Journal of Neuroimmunology 332 (2019) 112–125

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review Article

The immunological response to traumatic brain injury

Needham E.J.[a,*], Helmy A.[a], Zanier E.R.[b], Jones J.L.[a], Coles A.J.[a], Menon D.K.[c]

[a] Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
[b] Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[c] Division of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge, UK

ARTICLE INFO

Keywords:
Traumatic brain injury
Neuroinflammation
Innate immune system
Adaptive immune system
Autoimmunity

ABSTRACT

Traumatic brain injury (TBI) is the leading cause of death and disability in young adults in the developed world. The accuracy of early outcome-prediction remains poor even when all known prognostic factors are considered, suggesting important currently unidentified variables. In addition, whilst survival and neurological outcomes have improved markedly with the utilisation of therapies that optimise physiology, no treatments specifically modulate the underlying pathophysiology. The immunological response to TBI represents both a potential contributor to outcome heterogeneity and a therapeutically tractable component of the acute disease process. Furthermore, chronic inflammation has been linked with neurodegeneration, and may mark a bridge between acute brain injury and the subsequent neurodegenerative process seen in a proportion of patients following TBI. Given the complexity of the immune response and its varying functions ranging from repair of injury to bystander damage of healthy tissue, attempts at immunomodulatory intervention must necessarily be highly targeted towards the maladaptive facets of the inflammatory process. In this review we aim to provide an integrated description of the immunological processes triggered by TBI in both humans and animal models, in particular considering the interplay between the innate immune system, danger-associated molecular patterns and loss of self-tolerance leading to adaptive autoimmunity.

1. Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in young adults in the developed world (Jennett, 1996). The initial primary injury causes direct mechanical damage to the brain parenchyma by shearing, tearing and stretching forces. In consequence of this insult, a cascade of metabolic, biochemical and inflammatory changes are initiated, leading to secondary injury (Pearn et al., 2017). Currently recognised prognostic factors account for only around 35% of heterogeneity in outcome between individuals with TBI (Lingsma et al., 2010), and it is likely that these processes of secondary injury contribute to this variation in outcome. In addition, around one quarter of people develop a progressive neurodegenerative syndrome after TBI (Hammond et al., 2004; Himanen et al., 2006; Millis et al., 2001; Ruff et al., 1991; Till et al., 2008; Whitnall, 2006). The underlying mechanisms are again unknown, but two main hypotheses have been proposed: either TBI establishes a neurodegenerative proteinopathy (Washington et al., 2016), or it triggers detrimental neuroinflammation. Increasingly the field of neurodegeneration is recognising the importance of inflammation in proteinopathies, and thus the two prevailing paradigms may be inherently intertwined.

Whilst the presence of substantial inflammatory response after a brain injury is expected; the clinical and biological consequences of this are, however, far from certain. The inflammatory reaction represents an important beneficial mechanism for clearing pathological debris and effecting repair (Neumann et al., 2008; Nielsen et al., 2009), but conversely may also contribute to neuronal damage (Hailer, 2008). Human studies demonstrate an association between late microglial activation after a single TBI, white matter degradation and worse cognitive outcomes, but a causal link cannot be drawn (Johnson et al., 2013; Ramlackhansingh et al., 2011; Scott et al., 2015).

The innate immune system provides the initial response to injury, but soon recruits and activate cells from the adaptive immune system by releasing chemokines, inducing adhesion molecules on the blood brain barrier (BBB) and expressing co-stimulatory molecules on microglia (Amor et al., 2010; Olson and Miller, 2004; Wong et al., 1999). The dynamics of the local cellular reaction are displayed in pathological specimens, which reveal an initial migration of neutrophils into injured brain regions, followed later by a more heterogenous infiltrate (Clausen et al., 2007; Holmin et al., 1998, 1995; Xu et al., 2016). Further proximate processes, such as the mechanotransductive alterations of cell adhesion molecules, and the release of neurogenic inflammatory

* Corresponding author.
E-mail address: edneedham@doctors.org.uk (E.J. Needham).

https://doi.org/10.1016/j.jneuroim.2019.04.005
Received 22 April 2018; Received in revised form 9 April 2019; Accepted 9 April 2019

compounds such as Substance P compound the "classical" inflammatory reaction (Hemphill et al., 2015; Vink et al., 2017).

In addition to this local response, TBI releases cerebral antigens into the peripheral circulation, lymph nodes via glymphatics (a perivascular system of waste clearance channels) (Mondello et al., 2017; Plog et al., 2015) and perhaps also by meningeal lymphatic vessels (Absinta et al., 2017), where they encounter naïve immune cells and trigger adaptive autoreactivity (Cox et al., 2006; Harling-Berg et al., 1989). Such injury-related immune responses are particularly relevant to the brain, which is still thought to display relative immune-privilege in adults (Erickson and Banks, 2018), increasing the risk that antigens may not be fully recognised as self. Tissue injury is known to induce harmful auto-immunity, with notable examples in post-myocardial infarction peri-carditis, or sympathetic ophthalmia, a granulomatous process in the contralateral uvea precipitated by optical trauma, which in severe cases can involve the retina, or even meninges (Jr et al., 2017). Conversely, in animal models of spinal cord and optic nerve injury, one research group has suggested that autoreactivity associates with attenuated secondary degeneration and improved outcome (Hauben et al., 2000; Moalem et al., 1999), raising the possibility for a protective function of auto-immunity.

In this review we aim to provide an integrated description of the immune responses to TBI across the innate and adaptive systems in both the acute and chronic setting.

2. Danger-associated molecular patterns and the inflammasome

The inflammatory response to TBI starts at the point of injury, with tissue damage leading to the release of danger-associated molecular patterns (DAMPs) such as high mobility group box-1 (HMGB1), ATP, heat-shock and S100 proteins (Braun et al., 2017). Circulating DAMPs are bound by Pattern Recognition Receptors (PRRs) such as Toll-like receptors (TLR) on myeloid and dendritic cells, and receptors of advanced glycosylation end-products (RAGE). Ligand recognition by these PRRs triggers the production of proinflammatory cytokines either through direct intracellular signal transduction, or by oligomerisation to form inflammasomes (notably NLRP1 and NLRP3). Inflammasomes are cytosolic multiprotein platforms, predominantly expressed in the central nervous system (CNS) by astrocytes, microglia and macrophages, that enable the cleavage and activation of pro- inflammatory caspases, which in turn activate cytokines such as IL-1β or IL-18 (Mortezaee et al., 2018). DAMPS bear the ability to initiate adaptive autoimmunity via the direct maturation of steady-state immature dendritic cells (DCs) into immunostimulatory DCs, with subsequent presentation of self-antigens to, and stimulation of, naïve T-cells (Land, 2015).

High levels of HMGB1 and other DAMPs such as S100b appear to be associated with poor outcome following TBI in humans (Wang et al., 2012; Thelin et al., 2013), and intervening therapeutically to reduce their influence is a feasible prospect. Blockade or knockout of the ATP-binding receptor P2X7 (a DAMP with potent NLRP3 activating properties) reduces cerebral oedema, lesion volume and expression of IL-1β in peri-lesional cortex both 12 and 24 hours post-injury, as well as neurobehavioural outcome in a murine model (Kimbler et al., 2012). Similarly, inhibition or knockout of TLR-4, a key microglial receptor for HMGB1, reduces cerebral oedema and cortical IL-6 production in mice (Laird et al., 2014), a finding corroborated by the anti-oedema effect of administering anti-HMGB1 monoclonal antibody to rats with TBI (Okuma et al., 2012). Assessment of this pathway further downstream yields similar results, with upregulation of the NLRP3 inflammasome (as measured by ELISA) associating with poor outcomes in humans (Wallisch et al., 2017). Targeting this cascade also appears to have beneficial effects in animal studies, with NLRP3 knock-out mice demonstrating preservation of cognitive function after TBI compared to wild-type mice, with less histological brain damage and lower levels of caspase-1 and subsequently IL-1β in brain lysate (Irrera et al., 2017).

3. Cytokines

The predominant consequence of tissue injury, DAMP release and inflammasome activation is a marked increase in synthesis of pro-inflammatory cytokines such as IL-1β, IL-6, IL-18 (a requisite co-activator for IFNγ production) and TNFα, accompanied by a counter-regulatory rise in levels of anti-inflammatory cytokines including IL-10 (Helmy et al., 2011b). It should be noted here that whilst allocating an individual cytokine to either a pro- or anti-inflammatory group provides a useful shorthand to appreciate its role in a broad sense, relying entirely on such classification misses the more complex and nuanced functions of such molecules. For example, IL-10, considered as an archetypal "anti-inflammatory" cytokine due to its suppressive effect on the Th1 axis, is a potent driver of B-cell activation, maturation and antibody synthesis, and can subsequently drive detrimental inflammation via B-cell mediated pathways (Tian et al., 2014).

In addition to the above responses, glial and neuronal damage leads to the production of a raft of chemokines such as IL-8, MCP1 and CCL5 (Helmy et al., 2011a), which serve to attract and activate both peripherally-derived and CNS-resident immune cells to the area, notably neutrophils, microglia and T-cells.

The repeated demonstration of prominent pro-inflammatory cytokine responses, with a "dose-dependent" relationship to poor outcome (reviewed comprehensively in articles by Woodcock and Helmy (Helmy et al., 2011b; Woodcock and Morganti-Kossmann, 2013)), as well as suggestions from genetic studies that polymorphisms in cytokine genes (IL-1β and TNF α) affect outcome (Uzan et al., 2005; Waters et al., 2013), led to the postulation that an excess of these mediators may contribute to secondary injury following TBI. Whilst in isolation Il-1β does not appear to cause direct neuronal death (in culture models), under certain circumstances (notably when neurons are co-cultured with glial cells, particularly in the presence of other pro-inflammatory cytokines such as TNFα (Chao et al., 1995; Dunn et al., 2002)) IL-1β induces neuronal death, presumably in part via its actions on glia as effector cells, which aside from their direct toxic effect from reactive oxygen and nitrogen species production, trigger a positive feedback loop of IFNγ and TNF-α production, subsequent "classical" microglial activation (Hu et al., 2015; Sica and Mantovani, 2012), and finally neuronal phagocytosis by microglia (Neniskyte et al., 2014). Additionally, IL-1β increases local expression of adhesion molecules catalysing ingress of leukocytes from the vasculature (Allan et al., 2005), the impact of which is discussed below.

With this in mind, reduction of the influence of IL-1β using either its natural inhibitor IL-1 receptor antagonist (IL-1ra) or neutralising anti-IL-1 antibodies has been employed in murine TBI models with demonstrable benefit reported in oedema, contusion volume, neurodegeneration, cognitive deficits and overall neurological recovery (Clausen et al., 2011, 2009; Sanderson et al., 1999; Tehranian et al., 2002; Toulmond and Rothwell, 1995). This improvement was accompanied histologically by a reduction in neutrophil and activated T-cell ingress, as well as an attenuation of microglial activation (Clausen et al., 2009). Recombinant IL-1ra has since been subjected to a human phase II randomised controlled trial in TBI, demonstrating safety, CNS penetration and modification of the cytokine milieu within brain extracellular space; the study was not powered to show a therapeutic benefit, and thus these data were not reported (Helmy et al., 2014).

Similarly, attempts have been made to target TNFα, a cytokine which serves similar and complementary effects to IL-1β in acute inflammation, in particular the upregulation of adhesion molecules and increased vascular permeability which facilitates leukocyte diapedesis into the injured area (Bradley, 2008). TNFα knockout mice subjected to controlled cortical impact had improved motor and cognitive performance, smaller lesion size and more benign histological appearances compared to wild-type mice; this protective phenotype was reversed when recombinant TNFα was administered prior to injury (Bermpohl et al., 2007; Khuman et al., 2011). Concordant improvements in

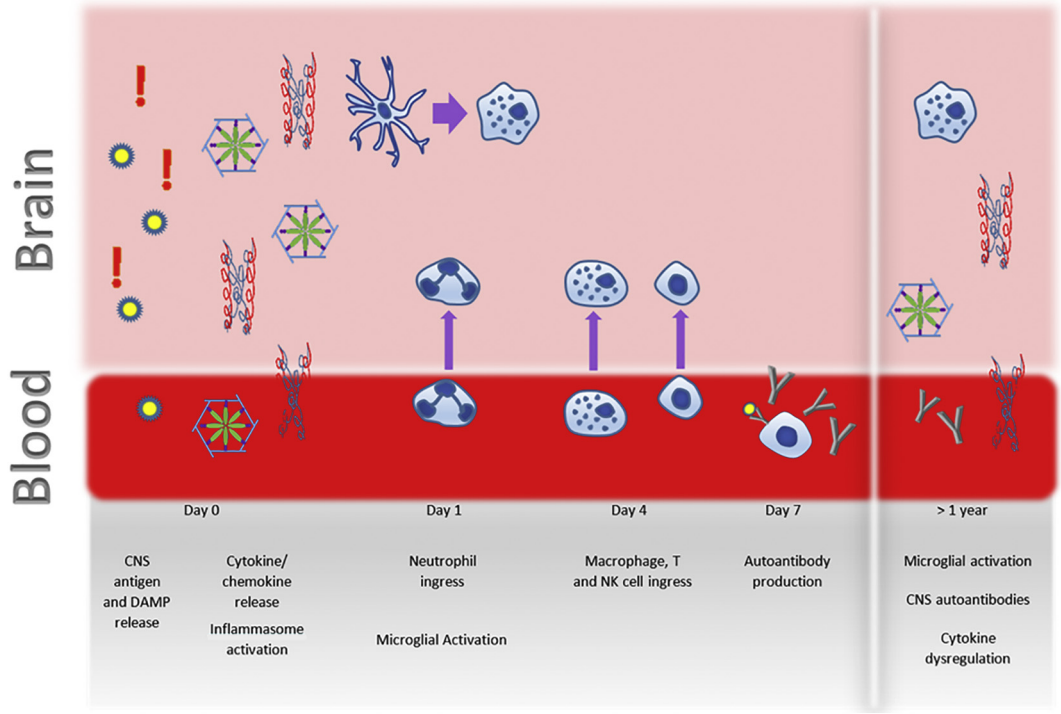

Fig. 1. Timeline of inflammatory response to TBI. Initial CNS antigen and DAMP release is rapidly followed by inflammasome activation and cytokine/chemokine release, which attracts and activates immune cells. This cellular infiltration initially consists solely of innate immune cells, but is joined by adaptive leukocytes within days. Whilst this response largely wanes, a proportion of patients display a persistent immune dyscrasia, with microglial activation, cytokine dysregulation and ongoing autoantibody production.

outcome have further been described in a rat model following the administration of monoclonal antibodies to TNFα (Chio et al., 2010). However, the literature does display incongruity, perhaps reflecting the complexity of the roles of individual cytokines, with other studies describing a protracted recovery despite initial neuroprotection in TNFα knockout mice (Scherbel et al., 1999), exacerbation of cortical damage and blood-brain barrier disruption in TNF receptor knockout mice (Sullivan et al., 1999) and improved motor and histological outcomes following treatment with inhibitors of TNFα (Shohami et al., 1997, 1996), although note should be made of the non-specific nature of the later therapies compared with monoclonal antibody treatment. Translation from rodent studies into humans has as yet been unrewarding, with a negative phase III trial of dexanabinol, a drug with, but not limited to, TNF inhibition properties (Maas et al., 2006). It should be borne in mind that TNFα's pleiotropic functions in inflammation (including control of cell proliferation, differentiation, and apoptosis) are mediated by interactions with two, functionally distinct and often opposing, TNF receptors (TNFR1 and TNFR2), and thus global blockade of TNFα may be misguided. Data show that after TBI, TNFα may exacerbate neurobehavioral deficits and tissue damage selectively via TNFR1, whose inhibition may represent a specific therapeutic target after TBI (Longhi et al., 2013).

