Themed Section: Inflammation: maladies, models, mechanisms and molecules

REVIEW

Progressive inflammation-mediated neurodegeneration after traumatic brain or spinal cord injury

Alan I Faden, Junfang Wu, Bogdan A Stoica and David J Loane

*Department of Anesthesiology, Center for Shock, Trauma and Anesthesiology Research (STAR), University of Maryland School of Medicine, Baltimore, MD, USA***Correspondence**

Alan I Faden, Department of Anesthesiology, Center for Shock, Trauma and Anesthesiology Research (STAR), University of Maryland School of Medicine, Health Sciences Facility II (HSFII), #S247, 20 Penn Street, Baltimore, MD 21201, USA. E-mail: afaden@anes.umm.edu

Received

23 December 2014

Revised

31 March 2015

Accepted

14 April 2015

Traumatic brain injury (TBI) has been linked to dementia and chronic neurodegeneration. Described initially in boxers and currently recognized across high contact sports, the association between repeated concussion (mild TBI) and progressive neuropsychiatric abnormalities has recently received widespread attention, and has been termed chronic traumatic encephalopathy. Less well appreciated are cognitive changes associated with neurodegeneration in the brain after isolated spinal cord injury. Also under-recognized is the role of sustained neuroinflammation after brain or spinal cord trauma, even though this relationship has been known since the 1950s and is supported by more recent preclinical and clinical studies. These pathological mechanisms, manifested by extensive microglial and astroglial activation and appropriately termed chronic traumatic brain inflammation or chronic traumatic inflammatory encephalopathy, may be among the most important causes of post-traumatic neurodegeneration in terms of prevalence. Importantly, emerging experimental work demonstrates that persistent neuroinflammation can cause progressive neurodegeneration that may be treatable even weeks after traumatic injury.

LINKED ARTICLES

This article is part of a themed section on Inflammation: maladies, models, mechanisms and molecules. To view the other articles in this section visit <http://dx.doi.org/10.1111/bph.2016.173.issue-4>

Abbreviations

AD, Alzheimer's disease; CCI, controlled cortical impact; CTBI, chronic traumatic brain inflammation; CTE, chronic traumatic encephalopathy; CTIE, chronic traumatic inflammatory encephalopathy; DG, dentate gyrus; ERPs, event-related potentials; SCI, spinal cord injury; TBI, traumatic brain injury

Tables of Links

TARGETS
Catalytic receptors^a
IL-4 receptor α
Enzymes^b
Arginase 1
GPCR^c
mGlu ₅ receptor

LIGANDS	
A β , β -amyloid	IL-1 β
CCL2	TGF β
CCL3	TNF α
CCL21	
CHPG, 2-chloro-5-hydroxyphenylglycine	
Ibudilast	

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 (^{a,b,c}Alexander *et al.*, 2013a,b,c).

Introduction

Neuroinflammation is a prominent feature of many neurodegenerative diseases (Eikelenboom *et al.*, 2010; Perry *et al.*, 2010), and is increasingly being recognized as an important pathophysiological mechanism underlying chronic neurodegeneration following traumatic brain injury (TBI) or spinal cord injury (SCI). As the primary mediators of the innate immune response in the CNS, microglia play a critical role in neuroinflammation and secondary injury following CNS injury. Their persistent activation towards the M1-like neurotoxic phenotype may in part explain the progressive neuronal loss observed after CNS trauma.

Recent work, both experimental and clinical, has established that moderate or severe TBI may lead to chronic progressive neurodegeneration. A recent retrospective cohort study has shown that there is an increased risk of dementia after TBI (Gardner *et al.*, 2014). Specifically, it demonstrated the influence of age at injury and injury severity on dementia risk after TBI, revealing that even mild TBI (mTBI) increases dementia risk in those aged ≥ 65 years. An important outstanding question is which type of dementia results from prior brain trauma? It has long been suggested that a prior history of TBI increases the likelihood of subsequent Alzheimer disease (AD) (Mortimer *et al.*, 1985; 1991; Graves *et al.*, 1990; Plassman *et al.*, 2000). Moreover, consistent with the β -amyloid (A β) hypothesis as a key mechanism of AD, brain trauma increases amyloid precursor protein, presenilins and β -amyloid converting enzyme 1 in injured axons, and results in the deposition of the β -amyloid fragment, A β_{1-42} , in injured brain (see Johnson *et al.*, 2010). However, more recent epidemiological studies involving much larger patient cohorts do not give much support to such an association between TBI and AD (Dams-O'Connor *et al.*, 2013; Nordstrom *et al.*, 2014). In addition, recent clinical studies have increasingly called into question the role of A β as the major driver of cognitive decline in AD patients (Doody *et al.*, 2014; Salloway *et al.*, 2014; Murray *et al.*, 2015). Rather, there is a significant association with non-AD dementias (Wang *et al.*, 2012; Lee *et al.*, 2013; Barnes *et al.*, 2014; Nordstrom *et al.*, 2014; Faden and Loane, 2015).

Repeated mTBI, in boxers or athletes who participate in high contact sports, has been linked to later onset neurode-

generation. This chronic neurodegeneration may contribute to a pathologically distinct disease known as chronic traumatic encephalopathy (CTE) that has a significant τ pathology including phosphorylated τ in neurofibrillary tangles, neurites and glial deposits (Omalu *et al.*, 2005; McKee *et al.*, 2009; 2013). Some cases of CTE also demonstrate diffuse A β plaques and pathological accumulations of phosphorylated forms of the DNA-binding protein TDP-43 (McKee *et al.*, 2013). Importantly, single TBI appears to have a different pathology. Acutely, it is associated with diffuse A β plaques (Roberts *et al.*, 1991; 1994), whereas fibrillary A β plaques can be observed in the chronic phase (Johnson *et al.*, 2012). Moreover, single TBI results in accumulation of phosphorylation-independent TDP-43 and a relative absence of pathological phosphorylated TDP-43 (Johnson *et al.*, 2011), which raises questions about whether the neuropathology following single, as distinct from repeated, TBI reflects poly-pathologies rather than a single entity (e.g. tauopathy; Smith *et al.*, 2013b).

Animal studies show that single moderate or severe TBI, or repeated mTBI, can cause progressive neurodegeneration with cognitive and other behavioural changes (Smith *et al.*, 1997; Pierce *et al.*, 1998; Dixon *et al.*, 1999; Aungst *et al.*, 2014; Loane *et al.*, 2014; Mouzon *et al.*, 2014). Delayed progressive pathological changes have been demonstrated in clinical TBI imaging studies (Trivedi *et al.*, 2007; Bendlin *et al.*, 2008; Ng *et al.*, 2008; Sidaros *et al.*, 2008; 2009; Kumar *et al.*, 2009; Farbota *et al.*, 2012). Post-traumatic neurodegeneration and/or neurological deficits have been linked to persistent neuroinflammation in preclinical (Nonaka *et al.*, 1999; Nagamoto-Combs *et al.*, 2007; Acosta *et al.*, 2013; Aungst *et al.*, 2014; Loane *et al.*, 2014; Mouzon *et al.*, 2014) and neuropathological (Johnson *et al.*, 2013) studies. Microglial activation has been proposed as an important pathobiological mechanism in major neurodegenerative disorders, including AD (Eikelenboom *et al.*, 2010; Perry *et al.*, 2010). Such neuroinflammation has also been reported in several case reports of CTE that described the presence of activated microglia throughout the brain following neurotrauma (McKee *et al.*, 2010; Goldstein *et al.*, 2012; Saing *et al.*, 2012). Although no formal studies of neuroinflammation in CTE have been conducted to date, these results are provocative, and the involvement of neuroinflammation in CTE, including pathological

evidence of microglia and astrocytes activation, has been previously noted (Daneshvar *et al.*, 2015). Preclinical studies strongly support a role for chronic neurotoxic neuroinflammation in post-traumatic degeneration and associated neurological or psychiatric symptoms, and several recent experimental studies have demonstrated that delayed, targeted anti-inflammatory treatments can limit behavioural and pathological changes (Byrnes *et al.*, 2012; Piao *et al.*, 2013; Rodgers *et al.*, 2014).

