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REVIEW

The complexity of neuroinflammation consequent to traumatic brain injury: from research evidence to potential treatments

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Abstract
This review recounts the definitions and research evidence supporting the multifaceted roles of neuroinflammation in the injured brain following trauma. We summarise the literature fluctuating from the protective and detrimental properties that cytokines, leukocytes and glial cells play in the acute and chronic stages of TBI, including the intrinsic factors that influence cytokine responses and microglial functions relative to genetics, sex, and age. We elaborate on the pros and cons that cytokines, chemokines, and microglia play in brain repair, specifically neurogenesis, and how such conflicting roles may be harnessed therapeutically to sustain the survival of new neurons. With a brief review of the clinical and experimental findings demonstrating early and chronic inflammation impacts on outcomes, we focus on the clinical conditions that may be amplified by neuroinflammation, ranging from acute seizures to chronic epilepsy, neuroendocrine dysfunction, dementia, depression, post-traumatic stress disorder and chronic traumatic encephalopathy. Finally, we provide an overview of the therapeutic agents that have been tested to reduce inflammation-driven secondary pathological cascades and speculate the future promise of alternative drugs.

Epidemiology of TBI

The World Health Organisation defines acute brain injury as the result of mechanical energy to the head from external physical forces. Traumatic brain injury (TBI) encompasses a spectrum of diseases that vary in severity, morphology, symptomatology, and outcomes. Traditionally classified with the Glasgow Coma Scale, TBI is grossly divided into severe, moderate, and mild, which includes concussions. Mortality in severe TBI remains high (> 30%) with approximately 60% of patients suffering from life-long consequences, which affect their health, psychiatric, professional, and personal wellbeing [110]. Even a mild TBI may cause long-term issues, particularly following repetitive trauma.

The estimated number of TBIs per annum equates to 2500,000 in the EU and 3500,000 in the US [110]. Epidemiological studies indicate a diminishing number of severe TBIs in the young population living in high-income countries, but a rise of TBIs in the elderly group. Conversely, emerging economic nations experience a rapid increase of TBIs, with deficits in prevention, diagnosis, treatment, and rehabilitation, causing overwhelming death rates.

Despite decades of research in brain trauma and the remarkable improvement in clinical diagnostics and management, we lack efficacious treatments to mitigate neurotoxic pathways aggravating the initial injury. Successful pharmaceutical therapies showing experimental efficacy have failed to translate in the clinic. To address the problem, clinicians and scientists have grouped into international consortia to establish vast TBI data collections for reassessing

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definitions, diagnosis, prognosis, management, and treatments [110].

Pathophysiology of primary and secondary brain damage

The sequelae of brain injury follow an ordered temporal and spatial evolution. Primary injury occurs at the time of the accident and is aggravated by acute systemic insults (hypotension, hypoxia, haemorrhage) and neurotoxic pathways, leading to secondary brain damage. Morphologically, brain injury is classified into focal and diffuse, mostly coexisting in different proportions. Focal TBI presents defined intraparenchymal lesion(s) and haemorrhages whereas diffuse TBI is a global pathology predominantly affecting the white matter and axons subjected to shearing and stretching forces [1].

Within minutes of a TBI, the healthy tissue surrounding the damaged area experiences the activation of intersecting molecular pathways alienating the normal physiology. They include glutamate-driven excitotoxicity, mitochondrial dysfunction, energy failure, oxidative stress, neuroinflammation, calpain degradation of axonal filaments, blood–brain barrier (BBB) dysfunction, and brain influx of fluid and blood components. Together these events lead to brain oedema, ischaemia, cytotoxic cell swelling and increased intracranial pressure, recognised as the main cause of death following TBI.

Inflammatory pathways occurring in the injured brain

Role of cytokines in cerebral inflammatory response

Inflammatory processes ensue within minutes from a TBI generating a complex network of distinct molecular and cellular pathways (see Fig. 1). Classical pro-inflammatory cytokines like interleukin(IL)-1β, tumour necrosis factor (TNF), IL-6, and chemokines (CCL2, IL-8/CXCL2) as well as other mediators corollary to inflammation [cell adhesion molecules CAMs, prostaglandins, complement, damage associated molecular patterns (DAMPs), lysophospholipids, miRNA are the first responders to trauma, stimulating further the upregulation of other factors to generate a multifaceted inflammatory loop [59, 171, 211].

Cytokines display powerful effects even at small concentrations. They exhibit opposing and redundant functions whose fate may depend on their concentration, the effector receptor they bind to, and the cell type they are acting upon. Cytokines also possess functions beyond their principal immunological purpose with an established role in the development, homeostasis, and repair of the nervous system. In fact, glia and even neurons are important producers of cytokines and cytokine receptors both in health and disease [227].

The humoral and cellular inflammatory response defines a consistent temporal profile with pro-inflammatory cytokine mRNAs being upregulated in the injured brain in the first hours (acute phase), followed by the synthesis of cytokine proteins, whereby pro-inflammatory mediators arise first peaking between 2- and 24-h post-injury, then followed by anti-inflammatory mediators to resolve the immune activation. This inflammatory milieu stimulates the activation of resident glial cells, and the extravasation of neutrophils and subsequently of macrophages, which continues over days [227].