In notable contrast to the replicable association between IL-1β and TNFα with poor outcome in both human and animal studies, IL-6, another prototypic "pro-inflammatory" cytokine appears to have predominantly neuroprotective effects in animal models (Penkowa et al., 2000, 2003), but associates variably with outcomes following TBI (Chiaretti et al., 2005; Kumar et al., 2015a, 2015b; Kushi et al., 2003; Singhal et al., 2002). Whilst this is likely to be the result of experimental variation (notably the "clean" model of selective Il-6 deficiency in a controlled cortical impact model versus the real-life situation of TBI with multiple co-morbidities including infection etc.), it is possible that it speaks of the complexity of function of certain cytokines. Whilst nominally a pro-inflammatory cytokine, IL-6 drives the move from early neutrophil ingress in inflammation to monocyte and lymphocyte infiltration by suppressing neutrophil attracting chemokines (CXCL1, CXCL8/IL-8), upregulating neutrophil apoptosis and enhancing monocyte/microglia (CCL2/MCP-1, CCL8/MCP-2, CXCL5/ENA-78, CXCL6/GCP-2) and lymphocyte (CCL5, CCL17, and CXCL10) attracting chemokines. In addition, it influences lymphocyte maturation, skewing T-helper cells towards Th2 and Th17 phenotype, and inhibiting Treg differentiation, whilst also enhancing IgG production from B-cells (Scheller et al., 2011).

The issue of extrapolating from biomarker to physiological role is further highlighted by the quintessential anti-inflammatory cytokine IL-10, where murine studies using IL-10 knockout strains or exogenously administered IL-10 suggest a beneficial role in the context of TBI (Chen et al., 2014a; Knoblach and Faden, 1998), yet observational clinical studies point towards high IL-10 associating with poor outcome (Bell et al., 1997; Kirchhoff et al., 2008; Shiozaki et al., 2005; Soares et al., 2012). A simple explanation for this relationship would be that the observed increases in IL-10 are homeostatic responses to a heightened inflammatory process; IL-10 downregulates synthesis of proinflammatory cytokines such as IFNγ and TNFα, inhibits effector functions of Th1 and activated CD8+ T-cells, supresses monocyte/macrophage and microglia activity (partly via repression of both constitutive and interferon-γ induced MHC class II expression) and induces differentiation of regulatory T-cells (Groux and Cottrez, 2003; Lobo-Silva et al., 2016; Mannino et al., 2015). However, to reduce the function of IL-10 to the above would be to ignore its pivotal role in driving antibody responses (Tian et al., 2014), and to underestimate the complexity of the network-effects of cytokine modulation; indeed therapeutic use of IL-10 in autoimmune diseases has been largely unrewarding (Saxena et al., 2015).

4. Cellular response

4.1. Neutrophils

Within hours of TBI, a marked ingress of neutrophils is demonstrable within injured tissue (Clark et al., 1994; Holmin et al., 1995; Soares et al., 1995), a finding compatible with the demonstration of early local production of the major neutrophil chemokine IL-8 in cerebral microdialysate (Helmy et al., 2011a). The IL-8 chemotactic gradient is complemented by an upregulation of vascular endothelium cell adhesion molecules such as E-selectin and Intercellular Adhesion Molecule 1 (ICAM-1), facilitating passage of neutrophils into injured parenchyma (Carlos et al., 1997). This neutrophilic predominance peaks by day 2, where upon numbers decline and a more diverse infiltrate of monocyte-derived macrophages, T lymphocytes and natural killer cells (Holmin et al., 1998, 1995) as well as activation of resident CNS microglia (Engel et al., 2000; Wang et al., 2013) (Fig. 1).

Whilst neutrophil invasion of injured tissue may have beneficial aspects such as removal of cell debris (Kolaczkowska and Kubes, 2013), the potential for compounding damage is well described, both through the direct toxic effects on neurons of matrix metalloproteinases, reactive oxygen species (ROS) and TNF-α (Dinkel et al., 2004; Nguyen et al., 2007) as well as an increase of vascular permeability which results in oedema and subsequent cellular metabolic stress (Lindbom, 2003; Schoettle et al., 1990). In an attempt to ameliorate these detrimental consequences, therapeutic neutrophil depletion has been trialled in animal models, with neutrophil-depleted mice demonstrating reduced oedema and brain tissue loss compared to immunocompetent mice (Kenne et al., 2012). Additionally the neutrophil-depleted mice showed reduced microglial activation, suggesting that intervening early in the inflammatory cascade may halt downstream processes. Manipulating neutrophil infiltration or function, using CXCR2 or neutrophil elastase knockout mice, supported this result, demonstrating reduced cell death in both knockout strains, but with little benefit in functional outcome (Semple et al., 2015, 2010). Inhibition of neutrophil and macrophage diapedesis into injured brain using an anti-CD11d monoclonal antibody which blocks the interaction between the CD11d/CD18 integrin and vascular cell adhesion molecule (VCAM)-1 did however show a benefit in neurological outcome in rats (Bao et al., 2012).

4.2. Microglia and astrocytes

Microglia represent the brain's resident immune cell, and make up between 5-20% glial cells (Kawabori and Yenari, 2015). In health, microglia play a wide and vital homeostatic role, including the surveillance of their territory for evidence of minor tissue damage or impairment in functional integrity, and phagocytosis of debris. in this housekeeper role, they constantly survey the microenvironment and are characterised morphologically by a ramified appearance, with motile, searching arborisations and processes (Hanisch and Kettenmann, 2007). In response to TLR binding of DAMPs released following frank CNS injury, microglia readily activate and undergo a morphological shift from ramified to amoeboid state (with enlarged soma and retracted processes), which renders them almost identical to peripherally-derived macrophages (Saijo and Glass, 2011). The environment in which activation occurs (namely the local Th1/Th2 cytokine balance) polarises microglia along a spectrum between a “classically-activated” M1-like phenotype, characterised by ROS release, pro-inflammatory cytokine (IL-1 β, TNF α) production, and Th1/Th17 lymphocyte activation via MHC-II expression and cytokine secretion (IL-12, TGF β), to an “alternatively-activated” M2-like phenotype capable of IL-10 production, Th2 cell recruitment, tissue repair and growth stimulation (Saijo and Glass, 2011; Sica and Mantovani, 2012). Traditionally seen as an immutable commitment to a particular phenotype, such “polarization” is now recognised as a malleable activation phenotype. Indeed microglia can move from one point of the spectrum to another, even attaining a “mixed” phenotype (Morganti et al., 2016).

Activation of microglia is demonstrable in human TBI soon after the initial neutrophil response begins to wane (Engel et al., 2000), and in mouse models, there appears to be intense microglia/macrophage activation as early as 24 hours post-injury (Zanier et al., 2015). Some reports suggest an M2-like predominance by 1 week post-injury, shifting to an M1-like pattern in a second peak 1 month post-injury; however, despite this apparent skew in phenotype, it should be noted that the majority of activated microglia show mixed characteristics (Jin et al., 2012; Morganti et al., 2016; Turtzo et al., 2014; Wang et al., 2013). In addition to this activation of local microglia, peripherally-derived monocytes/macrophages invade the injured tissue and, whilst experiencing only minor morphological changes on activation, undergo a similar complex differentiation along the M1/M2 spectrum (Hsieh et al., 2013; Kim et al., 2016), with the respective functional consequences. In addition to such post-migration phenotypic differentiation, the impact of these cells may also be dictated by pre-recruitment phenotype, with atypical CX3CR1-expressing monocytes, perhaps playing a more prominent role in secondary injury, as they migrate towards cognate ligands produced by damaged neurons (Makinde et al., 2017).

As previously alluded to, pro-inflammatory cytokines and ROS have the potential to cause direct neuronal damage, and this fact is again borne out in the setting of “classically-activated” microglia, which appear to propagate a self-perpetuating pro-inflammatory environment with resultant progressive brain injury (Block et al., 2007; Loane et al., 2014; Wang et al., 2013). This has led to attempts to manipulate both microglial activation and monocyte/macrophage invasion. Microglial depletion was successfully achieved by using either valganciclovir treatment in CD11b thymidine kinase mice, or CD11b diphtheria toxin receptor mice, but did not attenuate injury in either model (Bennett and Brody, 2014; Frieler et al., 2015). Conversely, inhibition of recruitment of monocyte/macrophages by targeting the chemokine receptor CCR2 achieved not only reduction of recruitment of peripheral macrophages to the brain following TBI, but also improved neurological outcomes (Hsieh et al., 2014; Morganti et al., 2015). The encouraging impact on early outcome may, however, be tempered by a predisposition towards subsequent tauopathy (Gyoneva et al., 2015), highlighting the need to carefully balance the potentially detrimental effects of acute inflammation with the important housekeeping role macrophages may play following injury. This dualism is further demonstrated in studies in mice models of mild (Febinger et al., 2015) and severe (Zanier et al., 2016) TBI, that consistently showed a time-dependent role for CX3CL1/CX3CR1 signaling that modulates microglial/macrophages activation and phenotype. CX3CR1 KO mice showed a significant reduction of sensorimotor deficits and lower cellular damage in the injured cortex within the first week after TBI. At 1 month post-TBI however, they showed a worsening of functional deficits and increased cell death compared to WT mice. These effects were associated with changes in microglia phenotypes, with CX3CR1 KO mice showing a predominant anti-inflammatory M2-like microglial/macrophages response in the acute phase and a more pronounced M1-like phenotype at 1 month. Inhibition of microglial activation, particularly of those with an M1-like phenotype, has been well described using the antibiotic minocycline (Adembri et al., 2014; Chen et al., 2014a, 2014b; Kobayashi et al., 2013), and again has been associated with improved early outcomes in animals (Homsi et al., 2010), but once more with the threat of late neurodegeneration, this time demonstrated in humans treated at least 6 months post-injury (Scott et al., 2018).

Whilst the contribution of astrocytes to neuroinflammation is less well defined than that of microglia, it is apparent that they are not only involved, but once more display a complex spectrum of phenotype with roles in both tissue damage and repair (Colombo and Farina, 2016). A controlled cortical impact (CCI) model, using glial fibrillary acidic protein–herpes simplex virus–thymidine kinase transgenic (GFAP-TK) mice treated with ganciclovir (which ablates their proliferating reactive

astrocytes), demonstrated that those mice who underwent ablation of reactive astrocytes demonstrated substantial neuronal loss and increase in microglial activation compared to control mice following moderate (but not severe) CCI, suggesting a largely protective function in this setting (Myer et al., 2006). It is worth noting at this point that the Positron-Emission Tomography (PET) ligand translocator protein 18 kDa (TSPO), used as a marker of microglial activation, also binds to activated astrocytes and thus confidently disentangling these two processes is not currently possible in vivo (Lavisse et al., 2012).

4.3. T-Lymphocytes

Recruitment of T-cells into traumatically injured brain appears to occur contemporaneously with monocyte/macrophages (Dreßler et al., 2007; Holmin et al., 1998, 1995), through the upregulation of cell adhesion molecules and local production of chemokines such as CCL5 (RANTES)(Carlos et al., 1997; Helmy et al., 2011a), and represents the engagement of the adaptive immune system. Whilst there is a suggestion that the earliest T-cell populations recruited may be IL-17 producing γδ T-cells (Gelderblom et al., 2014) (an intermediary between innate and adaptive immunity, activated by either major histocompatibility complex (MHC)-related or unrelated T-cell receptor (TCR) ligands), the majority are αβ T-cells. These αβ T-cells require TCR-antigen engagement alongside co-stimulatory receptor binding and stimulation of relevant cytokine receptors such as IL2 for activation, suggesting autoreactivity to self-CNS antigens. In health, the presence of cerebral antigens in the blood is negligible; trauma, however, leads to a massive release of CNS proteins both directly into the circulation and to the cervical lymph nodes via the glymphatic and meningeal lymphatic systems, where they may be phagocytosed by professional antigen-presenting cells, with the subsequent production of self-reactive T-cells (particularly in the company of DAMPs) (Land, 2015; Mondello et al., 2017; Plog et al., 2015). Once activated, T-cells express necessary surface molecules to cross the BBB, a mechanism which, in addition to chemokine production, is upregulated in the context of inflammation and microglial activation, significantly increasing T-cell ingress (Engelhardt and Ransohoff, 2005). Furthermore, antigen-specific CD8+ T-cells have been demonstrated to migrate into the CNS and co-localise to their cognate antigen (Ling, 2006).

Whilst CNS autoreactive T-cells are typically considered harmful given their involvement in autoimmune diseases such as multiple sclerosis (Fletcher et al., 2010), their role following CNS injury is less clear, with the literature diametrically split between autoreactivity resulting in a destructive process, or in “protective autoimmunity”. The concept of protective autoimmunity, largely promoted by one group, was first demonstrated by the attenuation of secondary degeneration of retinal ganglion cells following optic nerve crush injury in rats with the passive transfer of activated myelin basic protein (MBP)-reactive T cells (Moalem et al., 1999). Subsequent experiments using active immunisation with myelin products such as MBP or myelin oligodendrocyte glycoprotein (MOG) in diverse models of CNS injury including spinal cord and traumatic brain injuries supported the protective effect (Hauben et al., 2001, 2000; Hofstetter et al., 2003; Kipnis et al., 2001), as did pre-exposure to spinal cord injury prior to optic nerve crush injury (Yoles et al., 2001). The putative mechanism behind protective autoimmunity is the production of neurotropic factors by autoreactive lymphocytes (Schwartz, 2001).

Other groups, however, have demonstrated that the presence of MBP-reactive T-lymphocytes exacerbates neuropathology after CNS injury with corresponding impairment in function (Jones et al., 2002, 2004; Jones, 2014; Fee et al., 2003). Therapeutic use of fingolimod, a sphingosine-1-phosphate receptor modulator which inhibits lymphocyte egress from lymphoid tissue, decreased T and NK cell infiltration and increased Treg numbers (believed to be neuroprotective in TBI) (Li et al., 2015), with an additional beneficial impact on microglial activation patterns, axonal damage and neurological function in mice (Gao et al., 2016). In human TBI, however, only a single small study has assessed the impact of autoreactive T-cells, and favours the concept of protective autoimmunity (Cox et al., 2006).

Further mechanistic experiments exploring protective autoimmunity suggest that T-cell mediated neuroprotection is dominated by IL4 producing Th2 lymphocytes, and may well in fact be independent from MHC-II (i.e. antigen specific) signalling (Walsh et al., 2015). Conversely, M1 polarisation of infiltrated macrophages drives CD4+ cells down a Th1/Th17 route, and inhibits Treg production following TBI (Kirchhoff et al., 2008). Th17 lymphocytes themselves also stimulate M1-like microglial activation, pointing to the ability of pro-inflammatory states to self-perpetuate within the CNS (Murphy et al., 2010). It is likely therefore, that differing T-lymphocyte populations may variably exact detrimental or beneficial sequelae.