The analysis of the effects of SCI has, for long, focused on sensorimotor deficits, or secondary complications such as neuropathic pain or bladder/bowel/sexual dysfunction. Most early research on the pathophysiological changes following SCI was predominantly focused on the spinal cord and its afferent and efferent pathways. In contrast, minimal work has addressed the potential effects of SCI on brain regions that regulate learning and memory or emotions, despite accumulating clinical evidence showing significant neuropsychological changes. Recent MRI studies suggest that SCI can cause progressive and widespread brain changes (Nicotra *et al.*, 2006; Wrigley *et al.*, 2009; Freund *et al.*, 2013). Our recently published work demonstrates that SCI in both mouse and rat models causes a chronic neuroinflammatory response in the brain (Wu *et al.*, 2014a,b), similar to that observed experimentally and clinically after TBI. This chronic neuroinflammation is associated with progressive neurodegeneration in brain regions associated with cognitive decline and depressive-like behaviour (Wu *et al.*, 2014a,b).

Progressive neurodegeneration after TBI

Increasing evidence, both experimental and clinical, indicates that TBI can result in progressive neurodegeneration (Smith *et al.*, 1997; Dixon *et al.*, 1999; Trivedi *et al.*, 2007; Bendlin *et al.*, 2008; Sidaros *et al.*, 2008; Farbota *et al.*, 2012; Loane *et al.*, 2014). In the late 1990s, Smith *et al.* (1997) reported progressive brain atrophy and cell loss in multiple brain regions following fluid percussion induced injury in rats. More recently, Loane *et al.* (2014) found progressive lesion development and neuronal cell loss, using both repeated MRI and histological measurements, through 1 year after controlled cortical impact (CCI) injury in mice. An increasing number of clinical imaging TBI studies have shown progressive tissue loss and brain atrophy, which are likely to reflect chronic neurodegenerative changes, for months to years after TBI (Trivedi *et al.*, 2007; Bendlin *et al.*, 2008; Ng *et al.*, 2008; Sidaros *et al.*, 2008; 2009; Kumar *et al.*, 2009; Farbota *et al.*, 2012). Alterations have been identified in both grey and white matter. In several of these studies, imaging data were correlated with neurological deficits. Importantly, progressive neurodegeneration has been reported after mild as well as moderate or severe TBI (Trivedi *et al.*, 2007; Kumar *et al.*, 2009; Zhou *et al.*, 2013). Furthermore, studies in children have also reported similar progressive degeneration after head injuries (Keightley *et al.*, 2014).

Given the published reports on CTE and high-impact sports, there has been considerable interest in whether repeated concussive or even sub-concussive insults can lead

to chronic neurodegeneration. A recent study used MRI to examine hippocampal size in relation to concussion history in collegiate football players (Singh *et al.*, 2014). They demonstrated reduced hippocampal volumes in football players compared with age-matched non-football controls. The greatest changes were found in those with a documented concussion history and they reported an inverse relationship between hippocampal volumes or reaction times and years playing football. Other studies have also recently suggested that exposure to high-impact sports can lead to brain imaging changes including hyperactivity in the default mode network (Johnson *et al.*, 2014; Abbas *et al.*, 2015) or delayed recovery of cerebral blood flow post-concussion in slow-to-recover athletes (Meier *et al.*, 2015), suggesting that even repeated sub-concussive head exposures may lead to long-term pathological alterations in the brain.

Chronic neuroinflammation after TBI

TBI is known to cause acute neuroinflammation that is associated with cytokine release (Loane and Byrnes, 2010; Ziebell and Morganti-Kossmann, 2010). Indeed, many neuroprotective strategies have been directed at such inflammation or related factors (Kumar and Loane, 2012). Also well supported by clinical data, but less well appreciated is that clinical TBI can cause persistent microglial activation (Engel *et al.*, 2000; Gentleman *et al.*, 2004; Faden, 2011; Ramlackhansingh *et al.*, 2011; Johnson *et al.*, 2013; Smith *et al.*, 2013a; Coughlin *et al.*, 2015), and that such chronic neuroinflammation may contribute to neurodegeneration. Post-mortem autopsy studies have revealed the presence of reactive microglia at months to years following a single TBI (Gentleman *et al.*, 2004; Smith *et al.*, 2013a). In fact, a recent study demonstrated the presence of CD68-positive microglia in more than a quarter of brains examined with survival time of >1 year, and this was associated with white matter degeneration in these cases (Johnson *et al.*, 2013). Another clinical TBI study used the PET translocator protein 18 kDa (TSPO) ligand ($[^{11}\text{C}]\text{R-PK11195}$) to examine chronic neuroinflammatory changes in patients months to years after a single head injury. Brain TSPO levels are increased after TBI in experimental models, likely due to increased expression by activated microglia during secondary neuroinflammation (Papadopoulos and Lecanu, 2009). Increased $[^{11}\text{C}]\text{R-PK11195}$ binding was found diffusely at sites distant from the trauma locus, indicating chronic neuroinflammatory changes in patients who suffered moderate-to-severe TBI (Ramlackhansingh *et al.*, 2011). Moreover, localization of neuroinflammation in the diencephalon correlated with long-term cognitive changes in these studies. Contrary to the neuropathological studies, $[^{11}\text{C}]\text{R-PK11195}$ binding was not observed in corpus callosum of TBI patients, which may be due to reduced sensitivity of the PET ligand for highly activated phagocytic (CD68 positive) microglia or other limitations in current methods to image neuroinflammation at high resolution in the human brain. However, another neuroimaging study using a second-generation TSPO ligand, $[^{11}\text{C}]\text{DPA-713}$, in retired National Football Leagues (NFL) players supports the findings of Ramlackhansingh *et al.* and demonstrated increased radioligand binding in several brain regions, including supramarginal gyrus and right amygdala, in former NFL

Players compared with age-matched, healthy controls (Coughlin *et al.*, 2015). Significant atrophy of the right hippocampus as well as varied performance on tests of verbal learning and memory in NFL players were reported, suggesting that neuroinflammatory changes may play a role in cognitive dysfunction and depression among former athletes exposed to sport-related mTBI (Guskiewicz *et al.*, 2005; Hart *et al.*, 2013). In addition, recent biomarker studies have reported chronic increases of pro-inflammatory cytokines either in serum or in CSF after head injury, with such changes associated with unfavourable neuropsychiatric outcomes (Juengst *et al.*, 2014; Kumar *et al.*, 2014).

