain have been shown to be hyper-excitable (Busche et al., 2008, 2012; Hall et al., 2015). As such, there is emerging evidence to suggest that aggregation of tau into oligomers plays an important role in disease progression, as these tau species are mobile and facilitate spread of disease, while also disrupting synaptic function.

The site at which tau is phosphorylated also appears to be important for its ability to promote disease progression. Certain sites, such as Thr212, Ser214, Thr231, Ser235, and Ser262, are the major sites that inhibit tau binding to microtubules (Alonso et al., 2010). Indeed, an *in vitro* study by Sengupta and colleagues demonstrated that phosphorylation of tau at Ser262, Thr231 and Ser235 inhibited the ability of tau to bind to MTs by 35%, 25% and 10%, respectively (Sengupta et al., 1998). Following the generation of abnormal hyperphosphorylation at the Thr212, Thr231 and Ser262 sites of tau by site-directed mutation, caspase-3 activation and neurodegeneration were triggered, indicating a gain of tau toxicity (Alonso et al., 2010). In a *post mortem* study in individuals with either mild cognitive impairment (MCI) or AD, high expression of phosphorylation at the Ser422 site was identified as an early disease marker, correlating with degree of cognitive decline and increased degeneration of cholinergic basal forebrain neurons prior to NFT formation (Vana et al., 2011). Different phosphorylation sites also appear to be associated with different aggregation states of tau. For example, while phosphorylation at Thr231 precedes tau oligomerization, increased phosphorylation of Ser202 and Thr205 are related to later changes, such as the conversion to protofilaments and filaments (Lasagna-Reeves et al., 2012 1129). Indeed extracellular NFTs, consisting of a high ratio of filamentous tau, most prominently stain with antibodies to AT8 (pS199/pS202/pT205), AT100 (pT212/pS14) and PHF-1 (pS396/pS404) (Augustinack et al., 2002).

5. Evidence for alteration in tau dynamics following TBI

The effects of TBI on aberrant tau phosphorylation have been most clearly linked with a history of repeated concussion, due to its role in the development of CTE (McKee et al., 2013; Stein et al., 2014; McKee et al., 2015; Stein et al., 2015a). By definition, CTE is a tauopathy, as it is currently only diagnosed post-mortem and is recognized by a specific pattern of tau deposition, with NFTs, thorned astrocytes and dystrophic neurites deposited perivascularly and concentrated at the base of sulci (Omalu et al., 2005; McKee et al., 2016). In Stage I disease, there is limited, focal hyperphosphorylated tau deposition, mainly in the frontal cortex, whilst Stage IV is characterized by widespread NFT pathology, affecting most regions of the cerebral cortex and medial temporal lobe, accompanied by prominent astrocytic tangles, gliosis and neuronal loss (Stein et al., 2014).

Cumulative exposure to trauma, as in the number of years of engaging in contact sport, rather than the number of concussions, is linked to the severity of tau phosphorylation, suggesting that repetitive head injury encompassing sub-concussive impacts plays a primary role in the development of disease (Huber et al., 2016). CTE has been reported in relation to a number of contact sports, including American football, wrestling, soccer, ice hockey, rugby, as well as poorly controlled epilepsy, head banging behaviors, and military service, suggesting that trauma of diverse origin is capable of instigating CTE (Geddes et al., 1996; Geddes and Whitwell, 2004; Omalu et al., 2006, 2010, 2011; McKee et al., 2013). However, the relative incidence of the disease is not yet known.

Clinical studies on the effects of concussion acutely on tau phosphorylation are rare, with one report finding 4/6 cases who died within 6 months following a concussion positive for NFTs around small blood vessels at the depth of sulci (McKee et al., 2014). Pre-clinical models have demonstrated that repeated injury can lead to aberrant tau phosphorylation (Kane et al., 2012; Luo et al., 2014; Petraglia et al., 2014; Du et al., 2016; McAteer et al., 2016; Tan et al., 2016). For example, a single mTBI increased ptau at 1 month, but not 6 months post-injury, whilst repeated mTBI mice that received six concussive impacts daily for 6 days had a more marked neuroinflammatory response with elevated ptau (AT8) seen in the cortex at 6 months post-injury (Petraglia et al., 2014). This study utilized a model of closed head injury where a tip impacted the skull, which was protected by a metal helmet at a velocity of 5 m/s (Petraglia et al., 2014). Luo et al. also demonstrated diffuse AT8 immunoreactivity 6 months following rmTBI induced by a closed head injury induced by a rubber tip impacting the unprotected skull (3 injuries, 24 h apart) (Luo et al., 2014).