5. B-cells and autoantibodies

5.1. Detection of autoantibodies following TBI

By seven days post-injury, patients with TBI exhibit a high frequency of activated B-cells characterised by an increased proportion of memory (CD27+) and class-switched memory (CD27+ IgD-), suggesting germinal center (GC) reactions in the course of T cell-dependent immune responses (Chenouard et al., 2015). A key function of B-cell activation is the production of antibodies, and the role of autoantibodies in TBI has been questioned for over 40 years (Procházka et al., 1971; Shamreĭ, 1969), with early demonstrations of antibodies to brain antigens in both blood and cerebrospinal fluid (CSF) correlating in titre with injury severity (Detlav, 1976; Livshits and Shakarova, 1975). The details of the techniques used in these early experiments are now largely unavailable, although one study utilises the Hoigné method (Detlav, 1976), a procedure involving a highly sensitive nephelometer to measure optical density of serum as the antigen of study is added in increasing quantities. The first specifically identified antigenic target was MBP, a key component of myelin (Lisianyĭ et al., 1987). This finding was replicated many years later(Ngankam et al., 2011); unfortunately the methodological details for both these studies are also inaccessible.

Since this point, autoantibodies to a variety of cerebral proteins have been described in humans following TBI, including cytoskeletal structures and neurotransmitter receptors (Fig. 2; Table 1). Antibodies to the calcium-binding protein S100-b, a neurobiochemical marker of glial activation or death, are seen in both repeated mild TBI as well as single major TBI when measured by ELISA (Bazarian et al., 2014; Marchi et al., 2013; Morozov et al., 1996). Glial-fibrillary acidic protein (GFAP), an intermediate filament protein localising to astrocytes, GFAP breakdown products (GFAP-BDP) and the neuronal cytoskeleton component β tubulin 3 have been identified by western blot and ELISA respectively as antibody targets following severe TBI (Škoda et al., 2006; Zhang et al., 2014). Aside from these structural proteins, autoantibodies to neurotransmitter receptor targets including glutamate receptors of both the NMDA (NR_2A subunit) and AMPA ($GluR_1$ subunit) types (Goryunova et al., 2007; Sorokina et al., 2009), and the acetylcholine receptor (α-7 subunit) have been detected by ELISA (Sorokina et al., 2011). In addition to the above neuronal and glial targets, antibodies against the hypothalamic-pituitary axis (Tanriverdi et al., 2010, 2008), as well as to ubiquitously expressed proteins such as phospholipids, tissue transglutaminase and nuclear antigens have been demonstrated using indirect immunofluorescence and ELISA (López-Escribano et al., 2002).

Whilst these studies have attempted to identify specific antigenic targets, the western blot experiments suggest that there is a likely to be a polyantigenic response following TBI (Zhang et al., 2014). The temporal pattern of immunoglobulin production is typical of inoculation, with an initial short-lived IgM response followed by more protracted IgG synthesis (Škoda et al., 2006; Zhang et al., 2014). Importantly, the

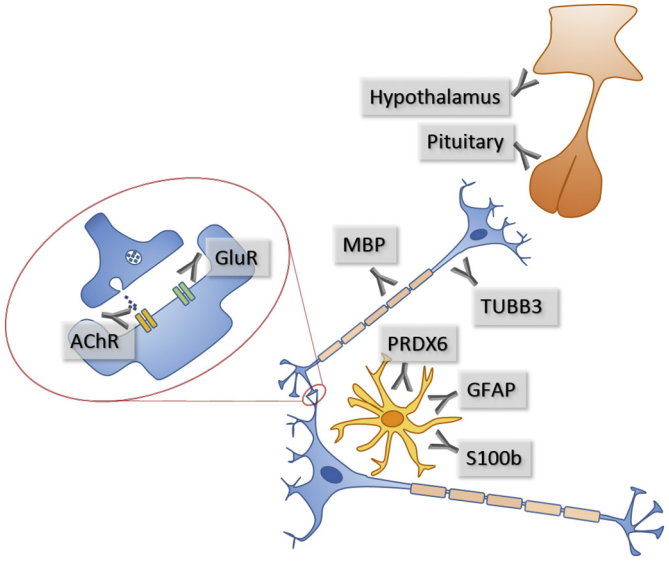

Fig. 2. Described CNS antibody targets following TBI (AChR = Acetylcholine Receptor, GluR = Glutmate Receptor, MBP = Myelin Basic Protein, PRDX6 = Peroxiredoxin 6, TUBB3 = Tubulin Beta Class 3, GFAP = Glial Fibrillary Acidic Protein). Autoantibodies have been described to numerous CNS antigens following TBI, including neurotransmitter receptors, myelin proteins and cytoskeletal components.

IgG response is seen to persist years after the injury (Tanriverdi et al., 2008; Wang et al., 2016), which might suggest ongoing antigen exposure and gives credence to the possibility that these autoantibodies could play a biologically relevant role in the chronic phase of TBI, rather than representing an innocuous bystander phenomenon.

Rat studies reflect the findings in human experiments, with antibodies to MBP(Li et al., 2008) and peroxiredoxin 6 (a primarily astrocytic antioxidant enzyme) (Buonora et al., 2015) detected by ELISA and western blot respectively, and binding to neurons, astrocytes and vascular basal lamina seen on tissue immunofluorescence (Rudehill et al., 2006).

5.2. Mechanisms of autoantibody production

Traditionally the central nervous system was viewed as an immunologically privileged site, protected from immune system recognition by the blood-brain barrier. Recognition that even common neurological disorders such as multiple sclerosis were at least in part immunologically mediated led to a reconsideration of the interaction between the central nervous and immune systems, and the role that the blood brain barrier (BBB) plays in both health and disease.

As mentioned previously, it is well documented that TBI releases cerebral antigens such as S100b and GFAP into the peripheral circulation (Marchi et al., 2013; Zhang et al., 2014), and therefore it is unsurprising that there should be immune recognition of these proteins. Indeed, the titre of serum anti-GFAP antibodies correlates directly with the titre of GFAP detected in the serum on day one post-injury (Zhang et al., 2014).

Whilst this release may be largely due to compromise of the blood-brain barrier, a conventional meningeal lymphatic drainage system has now been recognised (Absinta et al., 2017), and the recently described glymphatic pathway has been shown to drain CNS proteins directly to the cervical lymph nodes following TBI, where they can be presented to lymphocytes by professional antigen-presenting cells (APCs) (Plog et al., 2015). Furthermore, whilst dendritic cells (DCs) were traditionally believed to be absent from the CNS, leaving microglia and peripherally derived monocytes/macrophages to function as the predominant antigen-presenting cells, it is now recognised that they are not only present but active, particularly following CNS injury (D'Agostino et al., 2012). These DCs have been shown to phagocytose proteins within the CNS, mature, migrate into the periphery and subsequently activate peripheral T-cells, which play a crucial role in B-cell activation and subsequent antibody synthesis (Koutsilieri et al., 2012; Oberländer et al., 2011).

Whilst these mechanisms might explain the presence of detectable antibodies in the serum, to have a biologically significant effect the antibodies would have to gain access to the CNS. Aside from highly specific circumstances, such as cerebral infection, the BBB prevents antibodies from reaching the CNS and thus in principle mitigates against parenchymal binding. In the acute stage of TBI, there is BBB compromise, and autoreactive IgG can be seen to bind around cortical lesions (Stein et al., 2002). This lack of BBB integrity has been documented to persist long-term following the injury, and indeed IgG deposition can be seen at points of permeability years after the injury (Hay et al., 2015). Furthermore, activation of T-cells (even those without CNS specificity) has been shown to open the BBB to allow autoantibody ingress (Westland et al., 1999). In the context of a truly restored BBB, for antibodies to reside in this compartment later in the disease course they must be locally produced. The archetypal inflammatory brain disease, multiple sclerosis, is associated with intrathecal antibody production, and in the course of elucidating the mechanisms of this, it was discovered that B-cell maturation could be sustained within the CNS, leading to the establishment of B-cell follicles within the meninges (Magliozzi et al., 2007). Similar lymphoid follicles have been described in injured tissue following experimental traumatic spinal cord injury, a condition with substantial similarities to TBI (Ankeny et al., 2006). The biological consequences of this ectopic lymphoid tissue are, however, yet to be fully delineated.

In addition to antigen recognition, most B-cell processes require co-stimulation from antigen-specific T-cells to trigger antibody production. As detailed above, autoreactive T-cells are generated following TBI, and the ability of activated T-cells to enter the CNS provides the scope for them to co-activate resident B-cells, leading to autoantibody production within the CNS itself (Hickey, 2001). The fact that this can occur in the presence of an intact BBB (Knopf et al., 1998), suggests the potential for ongoing relevance after the BBB has reformed following a traumatic injury (Fig. 3).

5.3. Relevance of autoantibody production in TBI

Naturally occurring autoantibodies of the IgM type appear to have a regenerative homeostatic function, removing cell debris and neutralising pro-inflammatory cytokines (Gold et al., 2012; Warrington et al., 2001). Indeed, IgM autoantibodies to brain antigens are found not infrequently in both those with neurological illness as well as healthy controls (Dahm et al., 2014) (although one must pay caution to the idea of “healthy controls” in such studies, given the prevalence of minor traumatic or ischaemic brain injuries throughout a lifetime). In contrast, subject to the cytokine and alarmin/DAMP milieu accompanying antigen recognition, B-cells can undergo class switch recombination and somatic hypermutation with the subsequent production of high affinity IgG autoantibodies and complement-mediated cell destruction, highlighting the potential dualism of an autoimmune response.

The overriding association in the literature between outcome following TBI and autoantibody production is one of harm. The presence of MBP, GFAP/GFAP-BDP or acetylcholine receptor antibodies correlate with injury severity and neurological outcome (Ngankam et al., 2011; Sorokina et al., 2011; Zhang et al., 2014), S100b antibodies with diffusion tensor imaging abnormalities and cognitive impairment (Bazarian et al., 2014; Marchi et al., 2013) and pituitary and hypothalamic antibodies with endocrinopathy (Tanriverdi et al., 2010, 2008). The descriptions of glutamate receptor antibodies are less clear cut, occurring in higher titres in those with milder head injuries, but

Table 1
Autoantibodies detectable following traumatic brain injury. (NS = not stated in paper) Numerous autoantibodies have been described following TBI, and by diverse methods. Western Blot techniques suggest a polyantigenic response, and thus it is to be expected that multiple studies assessing for a single autoantibody have had positive results. More work is required to investigate whether particular individuals develop antibodies to many antigens and others to none, or whether the loss of self-tolerance is global but the autoantibody-specificity is variable between individuals.

Antibody	TBI Severity	Sample Source	Assay Technique	Antigen Type	Proportion Developing Antibodies	Clinical Association	Reference
Human Studies							
Acetylcholine Receptor	NS	Serum	NS	Peptide	NS	Association with injury severity	(Sorokina et al., 2011)
Antinuclear Antibodies	Severe	Serum	IIF	HEp-2 Cells	60%	NS	(López-Escribano et al., 2002)
Beta Tubulin Class 3	Severe	Serum	ELISA	Peptide	83%	NS	(Škoda et al., 2006)
Glial Fibrillary Acidic Protein	Severe	Serum	Western Blot	Human Brain lysate	75%	Association with injury severity and 6 month outcome	(Zhang et al., 2014)
	Mild-severe	Plasma	Western Blot	Protein from human brain lysate	NS	Increase in antibody level correlated with outcome at discharge NS	(Wang et al., 2016)
Glutamate Receptors	Mild-Severe	Serum	ELISA	Peptide	NS	Inverse association with severity	(Sorokina et al., 2009)
GluR1 & NR2a	Mild	Serum	ELISA	Peptide	All patients	Association between titre and residual neurological symptoms	(Goryunova et al., 2007)
Myelin Basic Protein	NS	CSF	NS	NS	NS	Association with injury severity and outcome	(Ngankam et al., 2011)
	NS	NS	NS	NS	NS	NS	(Lisianyĭ et al., 1987)
Phospholipids	NS	CSF	NS	NS	NS	Association with CSF protein and cellularity	(Ngankam et al., 2011)
	Severe	Serum	ELISA	NS	40%	NS	(López-Escribano et al., 2002)
S100b	Mild repeated	Serum	ELISA	Protein	~50%	Associated with unfavourable DTI and cognitive outcomes	(Marchi et al., 2013)
	NS	Serum	ELISA	NS	80%	NS	(Morozov et al., 1996)
	Mild repeated	Serum	ELISA	Protein	NS	Associated with unfavourable DTI outcomes	(Bazarian et al., 2014)
Tissue Transglutaminase	Severe	Serum	ELISA	NS	27%	NS	(López-Escribano et al., 2002)
Hypothalamus	NS	Serum	IIF	Baboon Hypothalamus	21%	Positive association with hypopituitarism	(Tanriverdi et al., 2010)
Pituitary	Mild-severe	Serum	IIF	Baboon Pituitary	45%	Association with hypopituitarism	(Tanriverdi et al., 2008)
	Mild Repeated	Serum	IIF	Baboon Pituitary	23%	Association with hypopituitarism	(Tanriverdi et al., 2010)
NS	NS	NS	NS	NS	NS	NS	(Shamreĭ, 1969)
	NS	NS	NS	NS	N	NS	(Procházka et al., 1971)
	NS	Blood	NS	NS	NS	Association with injury severity and repeated TBIs	(Livshits and Shakarova, 1975)
	NS	Blood; CSF	Hoigne Method	NS	NS	Association with injury severity	(Detlav, 1976)
Animal Studies							
Myelin Basic Protein	Experimental	Rats	ELISA	NS	NS	Myelinoclasis	(Li et al., 2008)
Peroxiredoxin 6	Experimental	Rats	Western Blot	Rat Brain Homogenate	NS	NS	(Buonora et al., 2015)
Neurons	Experimental	Rats	IIF	Rat brain slices	88%	NS	(Rudehill et al., 2006)
Astrocytes					13%		
Vascular Basal Lamina					75%		

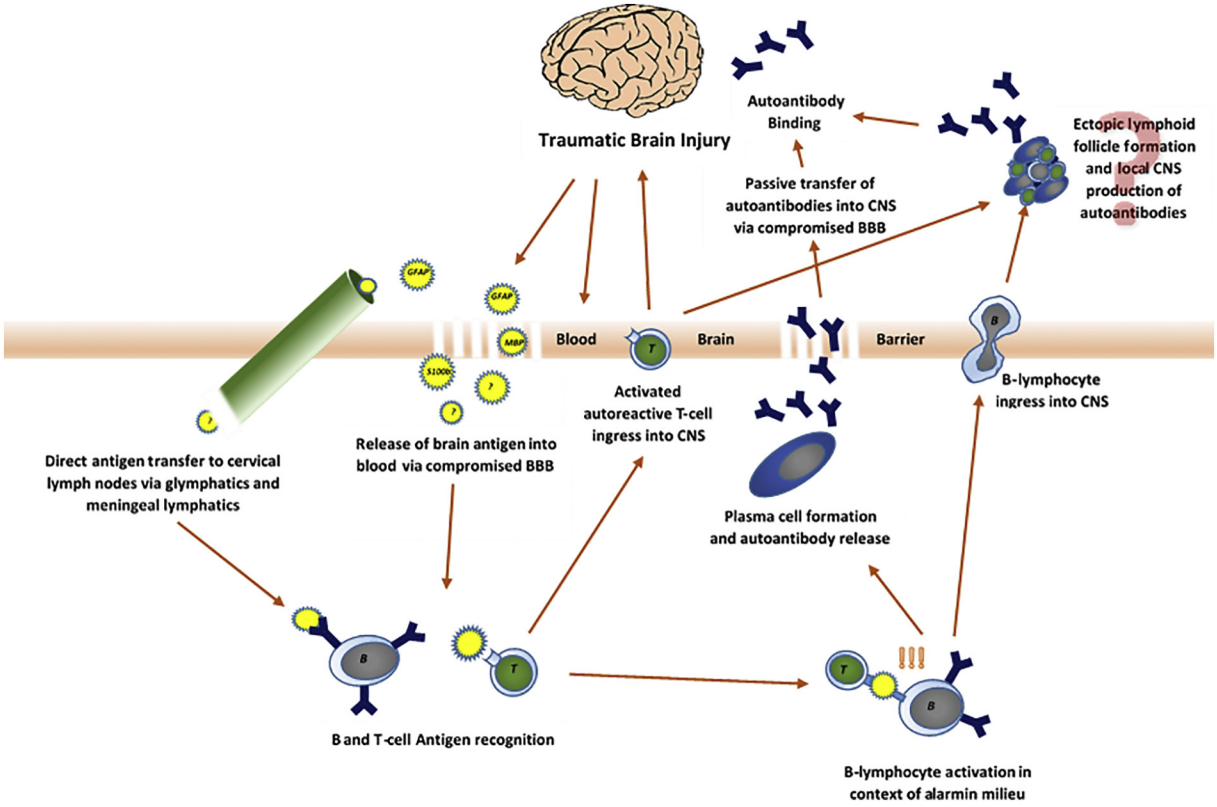

Fig. 3. Hypothesised Mechanism of Autoantibody Production in TBI. The release of large quantities of brain protein into the circulation and lymphatic system, in combination with a heightened DAMP environment, leads to presentation of self-antigen to lymphocytes and subsequent autoimmunity, explaining the presence of autoreactive T-cells and autoantibodies in the peripheral blood. Other inflammatory neurological diseases (including spinal cord injury) lead to the formation of tertiary lymphoid tissue within the CNS, although this has not so far been displayed in TBI.

associating with the presence of ongoing post-traumatic headache (Goryunova et al., 2007; Sorokina et al., 2009). In a rat model, titres of MBP antibodies correlated with extent of myelinoclasis (Li et al., 2008).