Experimental studies strongly support these clinical observations and suggest both possible mechanisms involved and potential therapeutic strategies (Holmin and Mathiesen, 1999; Nonaka *et al.*, 1999; Nagamoto-Combs *et al.*, 2007; Acosta *et al.*, 2013; Aungst *et al.*, 2014; Loane *et al.*, 2014; Mouzon *et al.*, 2014). We recently reported that moderate-level CCI in mice caused persistent microglial activation through 1 year post-trauma that was associated with progressively increased lesion volume and neurodegeneration (Loane *et al.*, 2014). Chronically activated microglia expressed major histocompatibility complex class II (CR3/43), CD68 and NADPH oxidase (NOX2) at the lesion margins at 1 year, along with evidence of oxidative stress. Several groups have shown that repeated mTBI can also cause chronic neuroinflammation associated with pathological changes (Shitaka *et al.*, 2011; Aungst *et al.*, 2014; Mouzon *et al.*, 2014). Utilizing a repeated closed head injury mouse model, Shitaka *et al.* (2011) reported that reactive microglia were identified adjacent to injured axons at 7 weeks after repetitive mTBI. Also using the repeated mTBI mouse model, Mouzon *et al.* (2014) demonstrated persistent neuroinflammation and related white matter degeneration, as well as chronic cognitive deficits through 18 months. Our group used a rat lateral fluid percussion model to show that repeated, but not single, mTBI resulted in chronic microglial activation and parallel behavioural deficits, electrophysiological changes and neuronal cell loss (Aungst *et al.*, 2014); importantly, repeated mTBI simulated alterations induced by a single moderate insult, with similar degrees of neuroinflammation, neurodegeneration and associated neurological deficits.

Given that persistent post-traumatic microglial activation is correlated with chronic neurodegeneration and functional deficits, several studies have addressed whether outcome can be improved by therapeutic targeting of such neuroinflammation late after the traumatic insult. Following CCI in mice, Byrnes *et al.* (2012) randomized animals at 1 month with the mGlu₅ receptor agonist 2-chloro-5-hydroxyphenylglycine (CHPG), vehicle or drug plus an allosteric mGlu₅ receptor antagonist. Delayed treatment starting at 1 month post-injury significantly improved cognitive and motor recovery, while decreasing neuroinflammation, lesion volume and neuronal loss at 4 months post-injury; in addition, *ex vivo* diffusion tensor imaging demonstrated considerably greater preservation of white matter tracks in treated animals than vehicle-treated TBI controls (Byrnes *et al.*, 2012). The protective effects of CHPG were blocked by the mGlu₅ receptor antagonist 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine, indicating that the neuroprotection was mediated by actions at mGlu₅ receptors. Similar protective actions and therapeutic

mechanisms were reported by Piao *et al.* (2013) using a delayed 4 week voluntary exercise regimen initiated 5 weeks after mouse CCI. Late, but not early, exercise implementation decreased chronic microglial activation and associated neurodegeneration, and ameliorated behavioural deficits after TBI (Piao *et al.*, 2013); protective effects were associated with an inhibition of NADPH oxidase (NOX2) in microglia. Recently, Rodgers *et al.* (2014) reported that anti-inflammatory treatment with the phosphodiesterase inhibitor ibudilast, beginning 1 month following fluid percussion injury in rats, resulted in decreased chronic anxiety-like behaviour as well as reactive gliosis at 6 months post-injury.

Microglia and infiltrating macrophages in the CNS are heterogeneous, with diverse functional phenotypes that range from pro-inflammatory (M1-like) phenotypes to immunosuppressive (M2-like) phenotypes (David and Kroner, 2011; Kumar and Loane, 2012). The 'M1/M2' paradigm has been increasingly studied in neurodegenerative diseases in an attempt to uncover mechanisms of immunopathogenesis, and advances in understanding of molecular and functional states of microglia/macrophages may provide a framework to help elucidate the relative beneficial versus destructive roles of microglia/macrophages after TBI. Although most studies to date underscore the neurotoxic actions of persistent M1-like microglial activation following TBI, it is now well recognized that M2-like phenotypes have anti-inflammatory and neurorestorative effects (Cherry *et al.*, 2014). For example, by removing cellular debris by phagocytosis and releasing neurotrophic factors and anti-inflammatory cytokines, microglia can prevent neuronal injury and restore tissue integrity in the injured brain (David and Kroner, 2011; Kumar and Loane, 2012).

Experimental studies in various models of CNS injury (SCI, stroke/ischaemia and TBI) have shown that the majority of microglia and recruited macrophages at the injury site have an M2-like profile, but that the M2-like response is short-lived, with a phenotypic shift towards an M1-like dominant response within 1 week (Kigerl *et al.*, 2009; Hu *et al.*, 2012; Kumar *et al.*, 2013; Wang *et al.*, 2013; Loane *et al.*, 2014). M1-like cells that dominate the lesion have reduced phagocytic activity, and increased secretion of pro-inflammatory and neurotoxic mediators (IL-1 β , TNF α , superoxide radicals, nitric oxide), that can exacerbate injury and contribute to pathology. Following focal TBI, there is a transient up-regulation of M2-like markers such as CD206, arginase 1, Ym1, CD163, Fizz1, IL-4 receptor α and TGF β (Hsieh *et al.*, 2013; Kumar *et al.*, 2013; Wang *et al.*, 2013; Loane *et al.*, 2014; Turtzo *et al.*, 2014), and the M2-like phenotype appears to peak between 3 and 5 days post-injury before tapering off significantly. This coincides with the peak of macrophage infiltration after TBI (Jin *et al.*, 2012). Such observations point to highly complex phenotypic and functional responses after TBI, with resident and infiltrating subsets of cells being activated dynamically to promote either anti-inflammatory and neuroprotective (M2-like) or chronic neurotoxic (M1-like) effects. Importantly, NOX2 activation, which we and others have implicated in post-traumatic neurotoxic neuroinflammation (Block *et al.*, 2007; Byrnes *et al.*, 2012; Gao *et al.*, 2012; Loane *et al.*, 2014), may serve as a switch that serves to increase M1 activation while suppressing M2 activation (Choi *et al.*, 2012). The concept of microglia/macrophage pheno-

type switching following TBI is at an early stage of development. Further research is needed to determine key regulatory mechanisms that control phenotype switching in microglia in order to develop therapeutic strategies to optimize functional recovery following TBI.

Cognitive impairment and remote neurodegeneration after SCI

Although not well appreciated by clinicians, there have been multiple reports that SCI patients frequently develop long-term cognitive impairments (Richards *et al.*, 1988; Roth *et al.*, 1989; Davidoff *et al.*, 1992; Dowler *et al.*, 1997; Lazzaro *et al.*, 2013). Using a battery of neuropsychological tests studies in SCI patients have identified performance impairments in memory span, executive functioning, attention, processing speed and learning ability (Roth *et al.*, 1989; Davidoff *et al.*, 1992; Dowler *et al.*, 1995; 1997; Strubreither *et al.*, 1997; Jensen *et al.*, 2007; Murray *et al.*, 2007; Lazzaro *et al.*, 2013). Moreover, central psychophysiological indices of information processing using scalp-recorded, late component, event-related potentials (ERPs) suggested that ERP alterations in SCI patients reflect impairments in distributed integrative cortical/subcortical networks that are engaged in stimulus detection, evaluation and executive functioning (Lazzaro *et al.*, 2013). However, such observations were often discounted as probably reflecting unappreciated concurrent head injuries. Yet, studies clearly show that SCI patients who present without a history of TBI may develop cognitive decline and neurological dysfunction (Hess *et al.*, 2003; Jensen *et al.*, 2007). After SCI, the incidence rate of depression more than doubles, increasing to between 25 and 47% (Umlauf, 1992; Arango-Lasprilla *et al.*, 2011). An earlier experimental study suggested cognitive decline after SCI, using a projectile injury in pigs wearing body armour (Zhang *et al.*, 2011). But the model, species and outcome used (conditioned feeding behaviour) make both interpretation and relevant comparison difficult. Our recent work revealed that SCI in both mouse and rat causes impairment of spatial and retention memory and depressive-like behaviour as demonstrated by diminished performance in the Morris water maze, Y-maze, novel objective recognition, sucrose preference and tail suspension tests (Wu *et al.*, 2014a,b). In addition to contributing to disability in their own right, these changes can also negatively affect rehabilitation and impair recovery. Remarkably, despite the clinical evidence showing SCI-induced cognitive and affective changes, these changes have been assumed to be situational or reactive, and neither clinical nor experimental studies have addressed these changes at a mechanistic level with a view towards limiting such deficits or promoting recovery. Our results (Wu *et al.*, 2014a,b) suggest that SCI can result in physiological changes in the brain that can be modified by inhibiting the post-traumatic neuroinflammatory response.