However, an increase in tau phosphorylation has not consistently been reproduced (Mouzon et al., 2012; Mannix et al., 2013; Winston et al., 2016). Mannix et al. noted no increase in ptau (AT8, AT180 or PHF-1) within the cortex or hippocampus at 6 months post-injury, in their model of rmTBI, where mice were subjected to 7 injuries within 9 days utilizing a modified version of the weight drop model with some rotation (Mannix et al., 2013). Lack of accumulation of ptau may be related to the fact that no chronic white matter changes were seen in their model, unlike that seen in human studies (McKee et al., 2014), as white matter damage is thought to be crucial for the development of tauopathy. Mouzon et al. similarly utilized a closed head injury model, but with 5 hits spaced 48 h apart, and also found no difference in levels of cortical or hippocampal ptau (CP13, RZ3, PHF1) at 6 or 12 months post-injury (Mouzon et al., 2012). There are differences in murine and human tau, as murine tau is resistant to the forming of neurotoxic aggregates *in vivo* (Hanes et al., 2009). Indeed, when the closed head injury model was replicated in aged htau mice, who express human tau, repeat, but not single, injury was associated with a trend towards increased ptau pathology in neuronal cell body and somatodendritic compartments compared to shams (Ojo et al., 2013). It is evident there is complex relationship between repeated concussion and the promotion of tau pathology and the interpretation of pre-clinical models is hampered by the disparities between the number of injuries induced and the spacing between injuries utilized in different studies. Indeed a number of different schedules have been reported, ranging from daily injuries for 5 days (Kane et al., 2012) or 6 days (Petraglia et al., 2014), 3 injuries spaced 24hrs (Luo et al., 2014) or 5 days apart (Tan et al., 2009; McAteer et al., 2016), 5 injuries with 48hr intervals (Mouzon et al., 2014).(Mouzon et al., 2012), or even 10 injuries over 12 days (Kane et al., 2012). As such, further research is needed to clarify how injury schedule influences tau phosphorylation and the relationship to the clinical situation, where much wider spacings between injuries are typically seen.

The link between single injuries and their effect on accumulation of aberrant tau species has received less attention. Early human studies investigating the effects of a single moderate- severe injury utilized antibodies against the late stage NFT marker, PHF-1, and reported positive immunoreactive dystrophic axons within white matter of excised brain tissue (Ikonomovic et al., 2004). However, only 11% of cases showed mis-localization of tau to the neuronal soma/dendrites, and a further 11% of cases had staining suggestive of the development of NFTs (Ikonomovic et al., 2004). Similarly Uryu et al. reported that11% of cases that survived up to one month following injury had evidence of PHF-1 positive immunoreactivity within neurons and glia, whilst Smith et al. found no differences in tau immunoreactivity using a pan-tau marker in acute TBI survivors (Smith et al., 2003a; Uryu et al., 2007). As only a late stage phosphorylation marker was employed, these studies may have missed more subtle increases in tau phosphorylation at early or intermediate sites that may precede the later development of more overt tau pathology. Indeed, in a study of individuals surviving 1–47 years following a single TBI, the presence of widespread NFTs was noted in 34% of long-term TBI survivors, compared to a more focal tau distribution (i.e. entorhinal cortex and hippocampus) in only 9% of those who had not previously experienced a TBI (Johnson et al., 2012). Of note, these NFTs were more likely to be located at the base of the sulci and in the superficial layers (i.e. layer II and the upper third of layer III) of the cortex (Johnson et al., 2012). In pre-clinical studies, an increase in ptau, including tau oligomers, has been reported acutely in the hours to days following either focal or diffuse injury (Tran et al., 2011; Hawkins et al., 2013; Shultz et al., 2015), with only one study looking more chronically, with a persistent diffuse elevation of AT8 immunoreactivity at 6 months following a lateral fluid percussion injury (Hoshino et al., 1998). As such, there is evidence to suggest that even a single more severe injury can be associated with accumulation of pathological tau.

Single blast injuries, have also received recent attention with reports of multifocal perivascular NFTs and glial tau inclusions in the brains of blast-exposed veterans that were similar to those seen in individuals with repeat concussion (Goldstein et al., 2012). Exposure to a blast can cause injury to the brain via a number of different mechanisms, including the shock wave itself, blunt or penetrating trauma and/or the head hitting the ground (Courtney and Courtney, 2015). Notably, recent research has focused on the effects of the shock wave itself, demonstrating that it has similar effects to a concussion. In animal models, a single moderate blast injury significantly increases tau phosphorylation (CP-13, AT8, AT180 A270, AT100) diffusely throughout the brain in regions such as the cortex, hippocampus and cerebellum in the acute stages following the insult (Goldstein et al., 2012; Li

et al., 2013; Sawmiller et al., 2014; Perez-Polo et al., 2015), with aberrant tau phosphorylation persisting to 30 days within the hippocampus (Huber et al., 2013). Thus tauopathy may not be a unique feature of repeated injury, but may be a potential complication of TBI in general, including moderate-severe TBI and blast injury.