These associations do not, however, demonstrate causality; importantly, greater injury severity results in more substantial protein release, which may provide a greater stimulus for antibody production. Only one study has attempted to further delineate the biological role of these autoantibodies. Human anti-GFAP antibodies bound strongly to injured rat hippocampi, and induced LDH release suggestive of glial cell injury, suggesting that autoantibodies have the potential to be immunologically active and contribute in some degree to the disease process (Zhang et al., 2014). The principle that autoantibodies can be deleterious has been demonstrated in the related condition of spinal cord injury (SCI), where comparable humoral responses have been described. The injection of serum from SCI mice into the hippocampi of naïve mice triggered glial activation and marked neuronal loss, whereas injection of serum from both uninjured mice and B-cell knockout SCI mice (those unable to mount an antibody response) led to no such reaction (Ankeny et al., 2006). This detrimental effect was corroborated by showing that B-cell knock out mice experienced a smaller reduction in motor function following SCI than did wild-type mice (Ankeny et al., 2009).

Whilst the general suggestion from the above is that autoantibody responses might be detrimental in CNS trauma, there is a literature suggesting potential for a neuroprotective or reparative role. Naturally occurring (usually IgM) autoantibodies (nAbs) have been demonstrated to activate oligodendrocytes to remyelinate denuded axons in a viral-induced murine demyelinating disease model, as well as to enhance neuronal outgrowth, with demonstrable clinical improvement (Rodriguez et al., 2009). Similarly, nAbs to pathological proteins such as β-amyloid have been shown to help to reduce their aggregation and subsequent injurious effects (Dodel et al., 2011; Kellner et al., 2009), which may have implications for TBI. Indeed, in a rat model of TBI, IgG was seen to bind to dying neurons, with the presumption that this facilitates phagocytic clearance of cell debris (Stein et al., 2002). The complexity of autoantibody responses is again highlighted here by the destructive effect of anti-amyloid antibodies in those who develop an aggressive inflammatory vasculopathy in response to amyloid deposition (Piazza et al., 2013).

The apparent paradoxes alluded to above suggest that viewing autoantibodies as a single functional group is certain to be a gross oversimplification. Different subsets of antibodies have specific, and sometimes conflicting actions. If the autoantibodies seen after TBI are functionally active, there may be a spectrum of responses ranging from beneficial to detrimental.

5.4. *Effector mechanisms – the role of complement, NK cells, and phagocytes*

Antibodies exert their destructive capabilities through two main mechanisms: complement dependent cytotoxicity and antibody-dependant cellular cytotoxicity (the opsonisation and engagement of effector cells, notably natural killer (NK) cells and macrophages). In addition, they can interfere with receptor functioning by blocking ligand-receptor interactions.

The complement system typically works as a key downstream effector of antibody binding by activation of the classical pathway with subsequent Major Attack Complex (MAC) formation and cell lysis. In health the CNS produces very little complement, and indeed autoantibodies may need additional complement to cause damage (Saadoun et al., 2010); TBI however, with its associated BBB compromise and direct parenchymal passage of blood demonstrates significant

complement deposition within the CNS (Bellander et al., 2001; Blasio et al., 2018).

The levels of intrathecal MAC in patients following TBI is markedly higher than controls, and of particular note is the generation of a second peak of intrathecal MAC generation in a subset of patients one week after the injury, presumably occurring as a consequence of adaptive immune responses (Stahel et al., 2001). Inhibition of the MAC in mice subjected to TBI reduces subsequent secondary neuron loss and promotes neurological recovery (Fluiter et al., 2014). In addition to its known destructive cascade, complement has been found to play a contrary role within the CNS, both mediating injury and affording protection. This is aptly displayed by the terminal pathway, which is traditionally seen as the end effector leading to cell lysis; whilst this does indeed occur at doses above a certain threshold, sub-lysis doses have demonstrable reparative effects, protecting oligodendrocytes from apoptosis, with induction of remyelination (Soane et al., 2001; Weerth et al., 2003).

With regards to the potential downstream cellular effectors of autoantibodies, there is little informative literature relating to TBI. Indeed, there are no publications assessing parenchymal NK cell infiltration following TBI. It is nonetheless recognised that NK cells do migrate into the CNS during pathological states such as malignancy (Domingues et al., 2012), infection (Alsharifi et al., 2006) and autoimmunity (Hao et al., 2011). The effect of these infiltrating NK cells in inflammation is complex and uncertain, with studies demonstrating both pro-inflammatory (Shi et al., 2000) and regulatory effects (putatively mediated by the killing of microglia) (Hammarberg et al., 2000; Hao et al., 2011; Lünemann et al., 2008).

In contrast to the paucity of data regarding NK cells, there is a wealth of evidence demonstrating ongoing microglial activation after TBI. The underlying mechanisms behind microglial activation in this setting are not fully known, but antibody-antigen complexes are recognised as a potent microglial activator via the Fcγ receptor, and could represent a bridge between adaptive immune responses and ongoing innate activation (Winter et al., 2016).

6. Chronic inflammation following traumatic brain injury

Whilst inflammation is a predictable response to brain injury, its perpetuation beyond the acute phase is not, and marks TBI as an ongoing active process resulting from an initial insult. In keeping with the surge of interest regarding inflammation in the pathogenesis of neurodegenerative conditions such as Alzheimer's and Parkinson's diseases (Ransohoff, 2016), there is a question as to whether ongoing inflammation may be contributory to the neurodegeneration seen in a subset of patients post-TBI (Faden and Loane, 2015). Persistent microglial activation is seen in both pathological specimens and PET studies years, indeed decades, after the injury (Johnson et al., 2013; Ramlackhansingh et al., 2011). Furthermore, the ongoing inflammation associates with degree of white matter tract damage (Pischiutta et al., 2018; Scott et al., 2015), although a relationship with progression of damage has yet to be demonstrated. Also unanswered is whether the ongoing microglial activation is the result of a parallel underlying process (such as abnormal protein deposition acting as a DAMP (Amor et al., 2010)), or a consequence of failure to deactivate following the acute injury ("microgliosis"(Saijo et al., 2013)). Either way, chronic microglial activation has been implicated directly in neurotoxicity by ROS production via NADPH oxidase and pro-inflammatory cytokines such as TNFα (Lull and Block, 2010); indeed microglial activation has itself been demonstrated to drive hyperphosphorylation and aggregation of tau protein, further complicating the relationship between proteinopathy and inflammation (Maphis et al., 2015).

In addition to persistent local inflammation, patients with TBI demonstrate altered peripheral immunity months after injury. Increased levels of pro-inflammatory cytokines including IL-1β, IL-6, IL-18 and TNFα persist, and associate with outcome in a dose-dependent manner (Ciaramella et al., 2014; Kumar et al., 2015a, 2015b). CSF IL1β levels are predictive of development of post-traumatic epilepsy (Diamond et al., 2014). Even after a single severe TBI IgG autoantibodies to GFAP remain detectable months post-injury (Wang et al., 2016).

7. Conclusions

A growing body of evidence points towards the influence of immunological processes on outcome following TBI, both in the acute and chronic settings. Modulation of these processes offers a tangible mechanism to influence secondary neuronal injury and improve patient outcomes. A significant proportion of the current literature relies on animal models, interpretation of which is limited by both interspecies immune system differences and experimental environment (for example the impact of concomitant injury or sepsis which is ubiquitous in human TBI, but not in CCI mouse models). The relative positive or negative effects of inflammation are still far from certain, and it is likely that relatively subtle skewing of immune responses could affect the subsequent impact on outcome. With this in mind, for therapeutic interventions to be both safe and effective, they must necessarily be highly focussed in terms of both immunological target as well as timeframe. Furthermore, the interindividual variation in immune response seen across the majority of human TBI studies, in the context of significant currently unexplained discrepancy in outcomes following TBI, raises the possibility that particular subsets of patients might benefit from immune-modulating treatments, necessitating the discovery and utilisation of early biomarkers to identify those in whom treatment might be effective.

Acknowledgements

EJN, AH, AJC and DKM are supported by the Medical Research Council (UK) within the framework of ERA-NET NEURON. ERZ is supported by the Ministero della Salute (Italy) within the framework of ERA-NET NEURON.

References

Absinta, M., Ha, S.-K., Nair, G., Sati, P., Luciano, N.J., Palisoc, M., Louveau, A., Zaghloul, K.A., Pittaluga, S., Kipnis, J., Reich, D.S., 2017. Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. eLife 6. https://doi.org/10.7554/eLife.29738.

Adembri, C., Selmi, V., Vitali, L., Tani, A., Margheri, M., Loriga, B., Carlucci, M., Nosi, D., Formigli, L., De Gaudio, A.R., 2014. Minocycline but not tigecycline is neuroprotective and reduces the neuroinflammatory response induced by the superimposition of sepsis upon traumatic brain injury. Crit. Care Med. 42, e570–e582. https://doi.org/10.1097/CCM.0000000000000414.

Allan, S.M., Tyrrell, P.J., Rothwell, N.J., 2005. Interleukin-1 and neuronal injury. Nat. Rev. Immunol. 5, 629. https://doi.org/10.1038/nri1664.

Alsharifi, M., Lobigs, M., Simon, M.M., Kersten, A., Müller, K., Koskinen, A., Lee, E., Müllbacher, A., 2006. NK cell-mediated immunopathology during an acute viral infection of the CNS. Eur. J. Immunol. 36, 887–896. https://doi.org/10.1002/eji.200535342.

Amor, S., Puentes, F., Baker, D., van der Valk, P., 2010. Inflammation in neurodegenerative diseases. Immunology 129, 154–169. https://doi.org/10.1111/j.1365-2567.2009.03225.x.

Ankeny, D.P., Lucin, K.M., Sanders, V.M., McGaughy, V.M., Popovich, P.G., 2006. Spinal cord injury triggers systemic autoimmunity: evidence for chronic B lymphocyte activation and lupus-like autoantibody synthesis. J. Neurochem. 99, 1073–1087. https://doi.org/10.1111/j.1471-4159.2006.04147.x.

Ankeny, D.P., Guan, Z., Popovich, P.G., 2009. B cells produce pathogenic antibodies and impair recovery after spinal cord injury in mice. J. Clin. Invest. 119, 2990–2999. https://doi.org/10.1172/JCI39780.

Bao, F., Shultz, S.R., Hepburn, J.D., Omana, V., Weaver, L.C., Cain, D.P., Brown, A., 2012. A CD11d monoclonal antibody treatment reduces tissue injury and improves neurological outcome after fluid percussion brain injury in rats. J. Neurotrauma 29, 2375–2392. https://doi.org/10.1089/neu.2012.2408.

Bazarian, J.J., Zhu, T., Zhong, J., Janigro, D., Rozen, E., Roberts, A., Javien, H., Merchant-Borna, K., Abar, B., Blackman, E.G., 2014. Persistent, long-term cerebral white matter changes after sports-related repetitive head impacts. PLoS One 9, e94734. https://doi.org/10.1371/journal.pone.0094734.

Bell, M.J., Kochanek, P.M., Doughty, L.A., Carcillo, J.A., Adelson, P.D., Clark, R.S., Wisniewski, S.R., Whalen, M.J., DeKosky, S.T., 1997. Interleukin-6 and interleukin-10 in cerebrospinal fluid after severe traumatic brain injury in children. J.