SCI can produce extensive long-term reorganization of the cerebral cortex (Endo *et al.*, 2007; Freund *et al.*, 2011), and complete thoracic SCI patients have decreased grey matter volume in primary motor cortex that is consistent with neuronal loss and/or atrophy (Wrigley *et al.*, 2009). Prospective

longitudinal MRI studies show that SCI can cause progressive reduction in grey matter volume not only in the sensorimotor cortex but also in the regions not directly connected to the injury site, such as cerebellar cortex, medial prefrontal and anterior cingulate cortices that are critical for the processing of emotional relevant information and the modulation of attentional states (Nicotra *et al.*, 2006; Wrigley *et al.*, 2009; Freund *et al.*, 2013). Crucially, myelin-sensitive MRI parameters measured at 1 year were reduced within, but also beyond, the atrophic areas of the lesion (Freund *et al.*, 2013). Collectively, these clinical studies suggest that SCI can cause progressive and widespread brain changes.

Until recently, assessment of neurodegeneration in the brain following experimental SCI focused on the sensorimotor cortex and medullary pyramid regions; results have been inconsistent, with outcomes ranging from no cell death to extensive retrograde degeneration (Kalil and Schneider, 1975; Feringa and Vahlsing, 1985; Ganchrow and Bernstein, 1985; Merline and Kalil, 1990; Bonatz *et al.*, 2000; Hains *et al.*, 2003a; Lee *et al.*, 2004; Wannier *et al.*, 2005; Kaas *et al.*, 2008; Nielson *et al.*, 2010; 2011). One of the limitations of these earlier SCI studies is that they were performed over poorly defined areas within the cerebral cortex and/or did not utilize rigorous quantitative assessment techniques. We used stereological methods with computer-driven, random, systematic sampling to provide quantitative analysis of neuronal densities in defined brain regions after SCI. Isolated thoracic SCI in both rat and mouse models resulted in significant neuronal loss in the hippocampus, cortex and thalamus at 10–12 weeks post-injury, but not at early time points (Wu *et al.*, 2014a,b). Importantly, significant long-term reduction in neurogenesis in the dentate gyrus (DG) subregion of the hippocampus has been reported after chronic cervical/thoracic SCI (Felix *et al.*, 2012; Wu *et al.*, 2014a). In addition to inflammatory mechanisms (see below), cannabinoid CB₁ receptors may be involved in such changes. CB₁ receptor immunoreactivity was significantly increased in hippocampal subregions (CA3 and DG) following contusion SCI in rats (Knerlich-Lukoschus *et al.*, 2011), and this receptor has been implicated in regulation of adult neurogenesis in the hippocampus, including modulation of proliferation, survival and maturation of new neurons (Wolf *et al.*, 2010).

Chronic neuroinflammation in the brain after SCI

SCI frequently causes neuropathic pain that is associated with chronic inflammation in both the dorsal horn and in spinothalamic projection sites in the thalamus (Schmitt *et al.*, 2000; Hains *et al.*, 2003b; Hains and Waxman, 2006; Zhao *et al.*, 2007a,b; Hulsebosch, 2008; Gwak *et al.*, 2013; Wu *et al.*, 2013a,b). Felix *et al.* (2012) reported increased inflammation in the brain after rat cervical SCI. Changes included increased mRNA expression of the chemokine receptor CCR5 in the dorsal vagal complex and elevated TNF α in the subventricular zone and subgranular zone of the DG. After severe contusion induced SCI, the chemokines CCL2 and CCL3 were chronically expressed in thalamus, hippocampus (CA3 and DG subregions) and periaqueductal grey matter (Knerlich-Lukoschus

et al., 2011). Very recently, we used the TSPO ligand [125 I]-iodoDPA-713 (Wang *et al.*, 2009) that was used to analyse chronic neuroinflammation in retired NFL players (Coughlin *et al.*, 2015), in autoradiography studies to assess brain inflammation after SCI in rats (Wu *et al.*, 2014b). All brain regions examined (cortex, thalamus, hippocampus, cerebellum, caudate/putamen) showed significantly elevated [125 I]-iodoDPA-713 binding. These data complemented microscopy data showing chronic microglial activation in the same brain regions after SCI that was associated with increased expression of markers for activated microglia, including TSPO, CD68 and the chemokine CCL21 (Wu *et al.*, 2014a,b). Notably, CCL21 is known to activate microglia at more distant sites following SCI (Zhao *et al.*, 2007b; Hulsebosch *et al.*, 2009). Collectively, these studies indicate that isolated SCI can cause chronic brain inflammation that is remarkably similar to that observed after TBI, resulting in progressive delayed neurodegeneration and functional deficits that include cognitive impairment and depressive-like behaviour (Wu *et al.*, 2014a,b). The functional changes were associated with chronic microglial activation and concurrent activation of cell cycle pathways and CCL21 in the brain. Early treatment with a cell cycle inhibitor following SCI largely prevented both the post-traumatic neuroinflammation in the brain and the long-term cognitive dysfunction (Wu *et al.*, 2014a,b).

SCI in both rat and mouse models causes significant increases of M1-like microglial activation genes and MHC II expression in the hippocampus, along with changes in M2-like markers that are species dependent (Wu *et al.*, 2014a,b). M1/M2-like phenotypic switching probably depends on the local signals in the microenvironment. However, as our analyses used tissue homogenates, the cellular origin of the gene expression changes remains to be determined.

Chronic traumatic inflammatory encephalopathy (CTIE): linking acute and chronic neurodegenerative disorders

Although acute neuroinflammation has been implicated in the pathophysiology of both TBI and SCI, a role for chronic brain inflammation and related neurodegeneration in neurotrauma has only recently been recognized (Faden and Loane, 2015). Neuroinflammation is implicated in the pathobiology of most chronic neurodegenerative disorders (Block *et al.*, 2007), and may provide a mechanistic link to the chronic brain neurodegeneration observed after brain or spinal cord trauma (Figure 1). There is no accepted nomenclature for persistent post-traumatic neuroinflammation. Chronic traumatic encephalitis probably best describes the persistent M1-like microglial activation and reactive astroglial changes that occur after TBI or SCI. It clearly shares key pathological features with other, better defined, non-infectious forms of chronic encephalitis, such as autoimmune encephalitis or paraneoplastic limbic encephalitis (Leypoldt and Wandinger, 2014; Leypoldt *et al.*, 2015). But the resulting abbreviation – CTE – would be confused with the well-established abbrevia-

Figure 1

Chronic inflammation-mediated neurodegeneration after TBI and SCI. In the acute phase after TBI, M1- and M2-like microglia are activated to limit the primary injury by removing damaged tissue by phagocytosis and resolving destructive pro-inflammatory responses to improve brain repair and promote neurorestoration. However, repeated mTBI or moderate-to-severe TBI results in chronic microglial activation characterized by a predominant M1-like activation state (i.e. NOX2-positive neurotoxic phenotype) that contributes to progressive neurodegeneration and loss of neurological function. Similarly, isolated SCI can cause chronic neuroinflammation in the cortex, hippocampus and thalamus at delayed time points after injury. CCL21 expression is up-regulated in the brain and is associated with increased microglial activation and neurodegeneration, which can cause long-term neurological deficits after SCI.