Of note, the alteration in tau dynamics following TBI may contribute to the secondary injury cascade. Complete ablation or partial reduction of tau prevented deficits in spatial memory and learning on the Barnes Maze, with a decreased latency to the target, after repeated mild frontal impact (Cheng et al., 2014). Furthermore, Gerson and colleagues (2016) demonstrated that injection of TBI-derived tau oligomers into the hippocampi of mice overexpressing hTau decreased the number of spontaneous alteration on the Y-maze, a test of spatial memory (Gerson et al., 2016). Interestingly, injection of these oligomers bilaterally into the hippocampi was capable of increasing levels of tau oligomer expression not just near the hippocampal injection sites in these mice, but also distal to the injection site, in the cerebellum, supporting the hypothesis that tau oligomers may seed the spread of tau neuropathology throughout the brain (Gerson et al., 2016). The ability of tau oligomers to spread is particularly concerning in TBI, given recent evidence that increasing neuronal activity may enhance tau release and spread (Wu et al., 2016), since TBI is known to induce significant long-term neuronal hyperexcitability (Alwis et al., 2016).

6. What causes alternation in tau dynamics following TBI?

Given the evidence that tau is abnormally phosphorylated following TBI and may contribute to later neurodegeneration, it is important to understand how alteration in tau dynamics occurs. Key evidence links axonal injury associated with TBI with tauopathy (Ahmadzadeh et al., 2014) (Fig 1), but less is understood about the role that other injury factors, including the inflammatory response, may play. Diffuse axonal injury is a term applied to TBI-induced scattered destruction of white matter tracts (Adams et al., 1989), occurring not only at the time of injury, but evolving over time. The initiating event is thought to be an alteration in axolemmal permeability involving mechanoporation of the axolemma evoked by the shearing forces of the injury (Pettus et al., 1994; Povlishock and Pettus, 1996; Maxwell et al., 1997). Disruption of the axolemma allows local intra-axonal calcium accumulation, with subsequent activation of various calcium-dependent cysteine protease (calpain) pathways capable of degrading the cytoskeletal network within the axon (Christman et al., 1997).

Calpain-mediated degradation of the cytoskeleton has been shown to occur at sites of axonal damage and disconnection in numerous immunohistochemical studies employing antibodies directed towards its specific proteolytic breakdown products (Buki et al., 1999a,b; Saatman et al., 2003; Serbest et al., 2007). Other members of the cysteine protease family, the caspases, are also thought to be activated within damaged axons (Buki et al., 2000). Although caspases are principally mediators of apoptotic cell death, in severely injured axons, they are thought to participate in the terminal degradation of the cytoskeleton, leading to irreversible collapse of the subaxolemmal membrane skeleton, rather than causing direct apoptotic changes in the soma (Buki and Povlishock, 2006). Cytoskeletal breakdown disrupts axonal transport, causing organelle and vesicular accumulation with resultant axonal swelling and eventual detachment (Smith et al., 2003b).

The high strain placed on axons in TBI means that tau proteins behave more stiffly than usual. This may inhibit the ability of adjacent microtubules to slide past each other in response to axonal stretching, resulting in the subsequent rupture (Ahmadzadeh et al., 2014). As tau becomes unbound from the microtubule, it facilitates phosphorylation at disease related sites (Ballatore et al., 2007; Planel et al., 2008; Feuillette et al., 2010; Miyasaka et al., 2010), and promotes aggregation into oligomers and NFTs (Perez et al., 2007; Thies and Mandelkow, 2007; Fischer et al., 2009). The mechanical forces at the point of injury, allow tau to become detached from the microtubule, facilitating its phosphorylation and aggregation (Abisambra and Scheff, 2014). Notably NFTs