Cellular infiltration and glial activation in the injured brain

Neutrophils are the most abundant circulating granulocytes and are the first immune cells at the site of injury. Their transmigration across the BBB depends on the interaction between chemokines, their receptors and CAMs expressed at the BBB [156]. Neutrophil accumulation mostly occurs within the first 24 h from injury. Clinical studies have found that the absolute number and frequency of circulating neutrophils is significantly increased after TBI, with one study reporting a 4.5-fold increase as early as 3 h [142]. Experimentally, CXCR2 (receptor for CXCL2, homologue to human IL-8) KO mice display decreased neutrophil accumulation [156], which was associated with reduced lesion volume, neuronal loss and altered brain cytokine profiles, but no reduction in BBB dysfunction and motor impairment. Thus, suggesting that neutrophils may aggravate secondary brain damage. Indeed, neutrophils produce reactive oxygen species (ROS), which are known drivers of secondary injury cascades initiated by TBI. Further, neutrophils can influence microglial responses following TBI due to their release of ROS, lipocalin-2, and MMP-9 [106].

Microglia play a dynamic role within the brain, functioning as debris scavengers and aiding in synaptic regulation and circuit organisation [115]. Their wide distribution in the brain is vital for functions that range from immune-related duties (removal of dead tissue) to classical maintenance tasks (release of neurotrophic factors, and synaptic modelling) during development [115]. Microglial morphology undergoes changes relative to function, with ramified microglia being in a surveillance state and other morphologies aligning to various degrees of activation. This simplistic view is now being challenged, with data indicating a more complex picture, whereby microglial surface antigens change conditional to the stimulus, which may result into distinct roles microglia play.

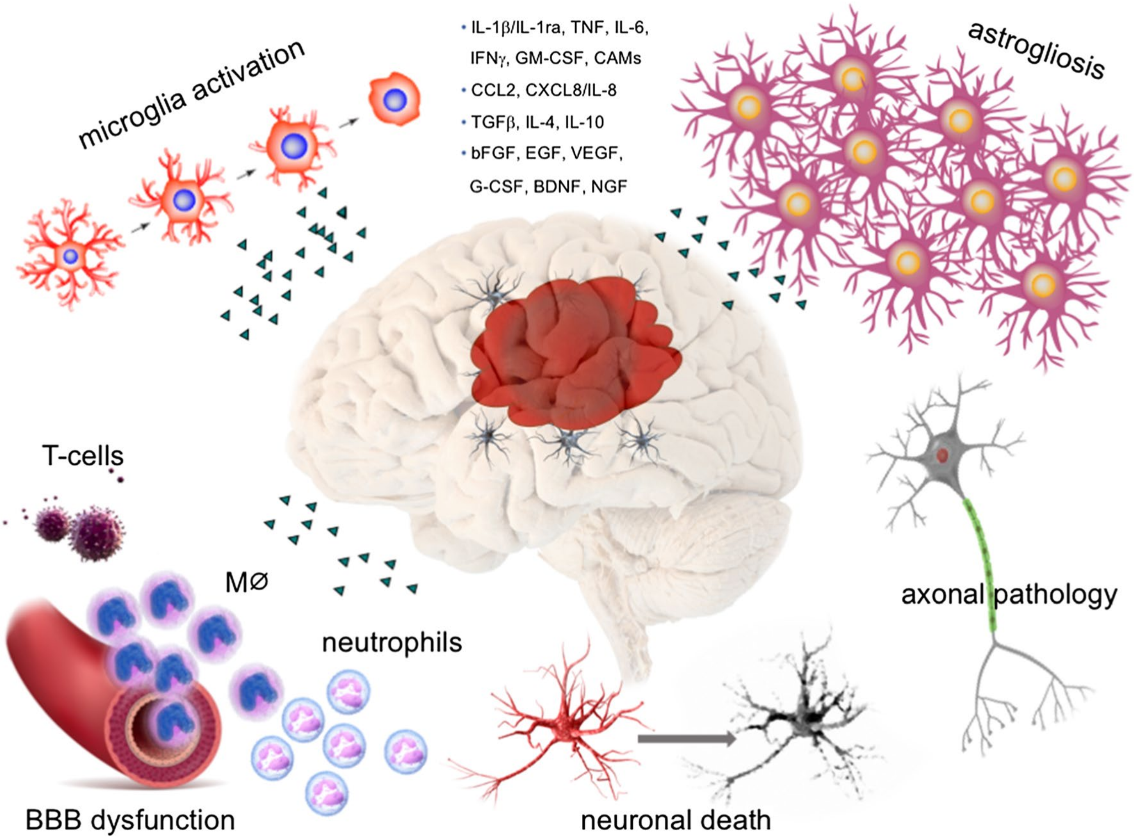

Fig. 1 The complexity of neuroinflammatory responses after TBI. Humoral and cellular inflammation begins acutely after brain trauma to potentially become a chronic phenomenon. Humoral inflammation is characterised by early secretion of pro-inflammatory cytokines, chemokines, and the expression of cell adhesion molecules, followed by the upregulation of anti-inflammatory cytokines, and the release of neurotrophic factors. The expression profile of these distinct families of immunologically potent factors defines the temporal course of cerebral inflammation terminating with its suppression and the production of neurotrophic factors assisting in brain repair. The early accumulation of neutrophils crossing the BBB is followed by the migration of peripheral macrophages and to less degree of T cells. The presence of leukocytes and lymphocytes in the injured brain enhances the activation of resident glial cells, microglia and astrocytes. Although induced acutely, evidence shows that some cytokines as well as microglial responses persist for months to decades after a TBI, coinciding with progressive brain degeneration. Ongoing neuroinflammation also sustain BBB dysfunction, astroglial scar formation, neuronal death and axonal pathology