tion for the condition of chronic traumatic encephalopathy found after repeated head injuries (McKee *et al.*, 2009; 2013). Chronic posttraumatic neuroinflammation or chronic traumatic inflammatory encephalopathy (CTIE) appear to be more accurate descriptions, with the latter better conveying the association with brain dysfunction. Finally, chronic traumatic brain inflammation is appropriately descriptive and would have the abbreviation CTBI, although this does not convey the pathological association with neurodegeneration or dysfunction. Thus, either CTIE or CTBI would serve as reasonable descriptors for this important condition. Whatever term is used, this disorder may be a more common cause of progressive neuropsychiatric dysfunction after TBI than CTE. Unlike CTE, chronic neuroinflammation occurs following single moderate or severe TBI, as well as after repeated brain trauma. Moreover, as supported by recent research, CTIE/CTBI can be treated effectively weeks after injury (Byrnes *et al.*, 2012; Piao *et al.*, 2013; Rodgers *et al.*, 2014), which suggests the possibility of effective targeted clinical neuroprotection long after a traumatic insult.

Conclusions

Although CTE and AD have received the most attention as chronic brain disorders following TBI, CTIE/CTBI appears to be a more frequent and more likely contributing mechanism for progressive neurodegeneration and related cognitive decline. Surprisingly, SCI may also not uncommonly cause chronic brain inflammation and progressive neurodegeneration, with functional impairments. Thus, both TBI and SCI should be considered chronic, as well as acute, neurodegenerative disorders, in which potentially treatable chronic neuroinflammation plays a critical role.

Acknowledgement

This work was supported by NIH grants R01NS037313, R01NS052568, R01NR013601 (A. I. F.) and R01NS082308 (D. J. L.).

Conflict of interest

The authors declare they have no conflict of interest.

References

- Abbas K, Shenk TE, Poole VN, Breedlove EL, Leverenz LJ, Nauman EA *et al.* (2015). Alteration of default mode network in high school football athletes due to repetitive subconcussive mild traumatic brain injury: a resting-state functional magnetic resonance imaging study. *Brain Connect* 5: 91–101.
- Acosta SA, Tajiri N, Shinozuka K, Ishikawa H, Grimmig B, Diamond D *et al.* (2013). Long-term upregulation of inflammation and suppression of cell proliferation in the brain of adult rats exposed to traumatic brain injury using the controlled cortical impact model. *PLoS ONE* 8: e53376.
- Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Spedding M *et al.* (2013a). The Concise Guide to PHARMACOLOGY 2013/14: Catalytic Receptors. *Br J Pharmacol* 170: 1676–1705.
- Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Spedding M *et al.* (2013b). The Concise Guide to PHARMACOLOGY 2013/14: Enzymes. *Br J Pharmacol* 170: 1797–1867.
- Alexander SPH, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Spedding M *et al.* (2013c). The Concise Guide to PHARMACOLOGY 2013/14: G Protein-Coupled Receptors. *Br J Pharmacol* 170: 1459–1581.
- Arango-Lasprilla JC, Ketchum JM, Starkweather A, Nicholls E, Wilk AR (2011). Factors predicting depression among persons with spinal cord injury 1 to 5 years post injury. *Neurorehabilitation* 29: 9–21.
- Aungst SL, Kabadi SV, Thompson SM, Stoica BA, Faden AI (2014). Repeated mild traumatic brain injury causes chronic neuroinflammation, changes in hippocampal synaptic plasticity, and associated cognitive deficits. *J Cereb Blood Flow Metab* 34: 1223–1232.
- Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K (2014). Traumatic brain injury and risk of dementia in older veterans. *Neurology* 83: 312–319.
- Bendlin BB, Ries ML, Lazar M, Alexander AL, Dempsey RJ, Rowley HA *et al.* (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *Neuroimage* 42: 503–514.
- Block ML, Zecca L, Hong JS (2007). Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neurosci* 8: 57–69.
- Bonatz H, Rohrig S, Mestres P, Meyer M, Giehl KM (2000). An axotomy model for the induction of death of rat and mouse corticospinal neurons in vivo. *J Neurosci Methods* 100: 105–115.
- Byrnes KR, Loane DJ, Stoica BA, Zhang J, Faden AI (2012). Delayed mGluR5 activation limits neuroinflammation and neurodegeneration after traumatic brain injury. *J Neuroinflammation* 9: 43.
- Cherry JD, Olschowka JA, O'Banion MK (2014). Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. *J Neuroinflammation* 11: 98.
- Choi SH, Aid S, Kim HW, Jackson SH, Bosetti F (2012). Inhibition of NADPH oxidase promotes alternative and anti-inflammatory microglial activation during neuroinflammation. *J Neurochem* 120: 292–301.
- Coughlin JM, Wang Y, Munro CA, Ma S, Yue C, Chen S *et al.* (2015). Neuroinflammation and brain atrophy in former NFL players: an in vivo multimodal imaging pilot study. *Neurobiol Dis* 74: 58–65.
- Dams-O'Connor K, Gibbons LE, Bowen JD, McCurry SM, Larson EB, Crane PK (2013). Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. *J Neurol Neurosurg Psychiatry* 84: 177–182.
- Daneshvar DH, Goldstein LE, Kiernan PT, Stein TD, McKee AC (2015). Post-traumatic neurodegeneration and chronic traumatic encephalopathy. *Mol Cell Neurosci* pii: S1044-7431(15)00036-6.
- David S, Kroner A (2011). Repertoire of microglial and macrophage responses after spinal cord injury. *Nat Rev Neurosci* 12: 388–399.
- Davidoff GN, Roth EJ, Richards JS (1992). Cognitive deficits in spinal cord injury: epidemiology and outcome. *Arch Phys Med Rehabil* 73: 275–284.
- Dixon CE, Kochanek PM, Yan HQ, Schiding JK, Griffith RG, Baum E *et al.* (1999). One-year study of spatial memory performance, brain morphology, and cholinergic markers after moderate controlled cortical impact in rats. *J Neurotrauma* 16: 109–122.
- Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S *et al.* (2014). Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med* 370: 311–321.
- Dowler RN, O'Brien SA, Haaland KY, Harrington DL, Feel F, Fiedler K (1995). Neuropsychological functioning following a spinal cord injury. *Appl Neuropsychol* 2: 124–129.
- Dowler RN, Harrington DL, Haaland KY, Swanda RM, Fee F, Fiedler K (1997). Profiles of cognitive functioning in chronic spinal cord injury and the role of moderating variables. *J Int Neuropsychol Soc* 3: 464–472.
- Eikelenboom P, van Exel E, Hoozemans JJ, Veerhuis R, Rozemuller AJ, van Gool WA (2010). Neuroinflammation – an early event in both the history and pathogenesis of Alzheimer's disease. *Neurodegener Dis* 7: 38–41.
- Endo T, Spenger C, Tominaga T, Brene S, Olson L (2007). Cortical sensory map rearrangement after spinal cord injury: fMRI responses linked to Nogo signalling. *Brain* 130: 2951–2961.