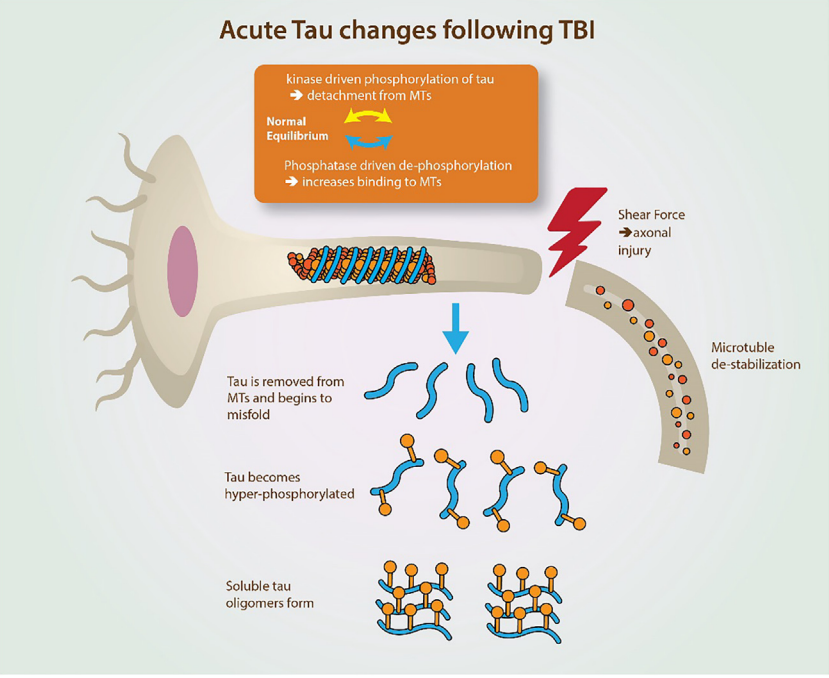

Fig. 1. Axonal injury following TBI may promote alteration in tau dynamics by promoting the detachment of tau from the microtubule, facilitating its phosphorylation and aggregation.

seen in CTE (McKee et al., 2013) and following a single moderate-severe TBI (Johnson et al., 2012) are typically at the base of the sulci, which is significant given that the forces associated with TBI are focused in this area (Cloots et al., 2008). Once generated, abnormal tau can then be secreted into the extracellular space, allowing the spread of pathological tau between neurons and propagating disease progression (Medina and Avila, 2014).

Although axonal injury may precipitate acute changes in tau phosphorylation, it is likely that other factors may also play a role. Of particular interest is the inflammatory response, given that it can persist for decades after the initial insult, and has been shown to play a role in accelerating disease progression in other tauopathies.

6.1. Persistent Inflammation Following TBI

A robust neuroinflammatory response develops acutely post-TBI, and is characterized by activation of resident cells, migration and recruitment of leukocytes and the release of inflammatory mediators (Ziebell and Morganti-Kossmann, 2010). Inflammation after TBI is triggered by several factors, including tissue debris and intracellular components that act as damage-associated molecular patterns (DAMPs), as well as extravasated blood products, complement fragments and reactive oxygen and nitrogen species (Manson et al., 2012; Woodcock and Morganti-Kossmann, 2013; Corps et al., 2015). The inflammatory response is characterized by a rapid rise in the levels of cytokines and chemokines. For example, following a moderate diffuse TBI in mice, levels of IL-1β, TNFα and IL-6 within the cortex peak at 3–9 h, before gradually subsiding (Bachstetter et al., 2013). Similarly, within human studies, examining levels of cytokines and chemokines within the CSF following moderate-severe TBI found increased levels of IL-6, TNFα, IL-10, CCL2 and IL-8 which peak within the first 24–48 h after TBI and then decrease over several weeks (Morganti-Kossman et al., 1997; Csuka et al., 1999; Semple et al., 2010). This acute inflammatory response has predictive value for outcome following injury, with Kumar et al. finding that individuals with high levels of IL-6 within the CSF in the week following injury had worsened outcome at 6 months post-injury (as measured by Glasgow Outcome Score) compared to those that had low levels of this cytokine (Kumar et al., 2015c)

The cellular response to injury differs slightly depending on whether the initiating insult is primarily focal or diffuse in nature. A focal injury is characterized by the early infiltration of neutrophils (peaking within a few days) (Soares et al., 1995; Holmin et al., 1998), followed by the migration of macrophages and lymphocytes, with activation and movement towards to the site of injury of resident microglia and astrocytes (Holmin et al., 1998). The acute phase of the inflammatory reaction appears to be mostly resolved by 10 days post-injury (Gyoneva and Ransohoff, 2015). In contrast, in diffuse injury, little to no neutrophil infiltration is seen, and early on macrophage and microglial accumulation and astrocytosis are most prominent in the white matter tracts, with the highest numbers at 14 days post-injury, the latest time-point investigated within the study (Hellewell et al., 2010). Even mild TBI is associated with induction of an inflammatory response, which is amplified with repeated injury. Using a model of diffuse mTBI in pigs, Lafrenaye et al. were able to demonstrate enhanced microglial activation associated with thalamic axonal injury at 6 h post-injury (Lafrenaye et al., 2015). In rats, a model of repeated concussion utilizing the lateral fluid percussion model showed an increase in activated microglia/macrophages at 24 h post-injury in the single injury group compared to shams, but almost 3x higher numbers again in groups receiving multiple injuries (Shultz et al., 2012).