In response to TBI, the transcriptional and proteomic profile of microglia is altered, causing morphological changes and the secretion of cytokines and chemokines ranging from pro-inflammatory (e.g., IL-1β, IL-6) to anti-inflammatory (e.g., IL-4, IL-10). Currently, it is debated whether microglia polarise to the M1/M2 classification of macrophages [92]. Compelling evidence suggests microglia evolve through a continuum, such that they are never purely M1 or M2 [118]. However, technical limitations make it difficult to unequivocally determine specific microglial phenotypes. A recent review has collated results of M1/M2 markers in TBI [48]. These data should be interpreted with caution as most studies use mixed cell populations (whole brain homogenate) rather than isolated microglia to specifically investigate transcriptomic factors. For example, mixed expression of M1 and M2 markers have been reported in mice following control cortical impact (CCI) injury, suggesting the concept of microglia polarisation may not be pertinent to TBI [118]. Conversely, in microglia isolated following CCI, the upregulation of M2-like phenotype occurred within the first days and was subsequently replaced at day 7 by predominantly M1-like markers [92], indicating the early M2-like response may become dysfunctional with time.

The role of microglia in TBI may vary with age, including both changes in morphology and cell surface marker expression. With age, microglia become dystrophic and undergo cytoplasmic fragmentation with cell processes appearing stripped of fine ramifications and acquiring spheroidal swellings [182]. Dystrophic microglia display an exaggerated pro-inflammatory response to stimuli (see Fig. 2). This implies that the age at time of injury may drastically affect microglial function [228]. LPS administration 5 days following a mild/diffuse TBI in rats produced an exaggerated pro-inflammatory cytokine production at 24 h, while at 3 months it caused

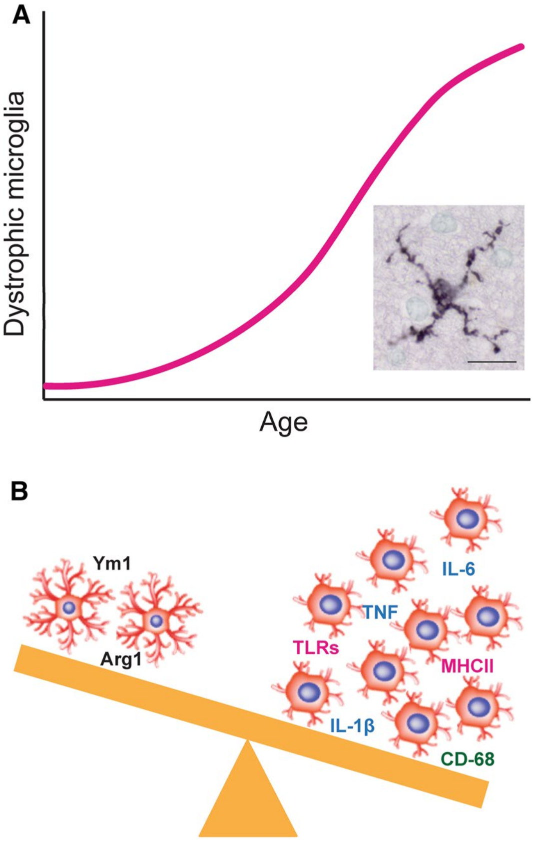

Fig. 2 Changes in microglial structure and function occur with age. Ageing increased dystrophic microglia are observed with reduced ramifications, see inset of dystrophic microglia in post-mortem tissue from 86 years old male stained with Iba1 (**a**). Ageing results in a shift of balance from ramified microglia to dystrophic; these microglia respond with an exaggerated pro-inflammatory response to changes in homeostasis (**b**)

persistent microglial activation and behavioural deficits [30]. In a porcine diffuse TBI model increased microglial density and activated morphology appeared as early as 15 min after trauma in proximity of damaged neurons showing membrane disruption and increased permeability, likely a consequence of ion imbalance [210]. These pathological features were exacerbated with repetitive impacts, synergistically amplifying the neuroinflammatory response possibly triggered by injured neurons themselves. In this context, the processes of activated, Iba-1 + microglia also colocalised with swollen APP + axons in the thalamus 6 h after mild diffuse TBI (cFPI) in the micro pig, nicely reflecting the vulnerability of the thalamus in human TBI in the absence of macroscopic tissue pathology [95].

It is hypothesised that TBI may prime microglia to premature brain ageing, and also contribute to the development of neurological diseases such as chronic traumatic encephalopathy (CTE), Parkinson's disease, or multiple sclerosis; however, empirical evidence is lacking. The ability to harness therapeutically the pro- and anti-inflammatory and/or the phagocytic capacity of microglia could potentially halt the development of chronic neuroinflammation and the relative neurological conditions arising from TBI.