Neurotrauma 14, 451–457. https://doi.org/10.1089/neu.1997.14.451.
Bellander, B.-M., Singhrao, S.K., Ohlsson, M., Mattsson, P., Svensson, M., 2001. Complement activation in the human brain after traumatic head injury. J. Neurotrauma 18, 1295–1311.
Bennett, R.E., Brody, D.L., 2014. Acute reduction of microglia does not alter axonal injury in a mouse model of repetitive concussive traumatic brain injury. J. Neurotrauma 31, 1647–1663. https://doi.org/10.1089/neu.2013.3320.
Bermpohl, D., You, Z., Lo, E.H., Kim, H.-H., Whalen, M.J., 2007. TNF alpha and fas mediate tissue damage and functional outcome after traumatic brain injury in mice. J. Cereb. Blood Flow Metab. 27, 1806–1818. https://doi.org/10.1038/sj.jcbfm.9600487.
Blasio, D.D., Fumagalli, S., Orsini, F., Neglia, L., Perego, C., Ortolano, F., Zanier, E.R., Picetti, E., Locatelli, M., Stocchetti, N., Longhi, L., Garred, P., Simoni, M.-G.D., 2018. Human brain trauma severity is associated with lectin complement pathway activation. J. Cereb. Blood Flow Metab. https://doi.org/10.1177/0271678X18758881. 0271678X18758881.
Block, M.L., Zecca, L., Hong, J.-S., 2007. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat. Rev. Neurosci. 8, 57–69. https://doi.org/10.1038/nrn2038.
Bradley, J.R., 2008. TNF-mediated inflammatory disease. J. Pathol. 214, 149–160. https://doi.org/10.1002/path.2287.
Braun, M., Vaibhav, K., Saad, N.M., Fatima, S., Vender, J.R., Baban, B., Hoda, M.N., Dhandapani, K.M., 2017. White matter damage after traumatic brain injury: A role for damage associated molecular patterns. Biochim. Biophys. Acta BBA - Mol. Basis Dis. 1863, 2614–2626. https://doi.org/10.1016/j.bbadis.2017.05.020.
Buonora, J.E., Mousseau, M., Jacobowitz, D.M., Lazarus, R.C., Yarnell, A.M., Olsen, C.H., Pollard, H.B., Diaz-Arrastia, R., Latour, L., Mueller, G.P., 2015. Autoimmune profiling reveals peroxiredoxin 6 as a candidate traumatic brain injury biomarker. J. Neurotrauma 32, 1805–1814. https://doi.org/10.1089/neu.2014.3736.
Carlos, T.M., Clark, R.S., Franicola-Higgins, D., Schiding, J.K., Kochanek, P.M., 1997. Expression of endothelial adhesion molecules and recruitment of neutrophils after traumatic brain injury in rats. J. Leukoc. Biol. 61, 279–285.
Chao, C.C., Hu, S., Ehrlich, L., Peterson, P.K., 1995. Interleukin-1 and tumor necrosis factor-alpha synergistically mediate neurotoxicity: involvement of nitric oxide and of N-methyl-D-aspartate receptors. Brain Behav. Immun. 9, 355–365.
Chen, X., Duan, X.-S., Xu, L.-J., Zhao, J.-J., She, Z.-F., Chen, W.-W., Zheng, Z.-J., Jiang, G.-D., 2014a. Interleukin-10 mediates the neuroprotection of hyperbaric oxygen therapy against traumatic brain injury in mice. Neuroscience 266, 235–243. https://doi.org/10.1016/j.neuroscience.2013.11.036.
Chen, Y., Won, S.J., Xu, Y., Swanson, R.A., 2014b. Targeting microglial activation in stroke therapy: pharmacological tools and gender effects. Curr. Med. Chem. 21, 2146–2155.
Chenouard, A., Chesneau, M., Braza, F., Dejoie, T., Cinotti, R., Roquilly, A., Brouard, S., Asehnoune, K., 2015. Phenotype and functions of B cells in patients with acute brain injuries. Mol. Immunol. 68, 350–356. https://doi.org/10.1016/j.molimm.2015.09.001.
Chiaretti, A., Genovese, O., Aloe, L., Antonelli, A., Piastra, M., Polidori, G., Rocco, C.D., 2005. Interleukin 1β and interleukin 6 relationship with paediatric head trauma severity and outcome. Childs Nerv. Syst. 21, 185–193. https://doi.org/10.1007/s00381-004-1032-1.
Chio, C.-C., Lin, J.-W., Chang, M.-W., Wang, C.-C., Kuo, J.-R., Yang, C.-Z., Chang, C.-P., 2010. Therapeutic evaluation of etanercept in a model of traumatic brain injury. J. Neurochem. 115, 921–929. https://doi.org/10.1111/j.1471-4159.2010.06969.x.
Ciaramella, A., Della Vedova, C., Salani, F., Viganotti, M., D'Ippolito, M., Caltagirone, C., Formisano, R., Sabatini, U., Bossù, P., 2014. Increased levels of serum IL-18 are associated with the long-term outcome of severe traumatic brain injury. Neuroimmunomodulation 21, 8–12. https://doi.org/10.1159/000354764.
Clark, R.S., Schiding, J.K., Kaczorowski, S.L., Marion, D.W., Kochanek, P.M., 1994. Neutrophil accumulation after traumatic brain injury in rats: comparison of weight drop and controlled cortical impact models. J. Neurotrauma 11, 499–506. https://doi.org/10.1089/neu.1994.11.499.
Clausen, F., Lorant, T., Lewén, A., Hillered, L., 2007. T lymphocyte trafficking: a novel target for neuroprotection in traumatic brain injury. J. Neurotrauma 24, 1295–1307. https://doi.org/10.1089/neu.2006.0258.
Clausen, F., Hånell, A., Björk, M., Hillered, L., Mir, A.K., Gram, H., Marklund, N., 2009. Neutralization of interleukin-1β modifies the inflammatory response and improves histological and cognitive outcome following traumatic brain injury in mice. Eur. J. Neurosci. 30, 385–396. https://doi.org/10.1111/j.1460-9568.2009.06820.x.
Clausen, F., Hånell, A., Israelsson, C., Hedin, J., Ebendal, T., Mir, A.K., Gram, H., Marklund, N., 2011. Neutralization of interleukin-1β reduces cerebral edema and tissue loss and improves late cognitive outcome following traumatic brain injury in mice. Eur. J. Neurosci. 34, 110–123. https://doi.org/10.1111/j.1460-9568.2011.07723.x.
Colombo, E., Farina, C., 2016. Astrocytes: key regulators of neuroinflammation. Trends Immunol. 37, 608–620. https://doi.org/10.1016/j.it.2016.06.006.
Cox, A.L., Coles, A.J., Nortje, J., Bradley, P.G., Chatfield, D.A., Thompson, S.J., Menon, D.K., 2006. An investigation of auto-reactivity after head injury. J. Neuroimmunol. 174, 180–186. https://doi.org/10.1016/j.jneuroim.2006.01.007.
D'Agostino, P.M., Gottfried-Blackmore, A., Anandasabapathy, N., Bulloch, K., 2012. Brain dendritic cells: biology and pathology. Acta Neuropathol. (Berl.) 124, 599–614. https://doi.org/10.1007/s00401-012-1018-0.
Dahm, L., Ott, C., Steiner, J., Stepniak, B., Teegen, B., Saschenbrecker, S., Hammer, C., Borowski, K., Begemann, M., Lemke, S., Rentzsch, K., Probst, C., Martens, H., Wienands, J., Spalletta, G., Weissenborn, K., Stöcker, W., Ehrenreich, H., 2014. Seroprevalence of autoantibodies against brain antigens in health and disease. Ann. Neurol. 76, 82–94. https://doi.org/10.1002/ana.24189.
Detlav, I.E., 1976. Anti-brain antibodies in serum and cerebrospinal fluid following cranio-cerebral trauma. Zhurnal Nevropatol. Psikhiatrii Im. SS Korsakova Mosc. Russ. 1952 (76), 344–348.
Diamond, M.L., Ritter, A.C., Failla, M.D., Boles, J.A., Conley, Y.P., Kochanek, P.M., Wagner, A.K., 2014. IL-1β associations with posttraumatic epilepsy development: a genetics and biomarker cohort study. Epilepsia 55, 1109–1119. https://doi.org/10.1111/epi.12628.
Dinkel, K., Dhabhar, F.S., Sapolsky, R.M., 2004. Neurotoxic effects of polymorphonuclear granulocytes on hippocampal primary cultures. Proc. Natl. Acad. Sci. U. S. A. 101, 331–336. https://doi.org/10.1073/pnas.0303510101.
Dodel, R., Balakrishnan, K., Keyvani, K., Deuster, O., Neff, F., Andrei-Selmer, L.-C., Röskam, S., Stüer, C., Al-Abed, Y., Noelker, C., Balzer-Geldsetzer, M., Oertel, W., Du, Y., Bacher, M., 2011. Naturally occurring autoantibodies against β-amyloid: investigating their role in transgenic animal and in vitro models of Alzheimer's disease. J. Neurosci. 31, 5847–5854. https://doi.org/10.1523/JNEUROSCI.4401-10.2011.
Domingues, P.H., Teodósio, C., Ortiz, J., Sousa, P., Otero, Á., Maillo, A., Bárcena, P., García-Macias, M.C., Lopes, M.C., de Oliveira, C., Orfao, A., Tabernero, M.D., 2012. Immunophenotypic identification and characterization of tumor cells and infiltrating cell populations in meningiomas. Am. J. Pathol. 181, 1749–1761. https://doi.org/10.1016/j.ajpath.2012.07.033.
Dreßler, J., Hanisch, U., Kuhlisch, E., Geiger, K.D., 2007. Neuronal and glial apoptosis in human traumatic brain injury. Int. J. Legal Med. 121, 365–375. https://doi.org/10.1007/s00414-006-0126-6.
Dunn, S.L., Young, E.A., Hall, M.D., McNulty, S., 2002. Activation of astrocyte intracellular signaling pathways by interleukin-1 in rat primary striatal cultures. Glia 37, 31–42. https://doi.org/10.1002/glia.10010.
Engel, S., Schluesener, H., Mittelbronn, M., Seid, K., Adjodah, D., Wehner, H.D., Meyermann, R., 2000. Dynamics of microglial activation after human traumatic brain injury are revealed by delayed expression of macrophage-related proteins MRP8 and MRP14. Acta Neuropathol. (Berl.) 100, 313–322.
Engelhardt, B., Ransohoff, R.M., 2005. The ins and outs of T-lymphocyte trafficking to the CNS: anatomical sites and molecular mechanisms. Trends Immunol. 26, 485–495. https://doi.org/10.1016/j.it.2005.07.004.
Erickson, M.A., Banks, W.A., 2018. Neuroimmune axes of the blood–brain barriers and blood–brain interfaces: bases for physiological regulation, disease states, and pharmacological interventions. Pharmacol. Rev. 70, 278–314. https://doi.org/10.1124/pr.117.014647.
Faden, A.I., Loane, D.J., 2015. Chronic neurodegeneration after traumatic brain injury: Alzheimer disease, chronic traumatic encephalopathy, or persistent neuroinflammation? Neurotherapeutics 12, 143–150. https://doi.org/10.1007/s13311-014-0319-5.
Febinger, H.Y., Thomasy, H.E., Pavlova, M.N., Ringgold, K.M., Barf, P.R., George, A.M., Grillo, J.N., Bachstetter, A.D., Garcia, J.A., Cardona, A.E., Opp, M.R., Gemma, C., 2015. Time-dependent effects of CX3CR1 in a mouse model of mild traumatic brain injury. J. Neuroinflammation 12 (154). https://doi.org/10.1186/s12974-015-0386-5.
Fee, D., Crumbaugh, A., Jacques, T., Herdrich, B., Sewell, D., Auerbach, D., Piaskowski, S., Hart, M.N., Sandor, M., Fabry, Z., 2003. Activated/effector CD4+ T cells exacerbate acute damage in the central nervous system following traumatic injury. J. Neuroimmunol. 136, 54–66. https://doi.org/10.1016/S0165-5728(03)00008-0.
Fletcher, J.M., Lalor, S.J., Sweeney, C.M., Tubridy, N., Mills, K.H.G., 2010. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. Clin. Exp. Immunol. 162, 1–11. https://doi.org/10.1111/j.1365-2249.2010.04143.x.
Fluiter, K., Opperhuizen, A.L., Morgan, B.P., Baas, F., Ramaglia, V., 2014. Inhibition of the membrane attack complex of the complement system reduces secondary neuroaxonal loss and promotes neurologic recovery after traumatic brain injury in mice. J. Immunol. 192, 2339–2348. https://doi.org/10.4049/jimmunol.1302793.
Frieler, R.A., Nadimpalli, S., Boland, L.K., Xie, A., Kooistra, L.J., Song, J., Chung, Y., Cho, K.W., Lumeng, C.N., Wang, M.M., Mortensen, R.M., 2015. Depletion of macrophages in CD11b diphtheria toxin receptor mice induces brain inflammation and enhances inflammatory signaling during traumatic brain injury. Brain Res. 1624, 103–112. https://doi.org/10.1016/j.brainres.2015.07.011.
Gao, C., Qian, Y., Huang, J., Wang, D., Su, W., Wang, P., Guo, L., Quan, W., An, S., Zhang, J., Jiang, R., 2016. A three-day consecutive fingolimod administration improves neurological functions and modulates multiple immune responses of CCI mice. Mol. Neurobiol. 1–13. https://doi.org/10.1007/s12035-016-0318-0.
Gelderblom, M., Arunachalam, P., Magnus, T., 2014. γδ T cells as early sensors of tissue damage and mediators of secondary neurodegeneration. Front. Cell. Neurosci. 8. https://doi.org/10.3389/fncel.2014.00368.
Gold, M., Pul, R., Bach, J.-P., Stangel, M., Dodel, R., 2012. Pathogenic and physiological autoantibodies in the central nervous system. Immunol. Rev. 248, 68–86. https://doi.org/10.1111/j.1600-065X.2012.01128.x.
Goryunova, A.V., Bazarnaya, N.A., Sorokina, E.G., Semenova, N.Y., Globa, O.V., Semenova, Z.B., Pinelis, V.G., Roshal', L.M., Maslova, O.I., 2007. Glutamate receptor autoantibody concentrations in children with chronic post-traumatic headache. Neurosci. Behav. Physiol. 37, 761–764. https://doi.org/10.1007/s11055-007-0079-3.
Groux, H., Cottrez, F., 2003. The complex role of interleukin-10 in autoimmunity. J. Autoimmun. 20, 281–285. https://doi.org/10.1016/S0896-8411(03)00044-1.
Gyoneva, S., Kim, D., Katsumoto, A., Kokiko-Cochran, O.N., Lamb, B.T., Ransohoff, R.M., 2015. Ccr2 deletion dissociates cavity size and tau pathology after mild traumatic brain injury. J. Neuroinflammation 12 (228). https://doi.org/10.1186/s12974-015-0443-0.
Hailer, N.P., 2008. Immunosuppression after traumatic or ischemic CNS damage: it is neuroprotective and illuminates the role of microglial cells. Prog. Neurobiol. 84, 211–233. https://doi.org/10.1016/j.pneurobio.2007.12.001.
Hammarberg, H., Lidman, O., Lundberg, C., Eltayeb, S.Y., Gielen, A.W., Muhallab, S.,