- Engel S, Schluesener H, Mittelbronn M, Seid K, Adjodah D, Wehner HD *et al.* (2000). Dynamics of microglial activation after human traumatic brain injury are revealed by delayed expression of macrophage-related proteins MRP8 and MRP14. *Acta Neuropathol* 100: 313–322.
- Faden AI (2011). Microglial activation and traumatic brain injury. *Ann Neurol* 70: 345–346.
- Faden AI, Loane DJ (2015). Chronic neurodegeneration after traumatic brain injury: Alzheimer disease, chronic traumatic encephalopathy, or persistent neuroinflammation? *Neurother* 12: 143–150.
- Farbota KD, Sodhi A, Bendlin BB, McLaren DG, Xu G, Rowley HA *et al.* (2012). Longitudinal volumetric changes following traumatic brain injury: a tensor-based morphometry study. *J Int Neuropsychol Soc* 18: 1006–1018.
- Felix MS, Popa N, Djelloul M, Boucraut J, Gauthier P, Bauer S *et al.* (2012). Alteration of forebrain neurogenesis after cervical spinal cord injury in the adult rat. *Front Neurosci* 6: 45.
- Feringa ER, Vahlsing HL (1985). Labeled corticospinal neurons one year after spinal cord transection. *Neurosci Lett* 58: 283–286.
- Freund P, Weiskopf N, Ward NS, Hutton C, Gall A, Ciccarelli O *et al.* (2011). Disability, atrophy and cortical reorganization following spinal cord injury. *Brain* 134: 1610–1622.
- Freund P, Weiskopf N, Ashburner J, Wolf K, Sutter R, Altmann DR *et al.* (2013). MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: a prospective longitudinal study. *Lancet Neurol* 12: 873–881.
- Ganchrow D, Bernstein JJ (1985). Thoracic dorsal funicular lesions affect the bouton patterns on, and diameters of, layer VB pyramidal cell somata in rat hindlimb cortex. *J Neurosci Res* 14: 71–81.
- Gao HM, Zhou H, Hong JS (2012). NADPH oxidases: novel therapeutic targets for neurodegenerative diseases. *Trends Pharmacol Sci* 33: 295–303.
- Gardner RC, Burke JF, Nettiksimmons J, Kaup A, Barnes DE, Yaffe K (2014). Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. *JAMA Neurol* 71: 1490–1497.
- Gentleman SM, Leclercq PD, Moyes L, Graham DI, Smith C, Griffin WS *et al.* (2004). Long-term intracerebral inflammatory response after traumatic brain injury. *Forensic Sci Int* 146: 97–104.
- Goldstein LE, Fisher AM, Tagge CA, Zhang XL, Velisek L, Sullivan JA *et al.* (2012). Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci Transl Med* 4: 134ra160.
- Graves AB, White E, Koepsell TD, Reifler BV, van Belle G, Larson EB *et al.* (1990). The association between head trauma and Alzheimer's disease. *Am J Epidemiol* 131: 491–501.
- Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Cantu RC, Randolph C *et al.* (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery* 57: 719–726.
- Gwak YS, Hassler SE, Hulsebosch CE (2013). Reactive oxygen species contribute to neuropathic pain and locomotor dysfunction via activation of CamKII in remote segments following spinal cord contusion injury in rats. *Pain* 154: 1699–1708.
- Hains BC, Waxman SG (2006). Activated microglia contribute to the maintenance of chronic pain after spinal cord injury. *J Neurosci* 26: 4308–4317.
- Hains BC, Black JA, Waxman SG (2003a). Primary cortical motor neurons undergo apoptosis after axotomizing spinal cord injury. *J Comp Neurol* 462: 328–341.
- Hains BC, Klein JP, Saab CY, Craner MJ, Black JA, Waxman SG (2003b). Upregulation of sodium channel Nav1.3 and functional involvement in neuronal hyperexcitability associated with central neuropathic pain after spinal cord injury. *J Neurosci* 23: 8881–8892.
- Hart J Jr, Kraut MA, Womack KB, Strain J, Didehban N, Bartz E *et al.* (2013). Neuroimaging of cognitive dysfunction and depression in aging retired National Football League players: a cross-sectional study. *JAMA Neurol* 70: 326–335.
- Hess DW, Marwitz JH, Kreutzer JS (2003). Neuropsychological impairments after spinal cord injury: a comparative study with mild traumatic brain injury. *Rehabil Psychol* 48: 151–156.
- Holmin S, Mathiesen T (1999). Long-term intracerebral inflammatory response after experimental focal brain injury in rat. *Neuroreport* 10: 1889–1891.
- Hsieh CL, Kim CC, Ryba BE, Niemi EC, Bando JK, Locksley RM *et al.* (2013). Traumatic brain injury induces macrophage subsets in the brain. *Eur J Immunol* 43: 2010–2022.
- Hu X, Li P, Guo Y, Wang H, Leak RK, Chen S *et al.* (2012). Microglia/macrophage polarization dynamics reveal novel mechanism of injury expansion after focal cerebral ischemia. *Stroke* 43: 3063–3070.
- Hulsebosch CE (2008). Gliopathy ensures persistent inflammation and chronic pain after spinal cord injury. *Exp Neurol* 214: 6–9.
- Hulsebosch CE, Hains BC, Crown ED, Carlton SM (2009). Mechanisms of chronic central neuropathic pain after spinal cord injury. *Brain Res Rev* 60: 202–213.
- Jensen MP, Kuehn CM, Amtmann D, Cardenas DD (2007). Symptom burden in persons with spinal cord injury. *Arch Phys Med Rehabil* 88: 638–645.
- Jin X, Ishii H, Bai Z, Itokazu T, Yamashita T (2012). Temporal changes in cell marker expression and cellular infiltration in a controlled cortical impact model in adult male C57BL/6 mice. *PLoS ONE* 7: e41892.
- Johnson B, Neuberger T, Gay M, Hallett M, Slobounov S (2014). Effects of subconcussive head trauma on the default mode network of the brain. *J Neurotrauma* 31: 1907–1913.
- Johnson VE, Stewart W, Smith DH (2010). Traumatic brain injury and amyloid-beta pathology: a link to Alzheimer's disease? *Nat Rev Neurosci* 11: 361–370.
- Johnson VE, Stewart W, Trojanowski JQ, Smith DH (2011). Acute and chronically increased immunoreactivity to phosphorylation-independent but not pathological TDP-43 after a single traumatic brain injury in humans. *Acta Neuropathol* 122: 715–726.
- Johnson VE, Stewart W, Smith DH (2012). Widespread tau and amyloid-Beta pathology many years after a single traumatic brain injury in humans. *Brain Pathol* 22: 142–149.
- Johnson VE, Stewart JE, Begbie FD, Trojanowski JQ, Smith DH, Stewart W (2013). Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain* 136: 28–42.
- Juengst SB, Kumar RG, Arenth PM, Wagner AK (2014). Exploratory associations with Tumor Necrosis Factor-alpha, disinhibition and suicidal endorsement after traumatic brain injury. *Brain Behav Immun* 41: 134–143.
- Kaas JH, Qi HX, Burish MJ, Gharbawie OA, Onifer SM, Massey JM (2008). Cortical and subcortical plasticity in the brains of humans,

- primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord. *Exp Neurol* 209: 407–416.
- Kalil K, Schneider GE (1975). Retrograde cortical and axonal changes following lesions of the pyramidal tract. *Brain Res* 89: 15–27.
- Keightley ML, Sinopoli KJ, Davis KD, Mikulis DJ, Wennberg R, Tartaglia MC *et al.* (2014). Is there evidence for neurodegenerative change following traumatic brain injury in children and youth? A scoping review. *Front Hum Neurosci* 8: 139.
- Kigerl KA, Gensel JC, Ankeny DP, Alexander JK, Donnelly DJ, Popovich PG (2009). Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. *J Neurosci* 29: 13435–13444.
- Knerlich-Lukoschus F, Noack M, von der Ropp-Brenner B, Lucius R, Mehdorn HM, Held-Feindt J (2011). Spinal cord injuries induce changes in CB1 cannabinoid receptor and C-C chemokine expression in brain areas underlying circuitry of chronic pain conditions. *J Neurotrauma* 28: 619–634.
- Kumar A, Loane DJ (2012). Neuroinflammation after traumatic brain injury: opportunities for therapeutic intervention. *Brain Behav Immun* 26: 1191–1201.
- Kumar A, Stoica BA, Sabirzhanov B, Burns MP, Faden AI, Loane DJ (2013). Traumatic brain injury in aged animals increases lesion size and chronically alters microglial/macrophage classical and alternative activation states. *Neurobiol Aging* 34: 1397–1411.
- Kumar R, Husain M, Gupta RK, Hasan KM, Haris M, Agarwal AK *et al.* (2009). Serial changes in the white matter diffusion tensor imaging metrics in moderate traumatic brain injury and correlation with neuro-cognitive function. *J Neurotrauma* 26: 481–495.
- Kumar RG, Boles JA, Wagner AK (2014). Chronic inflammation after severe traumatic brain injury: characterization and associations with outcome at 6 and 12 months postinjury. *J Head Trauma Rehabil*.
- Lazzaro I, Tran Y, Wijesuriya N, Craig A (2013). Central correlates of impaired information processing in people with spinal cord injury. *J Clin Neurophysiol* 30: 59–65.
- Lee BH, Lee KH, Kim UJ, Yoon DH, Sohn JH, Choi SS *et al.* (2004). Injury in the spinal cord may produce cell death in the brain. *Brain Res* 1020: 37–44.
- Lee YK, Hou SW, Lee CC, Hsu CY, Huang YS, Su YC (2013). Increased risk of dementia in patients with mild traumatic brain injury: a nationwide cohort study. *PLoS ONE* 8: e62422.
- Leypoldt F, Wandering KP (2014). Paraneoplastic neurological syndromes. *Clin Exp Immunol* 175: 336–348.
- Leypoldt F, Armangue T, Dalmau J (2015). Autoimmune encephalopathies. *Ann N Y Acad Sci* 1338: 94–114.
- Loane DJ, Byrnes KR (2010). Role of microglia in neurotrauma. *Neurother* 7: 366–377.
- Loane DJ, Kumar A, Stoica BA, Cabatbat R, Faden AI (2014). Progressive neurodegeneration after experimental brain trauma: association with chronic microglial activation. *J Neuropathol Exp Neurol* 73: 14–29.
- McKee AC, Cantu RC, Nowinski CJ, Hedley-Whyte ET, Gavett BE, Budson AE *et al.* (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol* 68: 709–735.
- McKee AC, Gavett BE, Stern RA, Nowinski CJ, Cantu RC, Kowall NW *et al.* (2010). TDP-43 proteinopathy and motor neuron disease in chronic traumatic encephalopathy. *J Neuropathol Exp Neurol* 69: 918–929.
- McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH *et al.* (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136: 43–64.
- Meier TB, Bellgowan PS, Singh R, Kuplicki R, Polanski DW, Mayer AR (2015). Recovery of cerebral blood flow following sports-related concussion. *JAMA Neurol* 72: 530–538.
- Merline M, Kalil K (1990). Cell death of corticospinal neurons is induced by axotomy before but not after innervation of spinal targets. *J Comp Neurol* 296: 506–516.
- Mortimer JA, French LR, Hutton JT, Schuman LM (1985). Head injury as a risk factor for Alzheimer's disease. *Neurology* 35: 264–267.
- Mortimer JA, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A *et al.* (1991). Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int J Epidemiol* 20 (Suppl. 2): S28–S35.
- Mouzon BC, Bachmeier C, Ferro A, Ojo JO, Crynen G, Acker CM *et al.* (2014). Chronic neuropathological and neurobehavioral changes in a repetitive mild traumatic brain injury model. *Ann Neurol* 75: 241–254.
- Murray ME, Lowe VJ, Graff-Radford NR, Liesinger AM, Cannon A, Przybelski SA *et al.* (2015). Clinicopathologic and 11C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer's disease spectrum. *Brain* 138 (Pt 5): 1370–1381.
- Murray RF, Asghari A, Egorov DD, Rutkowski SB, Siddall PJ, Soden RJ *et al.* (2007). Impact of spinal cord injury on self-perceived pre- and postmorbid cognitive, emotional and physical functioning. *Spinal Cord* 45: 429–436.
- Nagamoto-Combs K, McNeal DW, Morecraft RJ, Combs CK (2007). Prolonged microgliosis in the rhesus monkey central nervous system after traumatic brain injury. *J Neurotrauma* 24: 1719–1742.
- Ng K, Mikulis DJ, Glazer J, Kabani N, Till C, Greenberg G *et al.* (2008). Magnetic resonance imaging evidence of progression of subacute brain atrophy in moderate to severe traumatic brain injury. *Arch Phys Med Rehabil* 89: S35–S44.
- Nicotra A, Critchley HD, Mathias CJ, Dolan RJ (2006). Emotional and autonomic consequences of spinal cord injury explored using functional brain imaging. *Brain* 129: 718–728.
- Nielson JL, Sears-Kraxberger I, Strong MK, Wong JK, Willenberg R, Steward O (2010). Unexpected survival of neurons of origin of the pyramidal tract after spinal cord injury. *J Neurosci* 30: 11516–11528.
- Nielson JL, Strong MK, Steward O (2011). A reassessment of whether cortical motor neurons die following spinal cord injury. *J Comp Neurol* 519: 2852–2869.
- Nonaka M, Chen XH, Pierce JE, Leoni MJ, McIntosh TK, Wolf JA *et al.* (1999). Prolonged activation of NF-kappaB following traumatic brain injury in rats. *J Neurotrauma* 16: 1023–1034.
- Nordstrom P, Michaelsson K, Gustafson Y, Nordstrom A (2014). Traumatic brain injury and young onset dementia: a nationwide cohort study. *Ann Neurol* 75: 374–381.
- Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH (2005). Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery* 57: 128–134.
- Papadopoulos V, Lecanu L (2009). Translocator protein (18 kDa) TSPO: an emerging therapeutic target in neurotrauma. *Exp Neurol* 219: 53–57.