Being one of the most abundant cells in the brain, astrocytes are potent contributors to the inflammatory response after TBI. Astrocytes typically perform homeostatic functions and blood flow control by sequestering excess fluid and regulating the influx of blood-borne immune cells [177]. They are critical in maintaining the BBB and providing metabolic support to neurons. Astrocyte reactivity or astrogliosis begins rapidly after injury with upregulation of cytoskeletal proteins glial fibrillary acidic protein (GFAP), vimentin and S100, followed by their ability to proliferate and migrate towards the injured site.

Upon TBI astrocytes secrete a multitude of cytokines and chemokines. They are in fact the main producers of chemoattractants, stimulating the activation and migration of macrophages/microglia and neutrophils around the damaged tissue (review [158]). Astrocytes also amplify cytokine and chemokine production when stimulated in vitro with LPS and IL-1β [157]. In a model of closed head injury (CHI) the cortical lesion became progressively devoid of neurons, which were completely replaced by glial cells over weeks as shown in CCI [155]. Interestingly, repeated injuries, both in rodents and humans, amplify glial activation, (microglia and astrocytes) with increased cell density compared to a single injury [23, 131].

Astrocytes possess several beneficial functions with their ability to sequestrate excessive glutamate and reduce excitotoxicity, free radical production, and most importantly secrete neurotrophins upon cytokine challenge [177]. Conversely, astrocytes' mechanoreceptors change in response to mechanical forces, causing transmembrane ion exchange, including potassium efflux, calcium influx and secretion of ATP and glutamate. This ion imbalance initiates pathways contributing to cytotoxic oedema, mostly due to astrocyte swelling with the involvement of aquaporin4, as well as the activation of the nuclear transcription factor NFkB modulating oxidative stress and inflammation [77, 141]. Inhibition of NFkB in a fluid percussion injury (FPI) model and "injured" cultured astrocytes not only reduced swelling, but also brain oedema [77].

In focal TBI, reactive astrocytes form the glial scar. This essentially walls off the injured area to contain the migration of inflammatory cells, thereby limiting the spread of neurotoxins to unaffected brain areas (Fig. 3). The protective role of this barrier was demonstrated with the ablation of reactive astrocytes enhancing cortical tissue loss and cellular inflammation after CCI. However, the glial scar is detrimental since it impairs axonal outgrowth.

Although less numerous, T-lymphocytes or T cells are also involved in post-TBI inflammation and seem to