Svenningsson, A., Lindå, H., van der Meide, P.H., Cullheim, S., Olsson, T., Piehl, F., 2000. Neuroprotection by encephalomyelitis: rescue of mechanically injured neurons and neurotrophin production by CNS-infiltrating T and natural killer cells. J. Neurosci. 20, 5283–5291.
Hammond, F.M., Grattan, K.D., Sasser, H., Corrigan, J.D., Rosenthal, M., Bushnik, T., Shull, W., 2004. Five years after traumatic brain injury: a study of individual outcomes and predictors of change in function. NeuroRehabilitation 19, 25–35.
Hanisch, U.-K., Kettenmann, H., 2007. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat. Neurosci. 10, 1387. https://doi.org/10.1038/nn1997.
Hao, J., Campagnolo, D., Liu, R., Piao, W., Shi, S., Hu, B., Xiang, R., Zhou, Q., Vollmer, T., Van Kaer, L., La Cava, A., Shi, F.-D., 2011. IL-2/IL-2 Ab therapy induces target organ NK cells that inhibit CNS inflammation. Ann. Neurol. 69, 721–734. https://doi.org/10.1002/ana.22339.
Harling-Berg, C., Knopf, P.M., Merriam, J., Cserr, H.F., 1989. Role of cervical lymph nodes in the systemic humoral immune response to human serum albumin microinfused into rat cerebrospinal fluid. J. Neuroimmunol. 25, 185–193.
Hauben, E., Butovsky, O., Nevo, U., Yoles, E., Moalem, G., Agranov, E., Mor, F., Leibowitz-Amit, R., Pevsner, E., Akselrod, S., Neeman, M., Cohen, I.R., Schwartz, M., 2000. Passive or active immunization with myelin basic protein promotes recovery from spinal cord contusion. J. Neurosci. 20, 6421–6430.
Hauben, E., Agranov, E., Gothilf, A., Nevo, U., Cohen, A., Smirnov, I., Steinman, L., Schwartz, M., 2001. Posttraumatic therapeutic vaccination with modified myelin self-antigen prevents complete paralysis while avoiding autoimmune disease. J. Clin. Invest. 108, 591–599. https://doi.org/10.1172/JCI12837.
Hay, J.R., Johnson, V.E., Young, A.M.H., Smith, D.H., Stewart, W., 2015. Blood-brain barrier disruption is an early event that may persist for many years after traumatic brain injury in humans. J. Neuropathol. Exp. Neurol. 74, 1147–1157. https://doi.org/10.1093/jnen/74.12.1147.
Helmy, A., Carpenter, K.L., Menon, D.K., Pickard, J.D., Hutchinson, P.J., 2011a. The cytokine response to human traumatic brain injury: temporal profiles and evidence for cerebral parenchymal production. J. Cereb. Blood Flow Metab. 31, 658–670.
Helmy, A., De Simoni, M.-G., Guilfoyle, M.R., Carpenter, K.L.H., Hutchinson, P.J., 2011b. Cytokines and innate inflammation in the pathogenesis of human traumatic brain injury. Prog. Neurobiol. 95, 352–372. https://doi.org/10.1016/j.pneurobio.2011.09.003.
Helmy, A., Guilfoyle, M.R., Carpenter, K.L.H., Pickard, J.D., Menon, D.K., Hutchinson, P.J., 2014. Recombinant human interleukin-1 receptor antagonist in severe traumatic brain injury: a phase II randomized control trial. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 34, 845–851. https://doi.org/10.1038/jcbfm.2014.23.
Hemphill, M.A., Dauth, S., Yu, C.J., Dabiri, B.E., Parker, K.K., 2015. Traumatic brain injury and the neuronal microenvironment: a potential role for neuropathological mechanotransduction. Neuron 85, 1177–1192. https://doi.org/10.1016/j.neuron.2015.02.041.
Hickey, William F., 2001. Basic principles of immunological surveillance of the normal central nervous system. Glia 36, 118–124. https://doi.org/10.1002/glia.1101.
Himanen, L., Portin, R., Isoniemi, H., Helenius, H., Kurki, T., Tenovuo, O., 2006. Longitudinal cognitive changes in traumatic brain injury: a 30-year follow-up study. Neurology 66, 187–192. https://doi.org/10.1212/01.wnl.0000194264.60150.d3.
Hofstetter, H.H., Sewell, D.L., Liu, F., Sandor, M., Forsthuber, T., Lehmann, P.V., Fabry, Z., 2003. Autoreactive T cells promote post-traumatic healing in the central nervous system. J. Neuroimmunol. 134, 25–34.
Holmin, S., Mathiesen, T., Shetye, J., Biberfeld, P., 1995. Intracerebral inflammatory response to experimental brain contusion. Acta Neurochir. 132, 110–119.
Holmin, S., Söderlund, J., Biberfeld, P., Mathiesen, T., 1998. Intracerebral inflammation after human brain contusion. Neurosurgery 42, 291–298 discussion 298-299.
Homsi, S., Piaggio, T., Croci, N., Noble, F., Plotkine, M., Marchand-Leroux, C., Jafarian-Tehrani, M., 2010. Blockade of acute microglial activation by minocycline promotes neuroprotection and reduces locomotor hyperactivity after closed head injury in mice: a twelve-week follow-up study. J. Neurotrauma 27, 911–921. https://doi.org/10.1089/neu.2009.1223.
Hsieh, C.L., Kim, C.C., Ryba, B.E., Niemi, E.C., Bando, J.K., Locksley, R.M., Liu, J., Nakamura, M.C., Seaman, W.E., 2013. Traumatic brain injury induces macrophage subsets in the brain. Eur. J. Immunol. 43, 2010–2022. https://doi.org/10.1002/eji.201243084.
Hsieh, C.L., Niemi, E.C., Wang, S.H., Lee, C.C., Bingham, D., Zhang, J., Cozen, M.L., Charo, I., Huang, E.J., Liu, J., Nakamura, M.C., 2014. CCR2 deficiency impairs macrophage infiltration and improves cognitive function after traumatic brain injury. J. Neurotrauma 31, 1677–1688. https://doi.org/10.1089/neu.2013.3252.
Hu, X., Leak, R.K., Shi, Y., Suenaga, J., Gao, Y., Zheng, P., Chen, J., 2015. Microglial and macrophage polarization-new prospects for brain repair. Nat. Rev. Neurol. 11, 56–64. https://doi.org/10.1038/nrneurol.2014.207.
Irrera, N., Pizzino, G., Calò, M., Pallio, G., Mannino, F., Famà, F., Arcoraci, V., Fodale, V., David, A., Francesca, C., Minutoli, L., Mazzon, E., Bramanti, P., Squadrito, F., Altavilla, D., Bitto, A., 2017. Lack of the Nlrp3 inflammasome improves mice recovery following traumatic brain injury. Front. Pharmacol. 8. https://doi.org/10.3389/fphar.2017.00459.
Jennett, B., 1996. Epidemiology of head injury. J. Neurol. Neurosurg. Psychiatry 60, 362–369.
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. https://doi.org/10.1371/journal.pone.0041892.
Johnson, Victoria E., Stewart, J.E., Begbie, F.D., Trojanowski, J.Q., Smith, D.H., Stewart, W., 2013. Inflammation and white matter degeneration persist for years after a single traumatic brain injury. Brain 136, 28–42. https://doi.org/10.1093/brain/aws322.
Jones, T.B., 2014. Lymphocytes and autoimmunity after spinal cord injury. Spec. Issue Neuroimmunol. Spinal Cord Inj. 258, 78–90. https://doi.org/10.1016/j.expneurol.2014.03.003.
Jones, T.B., Basso, D.M., Sodhi, A., Pan, J.Z., Hart, R.P., MacCallum, R.C., Lee, S., Whitacre, C.C., Popovich, P.G., 2002. Pathological CNS autoimmune disease triggered by traumatic spinal cord injury: implications for autoimmune vaccine therapy. J. Neurosci. 22, 2690–2700.
Jones, T.B., Ankeny, D.P., Guan, Z., McGaughy, V., Fisher, L.C., Basso, D.M., Popovich, P.G., 2004. Passive or active immunization with myelin basic protein impairs neurological function and exacerbates neuropathology after spinal cord injury in rats. J. Neurosci. 24, 3752–3761. https://doi.org/10.1523/JNEUROSCI.0406-04.2004.
Jr, E.T.C., Kilmartin, D., Agarwal, M., Zierhut, M., 2017. Sympathetic ophthalmia. Ocul. Immunol. Inflamm. 25, 149–151. https://doi.org/10.1080/09273948.2017.1305727.
Kawabori, M., Yenari, M.A., 2015. The role of the microglia in acute CNS injury. Metab. Brain Dis. 30, 381–392. https://doi.org/10.1007/s11011-014-9531-6.
Kellner, A., Matschke, J., Bernreuther, C., Moch, H., Ferrer, I., Glatzel, M., 2009. Autoantibodies against β-amyloid are common in Alzheimer's disease and help control plaque burden. Ann. Neurol. 65, 24–31. https://doi.org/10.1002/ana.21475.
Kenne, E., Erlandsson, A., Lindbom, L., Hillered, L., Clausen, F., 2012. Neutrophil depletion reduces edema formation and tissue loss following traumatic brain injury in mice. J. Neuroinflammation 9 (17). https://doi.org/10.1186/1742-2094-9-17.
Khuman, J., Meehan, W.P., Zhu, X., Qiu, J., Hoffmann, U., Zhang, J., Giovannone, E., Lo, E.H., Whalen, M.J., 2011. Tumor necrosis factor alpha and Fas receptor contribute to cognitive deficits independent of cell death after concussive traumatic brain injury in mice. J. Cereb. Blood Flow Metab. 31, 778–789. https://doi.org/10.1038/jcbfm.2010.172.
Kim, C.C., Nakamura, M.C., Hsieh, C.L., 2016. Brain trauma elicits non-canonical macrophage activation states. J. Neuroinflammation 13. https://doi.org/10.1186/s12974-016-0581-z.
Kimbler, D.E., Shields, J., Yanasak, N., Vender, J.R., Dhandapani, K.M., 2012. Activation of P2X7 promotes cerebral edema and neurological injury after traumatic brain injury in mice. PLoS One 7. https://doi.org/10.1371/journal.pone.0041229.
Kipnis, J., Yoles, E., Schori, H., Hauben, E., Shaked, I., Schwartz, M., 2001. Neuronal survival after CNS insult is determined by a genetically encoded autoimmune response. J. Neurosci. 21, 4564–4571.
Kirchhoff, C., Buhmann, S., Bogner, V., Stegmaier, J., Leidel, B.A., Braunstein, V., Mutschler, W., Biberthaler, P., 2008. Cerebrospinal IL-10 concentration is elevated in non-survivors as compared to survivors after severe traumatic brain injury. Eur. J. Med. Res. 13, 464–468.
Knoblach, S.M., Faden, A.I., 1998. Interleukin-10 improves outcome and alters proinflammatory cytokine expression after experimental traumatic brain injury. Exp. Neurol. 153, 143–151. https://doi.org/10.1006/exnr.1998.6877.
Knopf, P.M., Harling-Berg, C.J., Cserr, H.F., Basu, D., Sirulnick, E.J., Nolan, S.C., Park, J.T., Keir, G., Thompson, E.J., Hickey, W.F., 1998. Antigen-dependent intrathecal antibody synthesis in the normal rat brain: tissue entry and local retention of antigen-specific B cells. J. Immunol. 161, 692–701.
Kobayashi, K., Imagama, S., Ohgomori, T., Hirano, K., Uchimura, K., Sakamoto, K., Hirakawa, A., Takeuchi, H., Suzumura, A., Ishiguro, N., Kadomatsu, K., 2013. Minocycline selectively inhibits M1 polarization of microglia. Cell Death Dis. 4, e525. https://doi.org/10.1038/cddis.2013.54.
Kolaczkowska, E., Kubes, P., 2013. Neutrophil recruitment and function in health and inflammation. Nat. Rev. Immunol. 13, 159. https://doi.org/10.1038/nri3399.
Koutsilieri, E., Lutz, M.B., Scheller, C., 2012. Autoimmunity, dendritic cells and relevance for Parkinson's disease. J. Neural Transm. 120, 75–81. https://doi.org/10.1007/s00702-012-0842-7.
Kumar, Raj G., Boles, J.A., Wagner, A.K., 2015a. Chronic inflammation after severe traumatic brain injury: characterization and associations with outcome at 6 and 12 months postinjury. J. Head Trauma Rehabil. 30, 369–381. https://doi.org/10.1097/HTR.0000000000000067.
Kumar, R.G., Diamond, M.L., Boles, J.A., Berger, R.P., Tisherman, S.A., Kochanek, P.M., Wagner, A.K., 2015b. Acute CSF interleukin-6 trajectories after TBI: associations with neuroinflammation, polytrauma, and outcome. Brain Behav. Immun. 45, 253–262. https://doi.org/10.1016/j.bbi.2014.12.021.
Kushi, H., Saito, T., Makino, K., Hayashi, N., 2003. L-8 is a key mediator of neuroinflammation in severe traumatic brain injuries. In: Brain Edema, X.I.I. (Ed.), Acta Neurochirurgica Supplements. Springer, Vienna, pp. 347–350. https://doi.org/10.1007/978-3-7091-0651-8_74.
Laird, M.D., Shields, J.S., Sukumari-Ramesh, S., Kimbler, D.E., Fessler, R.D., Shakir, B., Youssef, P., Yanasak, N., Vender, J.R., Dhandapani, K.M., 2014. High mobility group box protein-1 promotes cerebral edema after traumatic brain injury via activation of toll-like receptor 4. Glia 62, 26–38. https://doi.org/10.1002/glia.22581.
Land, W.G., 2015. The role of damage-associated molecular patterns in human diseases. Sultan Qaboos Univ. Med. J. 15, e9–e21.
Lavisse, S., Guillermier, M., Hérard, A.-S., Petit, F., Delahaye, M., Camp, N.V., Haim, L.B., Lebon, V., Remy, P., Dollé, F., Delzescaux, T., Bonvento, G., Hantraye, P., Escartin, C., 2012. Reactive astrocytes overexpress TSPO and are detected by TSPO positron emission tomography imaging. J. Neurosci. 32, 10809–10818. https://doi.org/10.1523/JNEUROSCI.1487-12.2012.
Li, W., Chen, S.-C., Wang, Z.-G., Song, X.-B., Wang, Y.-P., Zhang, M., 2008. Relationship between anti-myelin basic protein antibody and myelinoclasis in rat brain stem after brain trauma. Nan Fang Yi Ke Da Xue Xue Bao 28, 1028–1030.
Li, M., Lin, Y.-P., Chen, J.-L., Li, H., Jiang, R.-C., Zhang, J.-N., 2015. Role of regulatory T cell in clinical outcome of traumatic brain injury. Chin. Med. J. 128, 1072–1078. https://doi.org/10.4103/0366-6999.155094.
Lindbom, L., 2003. Regulation of vascular permeability by neutrophils in acute