Both microglia and astrocytes can serve a neuroprotective role immediately following injury by cleaning up damaged cell debris by phagocytosis, releasing anti-inflammatory cytokines and neurotrophic factors, (Lull and Block, 2010; Luo and Chen, 2012; Corps et al., 2015). Indeed, activated microglia demonstrate phenotypic subpopulations, characterized by a specific molecular signature of gene: M1 microglia, promote a classic pro-inflammatory state, releasing pro-inflammatory cytokines and oxidative metabolites, whilst M2 microglia are important for tissue remodeling and suppress the inflammatory response (Colton, 2009; David and Kroner, 2011). However, it is thought that prolonged M1-like activation hampers repair and can allow tissue damage to persist for years after the initial injury, with a hypothesis that, in a subset of TBI patients, there is incomplete resolution of the acute neuroinflammatory response (Bigler, 2013). Indeed, Kumar et al. showed that, following a CCI model of TBI, both M1 and M2 phenotypic markers were present early after TBI, but a predominant M1 phenotype was seen by 7 days post-injury (Kumar et al., 2015a). In support of this, Wang et al. also reported that both M1 and M2 microglia were seen in the cortex, striatum and corpus callosum within the first week following injury, with M2 microglia peaking at 5 days and then rapidly decreasing, whereas M1 microglia persisted at high levels up to two weeks following injury (Wang et al., 2013a). This suggests that a vicious cycle is initiated following the original insult, where release of pro-inflammatory factors by resident glial cells promotes further glial activation, leading to a progressive, chronic cycle of neuroinflammation (Lozano et al., 2015), which can have neurotoxic effects on neurons through mechanisms such as oxidative stress, apoptosis and excitotoxicity (Faden et al., 2016).

Multiple studies have demonstrated that a neuroinflammatory response may persist following resolution of the acute effects of a TBI, with inflammation markers present in the brain parenchyma, serum and cerebrospinal fluid of TBI patients at chronic time points (Smith et al., 2013). For example, Kumar and colleagues (2015b) found that levels of pro-inflammatory cytokines, including IL-1β, IL-6 and TFNα, were still elevated within serum at 3 months post-injury (Kumar et al., 2015b). In rodents, microglial activation has been demonstrated up to one-year following a focal TBI, with associated progressive lesion expansion, hippocampal degeneration, myelin loss and oxidative stress (Loane et al., 2014). In humans, reactive microglia have been found in brain tissue up to 18 years survival following single, moderate-to-severe TBI (Johnson et al., 2013). In models of repeated concussion, persistent inflammation, as characterized by microglial and astrocytic activation, has been demonstrated up to 12 months post-injury (Mouzon et al., 2014). The response is greatly amplified compared to animals receiving a single injury, with Aungst et al. finding that repeated, but not a single, mTBI was associated with microglial activation within the hippocampus at 1 month post-injury (Aungst et al., 2014). Indeed, it has been suggested that repeated concussion simulates a similar response to that seen following a single moderate insult, in terms of the levels of neuroinflammation and neurodegeneration (Faden et al., 2016).

Although the majority of studies investigating the chronic neuroinflammatory response following TBI have relied on post-mortem analysis, Ramlackhansingh et al. conducted a small clinical study evaluating the neuroinflammatory response to moderate to severe TBI *in vivo*. Positron emission tomography was used to demonstrate microglial activation persisting up to 17 years post-injury in multiple brain regions, including the thalami, putamen, occipital cortices, and posterior limb of the internal capsule. Even concussion, particularly repeated concussion, can have long-lasting inflammatory consequences, with retired National Football League players found to have increased microglial activation in the supramarginal gyrus and right amygdala compared to age matched healthy controls (Coughlin et al., 2015). Over time, these persistently elevated levels of reactive glial cells post-TBI may result in

increased release of cytokines, chemokines and other neurotoxic chemicals, which promote dementia development, along with the accumulation of pathological proteins, like tau (Zindler and Zipp, 2010).

This persistent inflammatory state induced following TBI may also be seen as an exaggerated neuroinflammatory response to other stimuli due to the phenomenon of microglial priming (Witcher et al., 2015). Microglial priming is seen as a higher baseline expression of inflammatory mediators, a lower threshold of activation and an exaggerated response following activation (Norden et al., 2015). These primed microglia can be identified by the increased expression of markers such as MHCII and CD68, with increased MHCII seen chronically following TBI (Johnson et al., 2013; Fenn et al., 2014; Loane et al., 2014; Muccigrosso et al., 2016). Furthermore, this phenomenon of priming has been demonstrated with an exaggerated neuroinflammatory response to a peripheral inflammatory stimulus (injection of lipopolysaccharide) seen at 1 month following a mild diffuse injury. TBI animals showed hyper-reactive microglial morphological profiles with an associated increased expression of pro-inflammatory cytokines, including IL-1β, CCL2, and TNFα, which led to an exacerbation of depressive-like behavior and impaired cognition (Fenn et al., 2014; Muccigrosso et al., 2016). Microglial priming may also play a role in repeated concussion, with the first concussion priming microglia to respond in an amplified manner to subsequent injuries. Of note the time interval between injuries may influence this microglial priming with Weil et al. demonstrating that two closed-head injuries spaced 3 days apart, but not 20 days apart, was associated with increased inflammation and worsening of axonal injury (Weil et al., 2014). Further investigation is needed to elucidate the role of microglial priming and the influence of the exaggerated response to other pro-inflammatory stimuli following both single and repeat injury in the development of a persistent neuroinflammatory state.