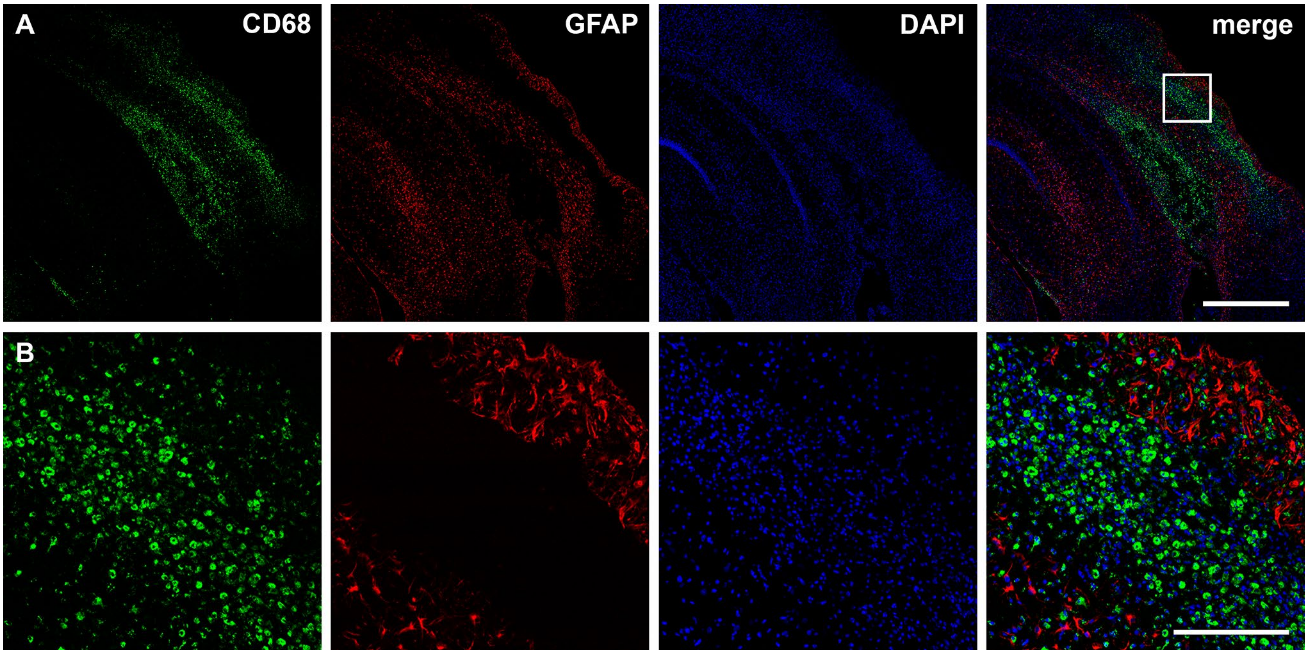

Fig. 3 Evidence of a robust cellular neuroinflammatory response after experimental TBI in the rat. Columns depict immunofluorescent staining for CD68 + macrophages/reactive microglia (green), GFAP + astrocytes (red) and DAPI + cell nuclei (blue), and a merged image. Representative coronal brain sections collected at 7 days after moderate-severe fluid percussion injury in the adult Long-Evans rat are presented. A glial scar comprised of reactive astrocytes appear to restrict the spread of macrophages from a discrete region of intense cellular staining in the lateral cortex ipsilateral to the impact site. The white box in the upper row (**a**) merged image indicates the field of view shown in the lower row images (**b**). Row A scale bar = 1000 µm; row B = 200 µm. *DAPI* 4′,6-diamidino-2-phenylindole, *GFAP* glial fibrillary acidic protein, *CD68* cluster of differentiation 68

negatively influence recovery in FPI [124]. T cells are vital constituents of the adaptive immune system. Through the T-cell receptor, T cells detect peptides that have been processed and then presented to MHC molecules, usually by microglia. After TBI, T cells are rapidly recruited, peaking at 2 days and declining by 7 days [124]. Severe TBI also results in a significant reduction in circulating T cells, which may underlie the susceptibility of patients to infections [67]. This decrease observed between 1 and 4 days reflects a decline in both CD8$^+$ cytotoxic and CD4$^+$ helper T cells [120]. It is hypothesised that lymphocyte retention in lymph nodes may be one mechanism to explain their reduction. Although T cells are also involved in the development of autoimmunity, their response to TBI seems to be largely beneficial [58].

Alternative early inflammatory mediators DAMPs and high-mobility group box protein 1 (HMGB1)

DAMPs exist as intracellularly sequestered molecules, which are released after cerebral injury either actively as dynamic immune modulators or passively by damaged or dying cells [103]. DAMPs are recognised via pattern-recognition receptors (PAMPs) expressed on macrophages, microglia, astrocytes and other cells of the innate immune system, and perpetuate the immune response by bolstering cytokine production as well as promoting tissue repair [103]. DAMPs can signal through toll-like receptors (TLRs), frequently TLR-2 and TLR4.

High-mobility group box protein 1 (HMGB1) modulates early neuroinflammation via activation of TLR-2 and TLR-4, as well as through the receptor for advanced glycation end products [108]. HMGB1 triggers astrocytic release of CXCL1, CXCL2 and CCL3 to recruit neutrophils, and CXCL1, CCL2, CCL5 and CCL20 to attract T cells [136], while neuronally derived HMGB1 stimulates microglial release of IL-6, IL-1β and TNF via the MAPK and NFκB signalling pathways [204]. The role of HMGB1 has been demonstrated in a FPI model by antibody neutralisation or via a TLR-4-KO, reducing neuroinflammation, restoring BBB integrity and improving recovery [132]. Peak HMGB1 levels in the cerebrospinal fluid (CSF) of children and adults with severe TBI correlated with poor outcomes [29] and distinguished survivors from non-survivors [29].

Inflammasomes

Inflammasomes are cytosolic multiprotein complexes acting as sensors for DAMPs. They are important players in the early neuroinflammatory response, as they enable the activation of IL-1β and IL-18 by caspase-1 [119]. Inflammasomes are composed of a cytosolic sensor, an adaptor protein and an effector caspase, which assemble upon recognition of DAMPs or PAMPs. Among several inflammasome complexes, the most pertinent for TBI are NACHT domain-, leucine-rich repeat-, and PYD-containing protein 1 (NLRP1) and NLRP3 [119], with NLRP3 being the most characterised. NLRP3 has been detected acutely up to 72 h in the CSF of children with severe TBI, whereby increased concentration correlated with poor outcomes [201]. The role of NLRP3 has been demonstrated in CCI, weight-drop and penetrating ballistic injury models [105] with a predominantly microglial derivation [214] and expression peaking around 24–48 h after penetrating ballistic injury [96]. The pivotal role of NLRP3 as an inducer of the acute inflammatory response and mediator of its downstream effects has been demonstrated in inhibitory and knockout studies, in which abrogated microglial activation, leukocyte recruitment, and dampened IL-1β levels occurred alongside tissue preservation, reduced oedema, and improved cognitive and neurological outcomes [75, 76, 214].

While NLRP3 has been associated with deleterious outcomes, the role of NLRP1 is less clear. Neutralisation of NLRP1 resulted in decreased caspase-1 and IL-1β, and contusion volume in FPI rats [40]. However, Nlrp1 null mice had persistent motor dysfunction, cell death and small lesion volumes after CCI, albeit with a reduction of IL-1β [10]. NLRP1 was also undetectable in CSF of children with severe TBI [201], suggesting that NLRP3, and not NLRP1 is a key mediator of post-traumatic neuroinflammation.

Mitochondrial DNA

Mitochondrial DNA (mtDNA) has received increasing attention for its capacity to directly activate neutrophils via TLR9 [221]. In a porcine model of diffuse TBI, mtDNA relative copy numbers in blood were elevated at 6 and 25 h, while in a porcine CCI model they were substantially lower and with slower release in blood, peaking at 25 h [85]. In a cohort of over 1000 patients with varying injury severities, mtDNA was associated with 6-month GOSE [14].