inflammation. Chem. Immunol. Allergy 83, 146–166.
Ling, C., 2006. Traumatic injury and the presence of antigen differentially contribute to T-cell recruitment in the CNS. J. Neurosci. 26, 731–741. https://doi.org/10.1523/JNEUROSCI.3502-05.2006.
Lingsma, H.F., Roozenbeek, B., Steyerberg, E.W., Murray, G.D., Maas, A.I., 2010. Early prognosis in traumatic brain injury: from prophecies to predictions. Lancet Neurol. 9, 543–554. https://doi.org/10.1016/S1474-4422(10)70065-X.
Lisianyĭ, N.I., Cheren'ko, T.M., Terletskaia, I.T., 1987. Detection of antibodies to myelin basic proteins in patients with closed cranio-cerebral trauma. Vrach. Delo 101–104.
Livshits, L.I., Shakarova, G.G., 1975. Clinico-diagnostic significance of autoimmune reactions in patients with cranio-cerebral injury. Vopr. Neĭrokhirurgii 33–37.
Loane, D.J., Kumar, A., Stoica, B.A., Cabatbat, R., Faden, A.I., 2014. Progressive neurodegeneration after experimental brain trauma: association with chronic microglial activation. J. Neuropathol. Exp. Neurol. 73, 14–29. https://doi.org/10.1097/NEN.0000000000000021.
Lobo-Silva, D., Carriche, G.M., Castro, A.G., Roque, S., Saraiva, M., 2016. Balancing the immune response in the brain: IL-10 and its regulation. J. Neuroinflammation 13. https://doi.org/10.1186/s12974-016-0763-8.
Longhi, L., Perego, C., Ortolano, F., Aresi, S., Fumagalli, S., Zanier, E.R., Stocchetti, N., De Simoni, M.-G., 2013. Tumor necrosis factor in traumatic brain injury: effects of genetic deletion of p55 or p75 receptor. J. Cereb. Blood Flow Metab. 33, 1182–1189. https://doi.org/10.1038/jcbfm.2013.65.
López-Escribano, H., Miñambres, E., Labrador, M., Bartolomé, M.J., López-Hoyos, M., 2002. Induction of cell death by sera from patients with acute brain injury as a mechanism of production of autoantibodies: Cell Death Induction and Autoantibody Production. Arthritis Rheum. 46, 3290–3300. https://doi.org/10.1002/art.10684.
Lull, M.E., Block, M.L., 2010. Microglial activation and chronic neurodegeneration. Neurotherapeutics 7, 354–365. https://doi.org/10.1016/j.nurt.2010.05.014.
Lünemann, A., Lünemann, J.D., Roberts, S., Messmer, B., da Silva, R.B., Raine, C.S., Münz, C., 2008. Human NK cells kill resting but not activated microglia via NKG2D and NKp46 mediated recognition. J. Immunol. Baltim. Md 181, 6170–6177.
Maas, A.I.R., Murray, G., Henney, H., Kassem, N., Legrand, V., Mangelus, M., Muizelaar, J.-P., Stocchetti, N., Knoller, N., investigators, Pharmos T.B.I., 2006. Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. Lancet Neurol. 5, 38–45. https://doi.org/10.1016/S1474-4422(05)70253-2.
Magliozzi, R., Howell, O., Vora, A., Serafini, B., Nicholas, R., Puopolo, M., Reynolds, R., Aloisi, F., 2007. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. Brain 130, 1089–1104. https://doi.org/10.1093/brain/awm038.
Makinde, H.M., Cuda, C.M., Just, T.B., Perlman, H.R., Schwulst, S.J., 2017. Nonclassical monocytes mediate secondary injury, neurocognitive outcome, and neutrophil infiltration after traumatic brain injury. J. Immunol. 199, 3583–3591. https://doi.org/10.4049/jimmunol.1700896.
Mannino, M.H., Zhu, Z., Xiao, H., Bai, Q., Wakefield, M.R., Fang, Y., 2015. The paradoxical role of IL-10 in immunity and cancer. Cancer Lett. 367, 103–107. https://doi.org/10.1016/j.canlet.2015.07.009.
Maphis, N., Xu, G., Kokiko-Cochran, O.N., Jiang, S., Cardona, A., Ransohoff, R.M., Lamb, B.T., Bhaskar, K., 2015. Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain. Brain 138, 1738–1755. https://doi.org/10.1093/brain/awv081.
Marchi, N., Bazarian, J.J., Puvenna, V., Janigro, M., Ghosh, C., Zhong, J., Zhu, T., Blackman, E., Stewart, D., Ellis, J., Butler, R., Janigro, D., 2013. Consequences of repeated blood-brain barrier disruption in football players. PLoS One 8, e56805. https://doi.org/10.1371/journal.pone.0056805.
Millis, S.R., Rosenthal, M., Novack, T.A., Sherer, M., Nick, T.G., Kreutzer, J.S., High Jr., W.M., Ricker, J.H., 2001. Long-term neuropsychological outcome after traumatic brain injury. J. Head Trauma Rehabil. 16, 343–355.
Moalem, G., Leibowitz–Amit, R., Yoles, E., Mor, F., Cohen, I.R., Schwartz, M., 1999. Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. Nat. Med. 5, 49–55. https://doi.org/10.1038/4734.
Mondello, S., Sorinola, A., Czeiter, E., Vámos, Z., Amrein, K., Synnot, A., Donoghue, E.L., Sándor, J., Wang, K.K.W., Diaz-Arrastia, R., Steyerberg, E.W., Menon, D., Maas, A., Buki, A., 2017. Blood-based protein biomarkers for the management of traumatic brain injuries in adults presenting with mild head injury to emergency departments: a living systematic review and meta-analysis. J. Neurotrauma. https://doi.org/10.1089/neu.2017.5182.
Morganti, J.M., Jopson, T.D., Liu, S., Riparip, L.-K., Guandique, C.K., Gupta, N., Ferguson, A.R., Rosi, S., 2015. CCR2 antagonism alters brain macrophage polarization and ameliorates cognitive dysfunction induced by traumatic brain injury. J. Neurosci. 35, 748–760. https://doi.org/10.1523/JNEUROSCI.2405-14.2015.
Morganti, J.M., Riparip, L.-K., Rosi, S., 2016. Call Off the Dog(ma): M1/M2 polarization is concurrent following traumatic brain injury. PLoS One 11, e0148001. https://doi.org/10.1371/journal.pone.0148001.
Morozov, S.G., Asanova, L.M., Gnedenko, B.B., Panchenko, L.F., Lavrova, T.N., 1996. Autoantibodies against nerve tissue proteins long after cranio-cerebral injury. Vopr. Meditsinskoĭ Khimii 42, 147–152.
Mortezaee, K., Khanlarkhani, N., Beyer, C., Zendedel, A., 2018. Inflammasome: its role in traumatic brain and spinal cord injury. J. Cell. Physiol. 233, 5160–5169. https://doi.org/10.1002/jcp.26287.
Murphy, Á.C., Lalor, S.J., Lynch, M.A., Mills, K.H.G., 2010. Infiltration of Th1 and Th17 cells and activation of microglia in the CNS during the course of experimental autoimmune encephalomyelitis. Brain Behav. Immun. 24, 641–651. https://doi.org/10.1016/j.bbi.2010.01.014.
Myer, D.J., Gurkoff, G.G., Lee, S.M., Hovda, D.A., Sofroniew, M.V., 2006. Essential protective roles of reactive astrocytes in traumatic brain injury. Brain 129, 2761–2772. https://doi.org/10.1093/brain/awl165.
Neniskyte, U., Vilalta, A., Brown, G.C., 2014. Tumour necrosis factor alpha-induced neuronal loss is mediated by microglial phagocytosis. FEBS Lett. 588, 2952–2956. https://doi.org/10.1016/j.febslet.2014.05.046.
Neumann, H., Kotter, M.R., Franklin, R.J.M., 2008. Debris clearance by microglia: an essential link between degeneration and regeneration. Brain 132, 288–295. https://doi.org/10.1093/brain/awn109.
Ngankam, L., Kazantseva, N.V., Gerasimova, M.M., 2011. [Immunological markers of severity and outcome of traumatic brain injury]. Zhurnal Nevrol. Psikhiatrii Im. SS Korsakova Minist. Zdr. Meditsinskoĭ Promyshlennosti Ross. Fed. Vserossiĭskoe Obshchestvo Nevrol. Vserossiĭskoe Obshchestvo Psikhiatrov 111, 61–65.
Nguyen, H.X., O'Barr, T.J., Anderson, A.J., 2007. Polymorphonuclear leukocytes promote neurotoxicity through release of matrix metalloproteinases, reactive oxygen species, and TNF-alpha. J. Neurochem. 102, 900–912. https://doi.org/10.1111/j.1471-4159.2007.04643.x.
Nielsen, H.H., Ladeby, R., Fenger, C., Toft-Hansen, H., Babcock, A.A., Owens, T., Finsen, B., 2009. enhanced microglial clearance of myelin debris in T cell-infiltrated central nervous system. J. Neuropathol. Exp. Neurol. 68, 845–856. https://doi.org/10.1097/NEN.0b013e3181ae0236.
Oberländer, U., Pletinckx, K., Döhler, A., Müller, N., Lutz, M.B., Arzberger, T., Riederer, P., Gerlach, M., Koutsilieri, E., Scheller, C., 2011. Neuromelanin is an immune stimulator for dendritic cells in vitro. BMC Neurosci. 12, 116. https://doi.org/10.1186/1471-2202-12-116.
Okuma, Y., Liu, K., Wake, H., Zhang, J., Maruo, T., Date, I., Yoshino, T., Ohtsuka, A., Otani, N., Tomura, S., Shima, K., Yamamoto, Y., Yamamoto, H., Takahashi, H.K., Mori, S., Nishibori, M., 2012. Anti–high mobility group box-1 antibody therapy for traumatic brain injury. Ann. Neurol. 72, 373–384. https://doi.org/10.1002/ana.23602.
Olson, J.K., Miller, S.D., 2004. Microglia initiate central nervous system innate and adaptive immune responses through multiple TLRs. J. Immunol. 173, 3916–3924. https://doi.org/10.4049/jimmunol.173.6.3916.
Pearn, M.L., Niesman, I.R., Egawa, J., Sawada, A., Almenar-Queralt, A., Shah, S.B., Duckworth, J.L., Head, B.P., 2017. Pathophysiology associated with traumatic brain injury: current treatments and potential novel therapeutics. Cell. Mol. Neurobiol. 37, 571–585. https://doi.org/10.1007/s10571-016-0400-1.
Penkowa, M., Giralt, M., Carrasco, J., Hadberg, H., Hidalgo, J., 2000. Impaired inflammatory response and increased oxidative stress and neurodegeneration after brain injury in interleukin-6-deficient mice. Glia 32, 271–285.
Penkowa, M., Giralt, M., Lago, N., Camats, J., Carrasco, J., Hernández, J., Molinero, A., Campbell, I.L., Hidalgo, J., 2003. Astrocyte-targeted expression of IL-6 protects the CNSagainst a focal brain injury. Exp. Neurol. 181, 130–148. https://doi.org/10.1016/S0014-4886(02)00051-1.
Piazza, F., Greenberg, S.M., Savoiardo, M., Gardinetti, M., Chiapparini, L., Raicher, I., Nitrini, R., Sakaguchi, H., Brioschi, M., Billo, G., Colombo, A., Lanzani, F., Piscosquito, G., Carriero, M.R., Giaccone, G., Tagliavini, F., Ferrarese, C., DiFrancesco, J.C., 2013. Anti–amyloid β autoantibodies in cerebral amyloid angiopathy–related inflammation: Implications for amyloid-modifying therapies. Ann. Neurol. 73, 449–458. https://doi.org/10.1002/ana.23857.
Pischiutta, F., Micotti, E., Hay, J.R., Marongiu, I., Sammali, E., Tolomeo, D., Vegliante, G., Stocchetti, N., Forloni, G., De Simoni, M.-G., Stewart, W., Zanier, E.R., 2018. Single severe traumatic brain injury produces progressive pathology with ongoing contralateral white matter damage one year after injury. Exp. Neurol. 300, 167–178. https://doi.org/10.1016/j.expneurol.2017.11.003.
Plog, B.A., Dashnaw, M.L., Hitomi, E., Peng, W., Liao, Y., Lou, N., Deane, R., Nedergaard, M., 2015. Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. J. Neurosci. 35, 518–526. https://doi.org/10.1523/JNEUROSCI.3742-14.2015.
Procházka, M., Voltnerová, M., Stefan, J., 1971. Studies of immunologic reactions after brain injury. II. Antibodies against brain tissue lipids after blunt head injury in man. Int. Surg. 55, 322–326.
Ramlackhansingh, A.F., Brooks, D.J., Greenwood, R.J., Bose, S.K., Turkheimer, F.E., Kinnunen, K.M., Gentleman, S., Heckemann, R.A., Gunanayagam, K., Gelosa, G., Sharp, D.J., 2011. Inflammation after trauma: Microglial activation and traumatic brain injury. Ann. Neurol. 70, 374–383. https://doi.org/10.1002/ana.22455.
Ransohoff, R.M., 2016. How neuroinflammation contributes to neurodegeneration. Science 353, 777–783. https://doi.org/10.1126/science.aag2590.
Rodriguez, M., Warrington, A.E., Pease, L.R., 2009. Invited article: human natural autoantibodies in the treatment of neurologic disease. Neurology 72, 1269–1276. https://doi.org/10.1212/01.wnl.0000345662.05861.e4.
Rudehill, S., Muhallab, S., Wennersten, A., von Gertten, C., Al Nimer, F., Sandberg-Nordqvist, A.C., Holmin, S., Mathiesen, T., 2006. Autoreactive antibodies against neurons and basal lamina found in serum following experimental brain contusion in rats. Acta Neurochir. 148, 199–205. https://doi.org/10.1007/s00701-005-0673-5.
Ruff, R.M., Young, D., Gautille, T., Marshall, L.F., Barth, J., Jane, J.A., Kreutzer, J., Marmarou, A., Levin, H.S., Eisenberg, H.M., Foulkes, M.A., 1991. Verbal learning deficits following severe head injury: heterogeneity in recovery over 1 year. Spec. Suppl. 75, S50–S58. https://doi.org/10.3171/sup.1991.75.1s.0s50.
Saadoun, S., Waters, P., Bell, B.A., Vincent, A., Verkman, A.S., Papadopoulos, M.C., 2010. Intra-cerebral injection of neuromyelitis optica immunoglobulin G and human complement produces neuromyelitis optica lesions in mice. Brain 133, 349–361. https://doi.org/10.1093/brain/awp309.
Saijo, K., Glass, C.K., 2011. Microglial cell origin and phenotypes in health and disease. Nat. Rev. Immunol. 11, 775–787. https://doi.org/10.1038/nri3086.
Saijo, K., Crotti, A., Glass, C.K., 2013. Regulation of microglia activation and deactivation by nuclear receptors. Glia 61, 104–111. https://doi.org/10.1002/glia.22423.
Sanderson, K.L., Raghupathi, R., Saatman, K.E., Martin, D., Miller, G., McIntosh, T.K.,

1999. Interleukin-1 receptor antagonist attenuates regional neuronal cell death and cognitive dysfunction after experimental brain injury. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 19, 1118–1125. https://doi.org/10.1097/00004647-199910000-00008.

Saxena, A., Khosraviani, S., Noel, S., Mohan, D., Donner, T., Hamad, A.R.A., 2015. Interleukin-10 paradox: A potent immunoregulatory cytokine that has been difficult to harness for immunotherapy. Cytokine 74, 27. https://doi.org/10.1016/j.cyto.2014.10.031.

Scheller, J., Chalaris, A., Schmidt-Arras, D., Rose-John, S., 2011. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim. Biophys. Acta BBA - Mol. Cell Res. 878–888. https://doi.org/10.1016/j.bbamcr.2011.01.034. Including the Special Section: 11th European Symposium on Calcium 1813.

Scherbel, U., Raghupathi, R., Nakamura, M., Saatman, K.E., Trojanowski, J.Q., Neugebauer, E., Marino, M.W., McIntosh, T.K., 1999. Differential acute and chronic responses of tumor necrosis factor-deficient mice to experimental brain injury. Proc. Natl. Acad. Sci. U. S. A. 96, 8721–8726.

Schoettle, R.J., Kochanek, P.M., Magargee, M.J., Uhl, M.W., Nemoto, E.M., 1990. Early polymorphonuclear leukocyte accumulation correlates with the development of posttraumatic cerebral edema in rats. J. Neurotrauma 7, 207–217. https://doi.org/10.1089/neu.1990.7.207.

Schwartz, M., 2001. Protective autoimmunity as a T-cell response to central nervous system trauma: prospects for therapeutic vaccines. Prog. Neurobiol. 65, 489–496. https://doi.org/10.1016/S0301-0082(01)00009-0.

Scott, G., Hellyer, P.J., Ramlackhansingh, A.F., Brooks, D.J., Matthews, P.M., Sharp, D.J., 2015. Thalamic inflammation after brain trauma is associated with thalamo-cortical white matter damage. J. Neuroinflammation 12. https://doi.org/10.1186/s12974-015-0445-y.

Scott, G., Zetterberg, H., Jolly, A., Cole, J.H., De Simoni, S., Jenkins, P.O., Feeney, C., Owen, D.R., Lingford-Hughes, A., Howes, O., Patel, M.C., Goldstone, A.P., Gunn, R.N., Blennow, K., Matthews, P.M., Sharp, D.J., 2018. Minocycline reduces chronic microglial activation after brain trauma but increases neurodegeneration. Brain 141, 459–471. https://doi.org/10.1093/brain/awx339.

Semple, B.D., Bye, N., Ziebell, J.M., Morganti-Kossmann, M.C., 2010. Deficiency of the chemokine receptor CXCR2 attenuates neutrophil infiltration and cortical damage following closed head injury. Neurobiol. Dis. 40, 394–403. https://doi.org/10.1016/j.nbd.2010.06.015.

Semple, B.D., Trivedi, A., Gimlin, K., Noble-Haeusslein, L.J., 2015. Neutrophil elastase mediates acute pathogenesis and is a determinant of long-term behavioral recovery after traumatic injury to the immature brain. Neurobiol. Dis. 74, 263–280. https://doi.org/10.1016/j.nbd.2014.12.003.

Shamreĭ, R.K., 1969. The value of determining autoantibodies in the diagnosis and expertise of closed brain injury. Voen.-Meditsinskiĭ Zhurnal 4, 39–43.