7. Role of the immune system in promoting tau phosphorylation

Extensive evidence suggests that the immune system can influence tau phosphorylation (Fig 2). Both acute and chronic activation of the innate immune system, via administration of lipopolysaccharide (LPS), have been shown to exacerbate tau phosphorylation and pathology in murine models of AD and other tauopathies (Li et al., 2003; Kitazawa et al., 2005; Lee et al., 2010; Sy et al., 2011). Further, in mice with a knockout of the neuronal chemokine CX3CL1 (fractakline) receptor, which suppresses microglial activation, there was an exaggerated neuroinflammatory response to LPS administration, as well as enhanced tau phosphorylation at the AT8 site (Bhaskar et al., 2010). When CX3CR1 knockout mice were crossed with an hTau model of tauopathy, the double transgenic mice also demonstrated accelerated tau phosphorylation (AT8, AT180 and PHF-1) and aggregation, which was associated with enhanced neuroinflammation (Bhaskar et al., 2010). Immune suppression has also been shown to be effective in models of tauopathy, with administration of the immunosuppressant FK506 to P3105 Tg mice increasing survival with an associated reduction in AT8 immunohistochemical staining (Yoshiyama et al., 2007).

The exact mechanisms whereby activation of the immune system promotes tau phosphorylation are yet to be fully elucidated, with the role of IL-1β receiving the greatest levels of scrutiny. Implantation of a slow release IL-1β pellet in the brain increased phosphorylation of tau (PHF-1) (Sheng et al., 2000), whilst application of IL-1β to neuronal-microglial co-cultures led to increases in ptau at the AT8 phosphorylation site (Li et al., 2003). Indeed, the aforementioned LPS-induced increase in tau phosphorylation appears to be mediated by IL-1β, as levels of IL-1β, but not IL-6 and TNFα, were elevated following chronic intermittent administration of LPS to 3Tg-Ad mice (Kitazawa et al., 2005). Indeed, IL-1β can accelerate tau deposition in tauopathy models. When 3xTgAD mice were crossed to IL-1β^{XAT} mice, allowing specific activation of human IL-1β expression within the hippocampus to be induced from 15 months of age, it enhanced tau phosphorylation at a number of sites, including pT205, AT180 and PHF1 (Ghosh et al., 2013). Inhibition of IL-1 via chronic administration of IL-1R for 6 months from 9 months of age in 3xTg-Ad mice significantly reduced the number of ptau-bearing neurons, as detected via AT8, AT100, and PHF-1, with an associated improvement of cognitive deficits (Kitazawa et al., 2011).

The role of other pro-inflammatory mediators on influencing tau phosphorylation is less clear. Application of TNFα *in vitro* to

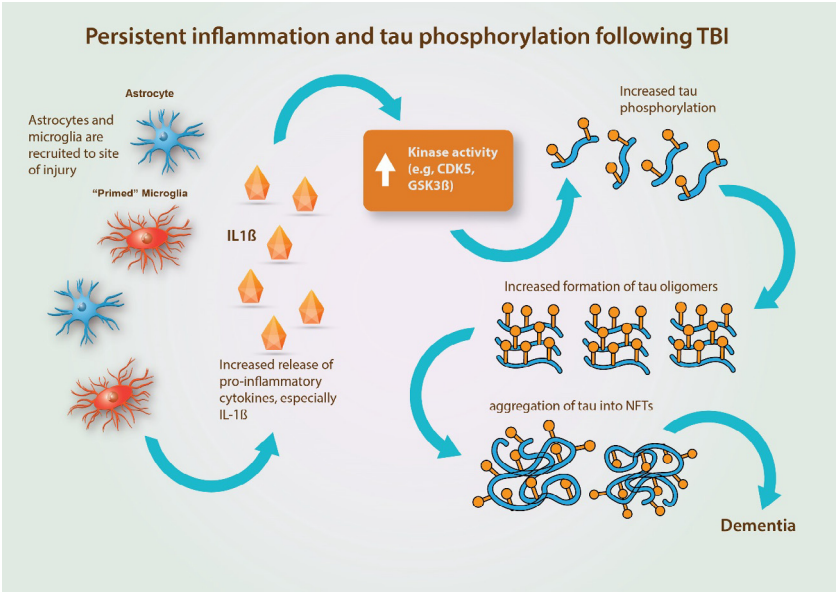

Fig. 2. The role of the immune system in promoting altered tau dynamics following TBI. Persistent activation of astrocytes and microglia, with the resultant release of inflammatory cytokines like IL-1β, activates kinases that promote hyperphosphorylation of tau that can then aggregate into oligomers and, eventually, NFTs characteristic of tauopathies, such as AD and CTE.