- Pawson AJ, Sharman JL, Benson HE, Faccenda E, Alexander SP, Buneman OP *et al.*; NC-IUPHAR (2014). The IUPHAR/BPS Guide to PHARMACOLOGY: an expert-driven knowledge base of drug targets and their ligands. *Nucl. Acids Res* 42 (Database Issue): D1098–D1106.
- Perry VH, Nicoll JA, Holmes C (2010). Microglia in neurodegenerative disease. *Nat Rev Neurol* 6: 193–201.
- Piao CS, Stoica BA, Wu J, Sabirzhanov B, Zhao Z, Cabatbat R *et al.* (2013). Late exercise reduces neuroinflammation and cognitive dysfunction after traumatic brain injury. *Neurobiol Dis* 54: 252–263.
- Pierce JE, Smith DH, Trojanowski JQ, McIntosh TK (1998). Enduring cognitive, neurobehavioral and histopathological changes persist for up to one year following severe experimental brain injury in rats. *Neuroscience* 87: 359–369.
- Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D *et al.* (2000). Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology* 55: 1158–1166.
- Ramlackhansingh AF, Brooks DJ, Greenwood RJ, Bose SK, Turkheimer FE, Kinnunen KM *et al.* (2011). Inflammation after trauma: microglial activation and traumatic brain injury. *Ann Neurol* 70: 374–383.
- Richards JS, Brown L, Hagglund K, Bua G, Reeder K (1988). Spinal cord injury and concomitant traumatic brain injury. Results of a longitudinal investigation. *Am J Phys Med Rehabil* 67: 211–216.
- Roberts GW, Gentleman SM, Lynch A, Graham DI (1991). Beta A4 amyloid protein deposition in brain after head trauma. *Lancet* 338: 1422–1423.
- Roberts GW, Gentleman SM, Lynch A, Murray L, Landon M, Graham DI (1994). Beta amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 57: 419–425.
- Rodgers KM, Deming YK, Bercum FM, Chumachenko SY, Wieseler JL, Johnson KW *et al.* (2014). Reversal of established traumatic brain injury-induced, anxiety-like behavior in rats after delayed, post-injury neuroimmune suppression. *J Neurotrauma* 31: 487–497.
- Roth E, Davidoff G, Thomas P, Doljanac R, Dijkers M, Berent S *et al.* (1989). A controlled study of neuropsychological deficits in acute spinal cord injury patients. *Paraplegia* 27: 480–489.
- Saing T, Dick M, Nelson PT, Kim RC, Cribbs DH, Head E (2012). Frontal cortex neuropathology in dementia pugilistica. *J Neurotrauma* 29: 1054–1070.
- Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M *et al.* (2014). Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med* 370: 322–333.
- Schmitt AB, Buss A, Breuer S, Brook GA, Pech K, Martin D *et al.* (2000). Major histocompatibility complex class II expression by activated microglia caudal to lesions of descending tracts in the human spinal cord is not associated with a T cell response. *Acta Neuropathol* 100: 528–536.
- Shitaka Y, Tran HT, Bennett RE, Sanchez L, Levy MA, Dikranian K *et al.* (2011). Repetitive closed-skull traumatic brain injury in mice causes persistent multifocal axonal injury and microglial reactivity. *J Neuropathol Exp Neurol* 70: 551–567.
- Sidaros A, Engberg AW, Sidaros K, Liptrot MG, Herning M, Petersen P *et al.* (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain* 131: 559–572.
- Sidaros A, Skimminge A, Liptrot MG, Sidaros K, Engberg AW, Herning M *et al.* (2009). Long-term global and regional brain volume changes following severe traumatic brain injury: a longitudinal study with clinical correlates. *Neuroimage* 44: 1–8.
- Singh R, Meier TB, Kuplicki R, Savitz J, Mukai I, Cavanagh L *et al.* (2014). Relationship of collegiate football experience and concussion with hippocampal volume and cognitive outcomes. *JAMA* 311: 1883–1888.
- Smith C, Gentleman SM, Leclercq PD, Murray LS, Griffin WS, Graham DI *et al.* (2013a). The neuroinflammatory response in humans after traumatic brain injury. *Neuropathol Appl Neurobiol* 39: 654–666.
- Smith DH, Chen XH, Pierce JE, Wolf JA, Trojanowski JQ, Graham DI *et al.* (1997). Progressive atrophy and neuron death for one year following brain trauma in the rat. *J Neurotrauma* 14: 715–727.
- Smith DH, Johnson VE, Stewart W (2013b). Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat Rev Neurol* 9: 211–221.
- Strubreither W, Hackbusch B, Hermann-Gruber M, Stahr G, Jonas HP (1997). Neuropsychological aspects of the rehabilitation of patients with paralysis from a spinal injury who also have a brain injury. *Spinal Cord* 35: 487–492.
- Trivedi MA, Ward MA, Hess TM, Gale SD, Dempsey RJ, Rowley HA *et al.* (2007). Longitudinal changes in global brain volume between 79 and 409 days after traumatic brain injury: relationship with duration of coma. *J Neurotrauma* 24: 766–771.
- Turtzo LC, Lescher J, Janes L, Dean DD, Budde MD, Frank JA (2014). Macrophagic and microglial responses after focal traumatic brain injury in the female rat. *J Neuroinflammation* 11: 82.
- Umlauf RL (1992). Psychological interventions for chronic pain following spinal cord injury. *Clin J Pain* 8: 111–118.
- Wang G, Zhang J, Hu X, Zhang L, Mao L, Jiang X *et al.* (2013). Microglia/macrophage polarization dynamics in white matter after traumatic brain injury. *J Cereb Blood Flow Metab* 33: 1864–1874.
- Wang H, Pullambhatla M, Guilarte TR, Mease RC, Pomper MG (2009). Synthesis of [(125)I]iodoDPA-713: a new probe for imaging inflammation. *Biochem Biophys Res Commun* 389: 80–83.
- Wang HK, Lin SH, Sung PS, Wu MH, Hung KW, Wang LC *et al.* (2012). Population based study on patients with traumatic brain injury suggests increased risk of dementia. *J Neurol Neurosurg Psychiatry* 83: 1080–1085.
- Wannier T, Schmidlin E, Bloch J, Rouiller EM (2005). A unilateral section of the corticospinal tract at cervical level in primate does not lead to measurable cell loss in motor cortex. *J Neurotrauma* 22: 703–717.
- Wolf SA, Bick-Sander A, Fabel K, Leal-Galicia P, Tauber S, Ramirez-Rodriguez G *et al.* (2010). Cannabinoid receptor CB1 mediates baseline and activity-induced survival of new neurons in adult hippocampal neurogenesis. *Cell Commun Signal* 8: 12.
- Wrigley PJ, Gustin SM, Macey PM, Nash PG, Gandevia SC, Macefield VG *et al.* (2009). Anatomical changes in human motor cortex and motor pathways following complete thoracic spinal cord injury. *Cereb Cortex* 19: 224–232.
- Wu J, Renn CL, Faden AI, Dorsey SG (2013a). TrkB.T1 contributes to neuropathic pain after spinal cord injury through regulation of cell cycle pathways. *J Neurosci* 33: 12447–12463.
- Wu J, Raver C, Piao C, Keller A, Faden AI (2013b). Cell cycle activation contributes to increased neuronal activity in the

posterior thalamic nucleus and associated chronic hyperesthesia after rat spinal cord contusion. *Neurother* 10: 520–538.

Wu J, Zhao Z, Sabirzhanov B, Stoica BA, Kumar A, Luo T *et al.* (2014a). Spinal cord injury causes brain inflammation associated with cognitive and affective changes: role of cell cycle pathways. *J Neurosci* 34: 10989–11006.

Wu J, Stoica BA, Luo T, Sabirzhanov B, Zhao Z, Guanciale K *et al.* (2014b). Isolated spinal cord contusion in rats induces chronic brain neuroinflammation, neurodegeneration, and cognitive impairment. *Cell Cycle* 13: 2446–2458.

Zhang B, Huang Y, Su Z, Wang S, Wang S, Wang J *et al.* (2011). Neurological, functional, and biomechanical characteristics after high-velocity behind armor blunt trauma of the spine. *J Trauma* 71: 1680–1688.

Zhao P, Waxman SG, Hains BC (2007a). Extracellular signal-regulated kinase-regulated microglia-neuron signaling by prostaglandin E2 contributes to pain after spinal cord injury. *J Neurosci* 27: 2357–2368.

Zhao P, Waxman SG, Hains BC (2007b). Modulation of thalamic nociceptive processing after spinal cord injury through remote activation of thalamic microglia by cysteine cysteine chemokine ligand 21. *J Neurosci* 27: 8893–8902.

Zhou Y, Kierans A, Kenul D, Ge Y, Rath J, Reaume J *et al.* (2013). Mild traumatic brain injury: longitudinal regional brain volume changes. *Radiology* 267: 880–890.

Ziebell JM, Morganti-Kossmann MC (2010). Involvement of pro- and anti-inflammatory cytokines and chemokines in the pathophysiology of traumatic brain injury. *Neurother* 7: 22–30.