Shi, F.-D., Takeda, K., Akira, S., Sarvetnick, N., Ljunggren, H.-G., 2000. IL-18 directs autoreactive T cells and promotes autodestruction in the central nervous system via induction of IFN- by NK cells. J. Immunol. 165, 3099–3104. https://doi.org/10.4049/jimmunol.165.6.3099.

Shiozaki, T., Hayakata, T., Tasaki, O., Hosotubo, H., Fuijita, K., Mouri, T., Tajima, G., Kajino, K., Nakae, H., Tanaka, H., Shimazu, T., Sugimoto, H., 2005. Cerebrospinal fluid concentrations of anti-inflammatory mediators in early-phase severe traumatic brain injury. Shock Augusta Ga 23, 406–410.

Shohami, E., Bass, R., Wallach, D., Yamin, A., Gallily, R., 1996. Inhibition of tumor necrosis factor alpha (TNFalpha) activity in rat brain is associated with cerebroprotection after closed head injury. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 16, 378–384. https://doi.org/10.1097/00004647-199605000-00004.

Shohami, E., Gallily, R., Mechoulam, R., Bass, R., Ben-Hur, T., 1997. Cytokine production in the brain following closed head injury: dexanabinol (HU-211) is a novel TNF-alpha inhibitor and an effective neuroprotectant. J. Neuroimmunol. 72, 169–177.

Sica, A., Mantovani, A., 2012. Macrophage plasticity and polarization: in vivo veritas. J. Clin. Invest. 122, 787–795. https://doi.org/10.1172/JCI59643.

Singhal, A., Baker, A.j., Hare, G.m.t., Reinders, F.x., Schlichter, L.c., Moulton, R.j., 2002. Association between cerebrospinal fluid interleukin-6 concentrations and outcome after severe human traumatic brain injury. J. Neurotrauma 19, 929–937. https://doi.org/10.1089/089771502320317087.

Škoda, D., Kranda, K., Bojar, M., Glosová, L., Bäurle, J., Kenney, J., Romportl, D., Pelichovská, M., Cvachovec, K., 2006. Antibody formation against β-tubulin class III in response to brain trauma. Brain Res. Bull. 68, 213–216. https://doi.org/10.1016/j.brainresbull.2005.05.032.

Soane, L., Cho, H.-J., Niculescu, F., Rus, H., Shin, M.L., 2001. C5b-9 terminal complement complex protects oligodendrocytes from death by regulating bad through phosphatidylinositol 3-kinase/Akt pathway. J. Immunol. 167, 2305–2311. https://doi.org/10.4049/jimmunol.167.4.2305.

Soares, H.D., Hicks, R.R., Smith, D., McIntosh, T.K., 1995. Inflammatory leukocytic recruitment and diffuse neuronal degeneration are separate pathological processes resulting from traumatic brain injury. J. Neurosci. 15, 8223–8233.

Soares, F.M.S., de Souza, N.M., Schwarzbold, M.L., Diaz, A.P., Nunes, J.C., Hohl, A., da Silva, P.N.A., Vieira, J., de Souza, R.L., Bertotti, M.M., Prediger, R.D.S., Linhares, M.N., Bafica, A., Walz, R., 2012. Interleukin-10 is an independent biomarker of severe traumatic brain injury prognosis. Neuroimmunomodulation 19, 377–385. https://doi.org/10.1159/000342141.

Sorokina, E.G., Semenova, Z.B., Bazarnaya, N.A., Meshcheryakov, S.V., Reutov, V.P., Goryunova, A.V., Pinelis, V.G., Granstrem, O.K., Roshal, L.M., 2009. Autoantibodies to glutamate receptors and products of nitric oxide metabolism in serum in children in the acute phase of craniocerebral trauma. Neurosci. Behav. Physiol. 39, 329–334. https://doi.org/10.1007/s11055-009-9147-1.

Sorokina, E.G., Vol'pina, O.M., Semenova, Z.B., Karaseva, O.V., Koroev, D.O., Kamynina, A.V., Reutov, V.P., Salykina, M.A., Panova, A.V., Goriunova, A.V., Pinelis, V.G., Roshal', L.M., 2011. Autoantibodies to α7-subunit of neuronal acetylcholine receptor in children with traumatic brain injury. Zhurnal Nevrol. Psikhiatrii Im. SS Korsakova Minist. Zdr. Meditsinskoĭ Promyshlennosti Ross. Fed. Vserossiĭskoe Obshchestvo Nevrol. Vserossiĭskoe Obshchestvo Psikhiatrov 111, 56–60.

Stahel, P.F., Morganti-Kossmann, M.C., Perez, D., Redaelli, C., Gloor, B., Trentz, O., Kossmann, T., 2001. Intrathecal levels of complement-derived soluble membrane attack complex (sC5b-9) correlate with blood-brain barrier dysfunction in patients with traumatic brain injury. J. Neurotrauma 18, 773–781.

Stein, T.D., Fedynyshyn, J.P., Kalil, R.E., 2002. Circulating autoantibodies recognize and bind dying neurons following injury to the brain. J. Neuropathol. Exp. Neurol. 61, 1100–1108. https://doi.org/10.1093/jnen/61.12.1100.

Sullivan, P.G., Bruce-Keller, A.J., Rabchevsky, A.G., Christakos, S., Clair, D.K.S., Mattson, M.P., Scheff, S.W., 1999. Exacerbation of damage and altered NF-κB activation in mice lacking tumor necrosis factor receptors after traumatic brain injury. J. Neurosci. 19, 6248–6256.

Tanriverdi, F., De Bellis, A., Bizzarro, A., Sinisi, A.A., Bellastella, G., Pane, E., Bellastella, A., Unluhizarci, K., Selcuklu, A., Casanueva, F.F., Kelestimur, F., 2008. Antipituitary antibodies after traumatic brain injury: is head trauma-induced pituitary dysfunction associated with autoimmunity? Eur. J. Endocrinol. 159, 7–13. https://doi.org/10.1530/EJE-08-0050.

Tanriverdi, F., De Bellis, A., Battaglia, M., Bellastella, G., Bizzarro, A., Sinisi, A.A., Bellastella, A., Unluhizarci, K., Selcuklu, A., Casanueva, F.F., Kelestimur, F., 2010. Investigation of antihypothalamus and antipituitary antibodies in amateur boxers: is chronic repetitive head trauma-induced pituitary dysfunction associated with autoimmunity? Eur. J. Endocrinol. 162, 861–867. https://doi.org/10.1530/EJE-09-1024.

Tehranian, R., Andell-Jonsson, S., Beni, S.M., Yatsiv, I., Shohami, E., Bartfai, T., Lundkvist, J., Iverfeldt, K., 2002. Improved recovery and delayed cytokine induction after closed head injury in mice with central overexpression of the secreted isoform of the interleukin-1 receptor antagonist. J. Neurotrauma 19, 939–951. https://doi.org/10.1089/089771502320317096.

Thelin, E.P., Johannesson, L., Nelson, D., Bellander, B.M., 2013 Apr 1. S100B is an important outcome predictor in traumatic brain injury. J. Neurotrauma. 30 (7), 519–528.

Tian, G., Li, J.-L., Wang, D.-G., Zhou, D., 2014. Targeting IL-10 in auto-immune diseases. Cell Biochem. Biophys. 70, 37–49. https://doi.org/10.1007/s12013-014-9903-x.

Till, C., Colella, B., Verwegen, J., Green, R.E., 2008. Postrecovery cognitive decline in adults with traumatic brain injury. Arch. Phys. Med. Rehabil. 89, S25–S34. https://doi.org/10.1016/j.apmr.2008.07.004.

Toulmond, S., Rothwell, N.J., 1995. Interleukin-1 receptor antagonist inhibits neuronal damage caused by fluid percussion injury in the rat. Brain Res. 671, 261–266.

Turtzo, L.C., Lescher, J., Janes, L., Dean, D.D., Budde, M.D., Frank, J.A., 2014. Macrophagic and microglial responses after focal traumatic brain injury in the female rat. J. Neuroinflammation 11, 82. https://doi.org/10.1186/1742-2094-11-82.

Uzan, M., Tanriverdi, T., Baykara, O., Kafadar, A., Sanus, G.Z., Tureci, E., Ozkara, C., Uysal, O., Buyra, N., 2005. Association between interleukin-1 beta (IL-1beta) gene polymorphism and outcome after head injury: an early report. Acta Neurochir. 147, 715–720. discussion 720. https://doi.org/10.1007/s00701-005-0529-z.

Vink, R., Gabrielian, L., Thornton, E., 2017. The role of substance P in secondary pathophysiology after traumatic brain injury. Front. Neurol. 8. https://doi.org/10.3389/fneur.2017.00304.

Wallisch, J.S., Simon, D.W., Bayır, H., Bell, M.J., Kochanek, P.M., Clark, R.S.B., 2017. Cerebrospinal fluid NLRP3 is increased after severe traumatic brain injury in infants and children. Neurocrit. Care. 27, 44–50. https://doi.org/10.1007/s12028-017-0378-7.

Walsh, J.T., Hendrix, S., Boato, F., Smirnov, I., Zheng, J., Lukens, J.R., Gadani, S., Hechler, D., Gölz, G., Rosenberger, K., Kammertöns, T., Vogt, J., Vogelaar, C., Siffrin, V., Radjavi, A., Fernandez-Castaneda, A., Gaultier, A., Gold, R., Kanneganti, T.-D., Nitsch, R., Zipp, F., Kipnis, J., 2015. MHCII-independent CD4+ T cells protect injured CNS neurons via IL-4. J. Clin. Invest. 125, 699–714. https://doi.org/10.1172/JCI76210.

Wang, K.-Y., Yu, G.-F., Zhang, Z.-Y., Huang, Q., Dong, X.-Q., 2012. Plasma high-mobility group box 1 levels and prediction of outcome in patients with traumatic brain injury. Clin. Chim. Acta 413, 1737–1741. https://doi.org/10.1016/j.cca.2012.07.002.

Wang, G., Zhang, J., Hu, X., Zhang, L., Mao, L., Jiang, X., Liou, A.K.-F., Leak, R.K., Gao, Y., Chen, J., 2013. Microglia/macrophage polarization dynamics in white matter after traumatic brain injury. J. Cereb. Blood Flow Metab. 33, 1864–1874. https://doi.org/10.1038/jcbfm.2013.146.

Wang, K.K.W., Yang, Z., Yue, J.K., Zhang, Z., Winkler, E.A., Puccio, A.M., Diaz-Arrastia, R., Lingsma, H.F., Yuh, E.L., Mukherjee, P., Valadka, A.B., Gordon, W.A., Okonkwo, D.O., Manley, G.T., the TRACK-TBI Investigators, Cooper, S.R., Dams-O'Connor, K., Hricik, A.J., Inoue, T., Maas, A.I.R., Menon, D.K., Schnyer, D.M., Sinha, T.K., Vassar, M.J., 2016. Plasma anti-glial fibrillary acidic protein autoantibody levels during the acute and chronic phases of traumatic brain injury: a transforming research and clinical knowledge in traumatic brain injury pilot study. J. Neurotrauma 33, 1270–1277. https://doi.org/10.1089/neu.2015.3881.

Warrington, A.E., Bieber, A.J., Ciric, B., Van Keulen, V., Pease, L.R., Mitsunaga, Y., Soldan, M.M.P., Rodriguez, M., 2001. Immunoglobulin-mediated CNS repair. J. Allergy Clin. Immunol. 108, S121–S125. https://doi.org/10.1067/mai.2001.118301.

Washington, P.M., Villapol, S., Burns, M.P., 2016. Polypathology and dementia after brain trauma: Does brain injury trigger distinct neurodegenerative diseases, or should they be classified together as traumatic encephalopathy? Exp. Neurol. 275, 381–388. https://doi.org/10.1016/j.expneurol.2015.06.015.

Waters, R.J., Murray, G.D., Teasdale, G.M., Stewart, J., Day, I., Lee, R.J., Nicoll, J.A.R., 2013. Cytokine gene polymorphisms and outcome after traumatic brain injury. J. Neurotrauma 30, 1710–1716. https://doi.org/10.1089/neu.2012.2792.

Weerth, S.H., Rus, H., Shin, M.L., Raine, C.S., 2003. Complement C5 in experimental autoimmune encephalomyelitis (EAE) facilitates remyelination and prevents gliosis. Am. J. Pathol. 163, 1069–1080.

Westland, K.W., Pollard, J.D., Sander, S., Bonner, J.G., Linington, C., McLeod, J.G., 1999. Activated non-neural specific T cells open the blood-brain barrier to circulating antibodies. Brain J. Neurol. 122 (Pt 7), 1283–1291.

Whitnall, L., 2006. Disability in young people and adults after head injury: 5–7 year follow up of a prospective cohort study. J. Neurol. Neurosurg. Psychiatry 77, 640–645. https://doi.org/10.1136/jnnp.2005.078246.

Winter, M., Baksmeier, C., Steckel, J., Barman, S., Malviya, M., Harrer-Kuster, M., Hartung, H., Goebels, N., 2016. Dose-dependent inhibition of demyelination and microglia activation by IVIG. Ann. Clin. Transl. Neurol. 3, 828–843. https://doi.org/10.1002/acn3.326.

Wong, D., Prameya, R., Dorovini-Zis, K., 1999. In vitro adhesion and migration of T lymphocytes across monolayers of human brain microvessel endothelial cells: regulation by ICAM-1, VCAM-1, E-selectin and PECAM-1. J. Neuropathol. Exp. Neurol. 58, 138–152. https://doi.org/10.1097/00005072-199902000-00004.

Woodcock, T., Morganti-Kossmann, M.C., 2013. The role of markers of inflammation in traumatic brain injury. Front. Neurol. 4. https://doi.org/10.3389/fneur.2013.00018.

Xu, K., Yang, Z., Shi, R., Luo, C., Zhang, Z., 2016. Expression of aryl hydrocarbon receptor in rat brain lesions following traumatic brain injury. Diagn. Pathol. 11. https://doi.org/10.1186/s13000-016-0522-2.

Yoles, E., Hauben, E., Palgi, O., Agranov, E., Gothilf, A., Cohen, A., Kuchroo, V., Cohen, I.R., Weiner, H., Schwartz, M., 2001. Protective autoimmunity is a physiological response to CNS trauma. J. Neurosci. 21, 3740–3748.

Zanier, E.R., Fumagalli, S., Perego, C., Pischiutta, F., De Simoni, M.-G., 2015. Shape descriptors of the “never resting” microglia in three different acute brain injury models in mice. Intensive Care Med. Exp. 3. https://doi.org/10.1186/s40635-015-0039-0.

Zanier, E.R., Marchesi, F., Ortolano, F., Perego, C., Arabian, M., Zoerle, T., Sammali, E., Pischiutta, F., De Simoni, M.-G., 2016. Fractalkine receptor deficiency is associated with early protection but late worsening of outcome following brain trauma in mice. J. Neurotrauma 33, 1060–1072. https://doi.org/10.1089/neu.2015.4041.

Zhang, Z., Zoltewicz, J.S., Mondello, S., Newsom, K.J., Yang, Z., Yang, B., Kobeissy, F., Guingab, J., Glushakova, O., Robicsek, S., Heaton, S., Buki, A., Hannay, J., Gold, M.S., Rubenstein, R., Lu, X.M., Dave, J.R., Schmid, K., Tortella, F., Robertson, C.S., Wang, K.K.W., 2014. Human traumatic brain injury induces autoantibody response against glial fibrillary acidic protein and its breakdown products. PLoS One 9, e92698. https://doi.org/10.1371/journal.pone.0092698.