neuronal-microglial co-cultures had no effect on levels of tau phosphorylation, as measured by AT8 levels (Li et al., 2003). However, treatment with the TNFα antagonist, inflixamib, reduced levels of pThr181 tau in 12-month-old APP/PS1 mice (Shi et al., 2011). This may not reflect the actions of TNFα directly, but rather an overall reduction in levels of inflammation, including levels of IL-1β. Similarly disparate results have been reported with IL-6, with both a Cdk5 dependent enhancement of tau phosphorylation (Quintanilla et al., 2004) and no effect on tau phosphorylation (Hull et al., 1999) reported following application of IL-6 to hippocampal cultures. Intriguingly, it has been suggested that activation of toll-like receptor 4, via LPS, may even influence tau phosphorylation independent of pro-inflammatory signaling. Despite knockout of 5LO (arachidonate 5-lipoxygenase) reducing levels of microglial and astrocytic activation with a corresponding decrease in IL-1β and IFN-γ, chronic LPS administration was still able to enhance levels of ptau in 3xTgAd mice in a similar manner to mice with 5LO (Joshi et al., 2014). Thus, further investigation is needed to determine the exact interaction between immune system signaling and activation of tau phosphorylation kinases.

Of note, the pattern of kinase activation appears to be dependent on the length and magnitude of immune stimulation, as well as the age and, hence the level, of pre-existing tau pathology. Following chronic administration of LPS to young pre-pathological 3xTg AD mice, Cdk5 activity (Kitazawa et al., 2005; Joshi et al., 2014), but not GSK-3β, p38-MAPK or JNK, was increased (Kitazawa et al., 2005). Indeed, administration of the Cdk5 antagonist roscovitine abolished the LPS-mediated effects on tau phosphorylation (Kitazawa et al., 2005). In contrast, in aged 3xTgAd mice, chronic administration of LPS led to enhanced tau phosphorylation and increased levels of insoluble tau were related to activation of GSKβ, but not Cdk5 (Boden and Fergusson, 2011). These findings are in line with previous reports that GSK-3β becomes the primary modulator of tau phosphorylation as mice age (Hooper et al., 2008). Indeed, in older mice, with established tau pathology, prolonged overexpression of IL-1 was associated with enhanced GSK3β activity, with enhanced p38-MAPK activity also noted (Ghosh et al., 2013), supporting previous reports indicating a role for p38 MAPK as a mediator of IL-1β induced tau phosphorylation (Li et al., 2003; Bhaskar et al., 2010).

It should be noted that activation of the immune system alone does not appear to be sufficient for persistent alterations in tau phosphorylation. In response to an acute systemic inflammatory response induced by administration of high-dose LPS to naïve mice, a rapid increase in levels of ptau (AT8 and PHF-1) was noted within the hippocampus, but this abated within 2 h (Roe et al., 2011). Direct activation via intracerebral injection appears to last slightly longer, with enhanced tau phosphorylation seen in naïve mice at 1 day (Sy et al., 2011), but not at 7 days (Lee et al., 2010). In contrast, rTg4510 mice, which express human tau with the P301 mutation linked to familial frontotemporal dementia, have persistent elevations of ptau at 7 days post LPS injection (Lee et al., 2010). Similarly, following a viral CNS infection, aged 3xTgAd mice, but not wildtype mice, demonstrated a persistent elevation in tau phosphorylation at 2 and 4 weeks post-(Sy et al., 2011). Thus, altered immune signaling may accelerate disease progression where there is a pre-existing alteration in tau phosphorylation, but is insufficient to produce tauopathy alone. In TBI, the pre-existing alteration appears to be primarily caused by the initial axonal injury, providing a setting whereby chronic persistent inflammation may drive disease progression, predisposing to later neurodegeneration.

8. Could targeting inflammation prevent the aggregation of tau and the subsequent development of dementia following TBI?

Given the long latency period between the initial injury and the later development of dementia, there is an opportunity for therapeutic intervention. One potential avenue may be targeting the immune response, with evidence from studies in AD suggesting that anti-inflammatory treatments may be effective in the early stages of the disease (Morris et al., 2014)

Perhaps the best-characterized target of inflammatory pathways in AD is the use of non-steroidal anti-inflammatory drugs (NSAIDs), drugs that are widely used and frequently prescribed as analgesics and antipyretics. NSAIDs are known to block the cyclooxygenase (COX) enzymes COX-1 and COX-2, inhibiting the production of prostaglandins and thromboxane. A variety of epidemiological evidence has supported the use of NSAIDs to prevent the development of AD (McGeer et al., 1996; in t' Veld et al., 2001; Deardorff and Grossberg, 2016). It should be noted however, that timing is crucial, with administration during the extended preclinical phase in the years or decades before onset of cognitive decline optimal (Woodling et al., 2016), as NSAIDs may actually adversely affect AD pathogenesis when given just prior to, or at the onset of, clinical symptoms (Imbimbo et al., 2010), due to potentially beneficial actions of microglia in removing Aβ plaques (Lee and Landreth, 2010).