Immune activation at the blood/CSF barrier

Endothelial cells are enormously active immune cells, expressing cytokines and their receptors to permit a saturable cytokine transport between the parenchyma and the circulation [6]. Endothelial cells and perivascular macrophages increase cyclooxygenase (COX)-1 expression and secrete prostaglandins and nitric oxide, thus perpetuating the immune response [162]. The influence of cerebral inflammation on BBB is supported by the ability of IL-1β and IL-6 to increase the permeability of cultured endothelial cells, and leukocyte adhesion in vivo [134]. The BBB is the interface through which post-traumatic cerebral inflammation influences peripheral physiology such as the acute phase response in the liver elicited by IL-1β and IL-6 [41]. The immunological dysfunction generated by brain-derived mediators can lead to a systemic immune response syndrome and hyperinflammation underlying the immune suppression observed in severe TBI patients relative to decreased T cells, and natural killer cells. The migration of immune cells to peripheral organs may lead to multi-organ dysfunction particularly in the liver, spleen and lung. Cell apoptosis has been identified in various organs of polytrauma patients, thus explaining multi-organ dysfunction and failure. While the spleen is the primary reservoir for macrophages, their excessive accumulation after TBI may exacerbate neural damage (reviewed in [39]). In fact, splenectomy immediately after mild FPI reduced brain cytokine production, mortality and cognitive impairment, likely by decreasing the peripheral pool of macrophages and their brain migration and consequently neuroinflammation.

Likewise, systemic cytokines, released upon extracranial injuries and infections may enter the brain, exacerbate neuroinflammation and brain pathophysiology through sympathetic activation, fever and alterations of the hypothalamic–pituitary axis [84].

TNF, IL-1β, and IL-6 produced in the injured brain stimulate the synthesis of CAMs on the endothelium. E-selectin and ICAM-1 have been extensively studied in TBI patients [138]. However, their role in mediating acute leukocyte extravasation is questioned as brain ICAM-1 expression peaked 4–7 days after TBI, subsequent to maximal leukocytes accumulation on 1 day. This suggests the involvement of other adhesion molecules. A pivotal role in BBB dysfunction is also played by metalloproteinases like MMP-9, which compromises the integrity of endothelial tight junctions [25].

Cytokine transport also occurs through the brain-CSF barrier, the boundary between the brain and the CSF. The choroid plexus produces CSF and is immunologically active. The ability of the blood-CSF-barrier to promote neuroinflammation is supported by CAM expression and loss of occludin3 on epithelial cells, mediating the extravasation of leukocytes across the choroid plexus [91].

There is a clear link between chronic neuroinflammation and the onset of autoimmunity possibly driven by the inability of the injured CNS to resolve the immune reaction. Failure in phagocytosing apoptotic cells liberates in the parenchyma a variety of cellular components, that act as immunogenic self-antigens, eliciting autoimmunity. In multiple sclerosis and SCI, clusters of T and B cells have been identified in regions of neuronal loss and linked to chronic white/grey matter pathology (reviewed in [153]).

Complement and Fc-receptor-binding macrophages, both activated by antigen–antibody complexes, appear to be critical to autoimmunity and tissue damage. This is corroborated by ameliorated axonal loss, demyelination and functional recovery in mice deficient in complement factor 3 (C3) and Fc-receptor gamma chain. Moreover, recovery after SCI is also observed in mice lacking B cells. Abundant research has demonstrated the activation of several complement factors in the injured brain and spinal cord including therapeutical approaches for its inhibition [148].

In TBI, autoimmunity may be also facilitated by the leakage of neural proteins and their bioproducts through the dysfunctional BBB, reaching lymphoid organs through the blood stream activating T and B cells. Autoantigens including GFAP, S100, and myelin proteins may activate self-reactive T- and B-lymphocytes [222]. Post-TBI autoimmunity may prolong neurodegeneration, hypothetically contributing to CTE, hypopituitarism and dementia [188]. However, it may serve to repair the injured brain by enhancing myelination. Understanding processes of autoimmunity may offer the opportunity for therapeutic intervention to halt progressive brain damage. Additionally, neural autoantibodies may become useful biomarkers and a diagnostic tool in chronic complications of TBI [222].

Studies investigating neuroinflammation in TBI models

Several models of TBI have been established to elucidate the pathophysiology of focal and diffuse TBI (reviewed in [116]). These experimental paradigms improved our understanding of each form of TBI. Most common animal models of focal TBI include CCI, CHI and the mixed focal/diffuse lateral FPI. Diffuse TBI is mainly reproduced with central FPI and impact acceleration/deceleration model of traumatic axonal injury (TAI).

The findings arising from focal TBI models support this sequential order of acute cytokine upregulation, including TNF, IL-1β, IL-6 and IL-10 [211]. Cytokine temporal profiles derive from measurement in cerebral tissue, both as homogenates or via microdialysis, CSF and blood samples [211]. Despite the almost unanimous data on TNF upregulation, we were unable to demonstrate a significant increase in TNF in the perilesional cortex following CHI unlike others using the same model [226].

Cytokine production may look different in diffuse brain injury produced by stretching and shearing forces on axons mostly in white matter regions [13]. Morphologically, the hallmark of diffuse TBI is the presence of axonal swellings and axonal bulbs, which progress over hours to days, ultimately causing axonal transport failure and possibly axonal disconnection. In TAI, while cerebral IL-1β and IL-6 are elevated acutely, TNF failed to increase unless rats were subjected to a 30-min hypoxic insult that concomitantly amplified the synthesis of IL-1β and IL-6, but not of IL-10 and IL-4. Enhanced inflammation was associated with worsened axonal pathology, cerebral metabolic depression, motor, and cognitive dysfunction [70, 216]. The distribution of CD68-positive macrophages and microglia differed as well, being mostly detected in the corpus callosum, rather than the cortex, and being heightened by post-traumatic-hypoxia.

In central FPI, microglial activation showed a global distribution within 2-day post-injury with a delayed expansion in regions of synaptic disruption and loss [83]. Interestingly, from 1 to 4 weeks, microglia displayed intracellular phagocytosed myelin debris. However, no causality was found between microglial aggregation and axonal pathology. Another feature of diffuse TAI is the lack of acute neutrophil infiltration, yet a sustained microglial activation that correlated well with prolonged sensorimotor deficit [32, 140].

The discrepancies around the role of cytokines in experimental TBI are difficult to reconcile and may be attributed to the variability of experimental settings each group uses. Different species (rats, mice) and mouse strains and their mutants may produce distinct cytokine profiles correlating to different behavioural performances [155, 156, 226]. The critical factor in modelling TBI also includes the heterogeneous approaches to measure molecular and behavioural outcome differences, which underlie the failure of translating successful experimental therapies into clinical practice [45]. Operation Brain Trauma Therapy, a multicentre preclinical initiative, aims to rectify this by comparing five pharmacological therapies and biomarkers in three rat models to understand inter-laboratory discrepancies relative to drug testing outcomes [90].

Studies investigating neuroinflammation in TBI patients

In the early 1990s, neuroinflammation became a new research area in human TBI. We refer to other reviews for details [211, 227]. Early reports of cytokine elevation in CSF alluded to a central synthesis, which has been extensively corroborated in animal models, in situ brain microdialysis [191] and post-mortem brain studies [60]. Here, protein levels of TNF, IL-1β, IL-6, IFNγ, GM-CSF, and IL-2 as well as IL-4 and IL-10 were elevated at 6 h post-injury, with IL-6 and IL-8 being at highest concentration. TNF mRNA was already upregulated a few minutes post-TBI whereas IL-6, IL-1β and IL-8 followed from 6 h onwards. Importantly, these molecules were upregulated in brain regions showing axonal pathology, cellular inflammation and gliosis [60].

In our laboratory we detected increased cytokine production in human CSF and serum up to 3-week post-injury, whereby CSF levels coincided with a lesser peripheral immunoactivation [33]. These prolonged cytokine profiles may indicate a predisposition toward chronic inflammation in humans. A recent systematic review discusses cytokine research from 32 severe TBI studies, comprising 1363 patients mostly of CSF analysis, and microdialysis [220]. The microdialysis approach corroborates the CSF findings, despite the limitations of poor cytokine retrieval and the subjectivity of the brain region used for probe implantation.

There have been several attempts to use cytokines as biomarkers of brain injury providing mixed results [211]. IL-1β, IL-6, IL-8, and IL-10 have been shown to predict outcome in both adult and paediatric TBI. While some groups have correlated CSF/microdialysate cytokine concentrations with initial injuries, intracranial pressure, mortality and GOSE scores, others have not found any associations with clinical parameters. Although there is no distinction in cytokine production in patients with focal and diffuse TBI, we found the concentrations of soluble intercellular cell adhesion molecule (ICAM)-1 in CSF to be proportional to the contusion size on CT scans. Soluble ICAM-1 also reflected BBB damage, which was shown to be most prevalent in focal TBI [65, 138].

Combining cytokines with injury biomarkers seems most promising for the prognosis of TBI [107]. In this study, while biomarkers taken individually failed to be positively predicting outcome, the combinations of S100 with either L-selectin or IL-6 provided an AUC of 0.98, with a specificity and sensitivity for unfavourable outcome prediction of 96% and 100%, respectively. For the NSE and L-selectin pair the AUC was 0.95, sensitivity 75% and specificity 96%, thus corroborating the validity of pairing brain-specific and inflammatory biomarkers to improve the specificity toward outcome prognosis. The inclusion of such an approach in the CENTER-TBI program awaits exciting information on how cytokines may increase the sensitivity to distinguish TBI severities and outcomes.

Importantly, progress in the statistical approach to the analysis of complex cytokine data as inflammatory biomarkers in TBI has allowed to incorporate variations in concentration, timing and reciprocal interactions of cytokines sharing similar functions in the immune response. As opposed to widely used multivariate analysis, Helmy et al. [71] proposed principal component analysis and partial least squares discriminant analysis of cytokines in TBI microdialysates where relative recovery represents a potential problem to streamline the data in a more efficient manner to build conceptual roles of cytokine in TBI.