The rationale for why modifying the immune system may prevent the development of AD are yet to be fully elucidated. However, there is evidence to suggest that alteration in tau dynamics may also be involved. Treatment with the anti-inflammatory minocycline for two weeks was associated with a reduction in tau phosphorylation at Ser-202 and Ser396/404 in young htau mice, as well as a reduction in the amount of insoluble tau (Noble et al., 2009). The effect of minocycline was linked to a reduction in astrocytosis within the cortex, as well as a reduction in levels of a number of pro-inflammatory cytokines, such as GM-CSF, eotaxin, MCP-1 and IL-6 (Garwood et al., 2010). Of note, a short period of minocycline treatment was less effective at 12 months of age when htau mice have existing NFT pathology, as minocycline was only able to reduce levels of tau aggregation, but not its phosphorylation (Noble et al., 2009). Furthermore, a more prolonged treatment of minocycline from 8 months of ages in the 3xTgAD mouse model found that, despite a reduction in astrocytosis, there were no differences in tau phosphorylated at the AT8, AT180 or AT270 sites, an increase in PHF-1 tau, but a reduction in AT100, as detected via western blot (Parachikova et al., 2010). Both PHF-1 and AT100 stain ptau that is found predominantly in NFTs, so the opposing changes seen in the Parchikova study may not lead to any differences in the level of tau aggregation (Augustinack et al., 2002). Thus, it appears anti-inflammatory treatment is more effective when given early in the disease. Indeed, prolonged prophylactic treatment with ibuprofen for 5 months in 3xTgAd mice led to a significant reduction in levels of ptau, as well as intraneuronal Aβ within the hippocampus at 6 months of age (McKee et al., 2008). It was initially proposed that the effect of NSAIDs was predominantly due to the role that NSAIDs have on γ-secretase modulation, which reduce levels of Aβ production (Weggen et al., 2001) However, a follow-up study utilizing the R-flurbiprofen, (Morihara et al., 2002) found that a 2 month period of treatment in young 3xTgAd mice actually reduced pathological levels of tau hyperphosphorylation, without significantly affecting the level of Aβ (Carreras et al., 2013). This reduction in levels of ptau was associated with an improvement in cognition on the radial arm maze, indicating the role of altered tau phosphorylation in promoting functional deficits (Carreras et al., 2013).

9. Future directions

Given the complexity of the neuroinflammatory response following TBI, it is likely that effective inflammation-based treatments for the prevention of abnormal tau and its associated effects on cognition will need to target specific aspects of the inflammatory response, rather than global inflammation, as is achieved with NSAID or minocycline administration. Furthermore, timing of administration post-TBI will be crucial, as the inflammatory response is important for repair in the immediate aftermath after injury. Indeed, long-term ibuprofen treatment initiated immediately after a fluid-percussion injury in rats worsened cognitive outcome at 4 months post-injury (Browne et al., 2006). Despite this, given the extended period of time between TBI occurrence and the emergence of dementia, targeting inflammation in the sub-chronic stage following TBI may be a highly effective strategy for preventing the later emergence of dementia. Future studies will need to more closely examine the inflammatory response following TBI, particularly the role of spacing and number of injuries in repetitive injury models, and the association with tau phosphorylation and aggregation to determine the optimal inflammatory pathways to target and when treatment may be most effective.

10. Conclusion

Extensive evidence over the last 25 years has suggested that sustaining a TBI may predispose to the later development of dementia. The exact mechanism that drives the connection between these two conditions has yet to be fully determined, and is likely complex. However, given the long latency between the initial TBI and later dementia, an opportunity exists for timely treatment. Importantly, given that pre-clinical research has suggested that treatment is most effective prior to the appearance of symptoms, this particular population would prove ideal for therapeutic intervention. Of interest, TBI is known to promote pathological accumulation of proteins, with the role of tau in promoting neurodegeneration becoming increasingly evident. Alteration in tau dynamics has been shown both acutely and chronically following TBI, and may be driven by the effects of the initial axonal injury exacerbated by a persistent inflammatory response. As such, timely intervention that modulates the immune response may prevent the hyperphosphorylation and subsequent aggregation of tau and reduce the risk of going on to develop dementia.

Acknowledgments

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