Research in clinical TBI is limited by the heterogeneity of injury patterns and the variability in the concomitant extracranial injuries exacerbating brain damage and inflammatory responses. Clinical studies suffer from small population size, which impairs a reliable statistical evaluation. The variability among TBI populations prevents us to unequivocally identify the pathogenic factors mediating secondary damage and utilise them as reliable biomarkers. Other confounders involve the complex pharmacological management that may alter the pathophysiology of TBI.

Acute insults following TBI exacerbate brain damage

Secondary insults occur in up to 50% in severe TBI patients, alone or in combination and may have intracranial or systemic origins [112]. They are most frequent at time of injury or in the acute post-TBI period, and significantly worsen outcomes [112]. The common secondary insults hypoxia, hypertension, and hyperthermia are particularly relevant to post-TBI inflammation (see Table 1).

Hypoxia

Hypoxia ensues frequently around the time of injury [181] from cerebral hypoperfusion, apnoea and hypoventilation, or pulmonary injury and respiratory obstruction. Up to 38% of severe TBI suffer from hypoxia increasing mortality rates [111]. Clinically, post-traumatic hypoxia enhances and prolongs the elevation of GM-CSF, IFN-γ, and TNF compared to normoxic patients [217]. Experimentally, systemic hypoxia superimposed on diffuse injury results in prolonged cerebral hypoxia in the thalamus, hippocampus and striatum [121], and exacerbated IL-1β and TNF production [216]. The most characterised cytokine is IL-6, which is elevated in models using post-traumatic hypoxia under mild [218], moderate [22], and severe TBI [216]. Indeed, IL-6 may be a key mediator of post-hypoxic neuroinflammation, since its neutralisation suppresses cytokine expression and abrogates motor deficits [218]. Increased IL-6 mRNA has been found in the cerebellum of post-mortem brains of patients dying from TBI-hypoxic injury [151]. While post-traumatic hypoxia induces pro-inflammatory cytokines, it does not coincide with macrophage recruitment to regions of pathology when hypoxia was administered acutely [69].

Hypotension

TBI is often complicated by haemodynamic changes, resulting from acute extracranial injury or neurogenic causes [24, 87]. In severe TBI hypotension occurs in approximately 35% patients [111, 112], with detrimental effects on mortality [111]. In patients with blunt trauma, pre-hospital hypotensive episodes elevated plasma concentrations of IL-1β, IL-6, GM-CSF, IL-7, IL-17 and chemokines CCL1, CCL3, CXCL10 [3]. In a porcine model of TBI with haemorrhagic shock a significant

Table 1 Changes in inflammatory profile associated with post-traumatic insults

Insult	Clinical preclinical	Findings	References
Hypoxia	Clinical	Elevated serum concentrations of IL-6, GM-CSF, IFN-γ, TNF	[217]
Hypoxia	Clinical (post-mortem)	Increased IL-6 mRNA in cerebellum	[151]
Hypoxia	Preclinical (impact acceleration)	Enhanced cortical production of IL-6, IL-1β, TNF; worsened motor deficit	[216]
Hypoxia	Preclinical (weight drop)	Elevated concentration of IL-6, neutralisation ameliorated motor deficit	[218]
Hypoxia	Preclinical (FPI)	Prolonged CSF and plasma release of IL-6	[22]
Hypoxia	Preclinical (impact acceleration)	No increase in macrophage number compared to normoxia	[69]
Hypotension	Clinical	Elevated plasma concentrations of IL-1β, IL-6, GM-CSF, IL-7, IL-17, CCL1, CCL3, CXCL10	[3]
Hypotension	Clinical	Increased serum IL-10, IL-1ra	[166]
Hypotension	Preclinical (haemorrhagic shock)	Increased plasma TNF	[169]
Hypotension	Preclinical (haemorrhagic shock)	Reduced serum IL-6, increased IL-10	[165]
Hyperthermia	Preclinical (CCI)	eightfold increase in neutrophil numbers	[207]
Hyperthermia	Preclinical (FPI)	Prolonged myeloperoxidase activity	[21]
Hyperthermia	Preclinical (FPI)	Accumulation of inflammatory cells in thermoregulatory and circadian nuclei	[192]
Hyperthermia	Preclinical (FPI)	Delayed hyperthermia increased BBB permeability	[46]

This table recapitulates the studies demonstrating the involvement of cellular inflammation and immune mediator production in the pathophysiology of secondary insults including hypoxia, hypotension, and hyperthermia. The literature includes evidence from both clinical and experimental TBI

FPI fluid percussion injury, *CCI* controlled cortical impact

elevation in plasma TNF was observed [169]. Interestingly, hypotension has been associated with increased anti-inflammatory cytokines IL-10 and IL-1ra in plasma [3], while patients with TBI and severe systemic trauma showed increased IL-10 and IL-1ra in CSF [166]. This is supported by a model of haemorrhagic shock superimposed onto mild-to-moderate CCI, lacking increased cytokines and chemokines [165], but higher serum IL-10, with a reduction in IL-6. Considering the robust pro-inflammatory response elicited by CCI alone, data indicates that changes in systemic blood flow alter the cerebral immunopathological response in a specific and nuanced fashion.

Hyperthermia

Post-traumatic hyperthermia correlates with severity of TBI [51]. It may be induced by cerebral inflammation, thrombophlebitis, or hypothalamic damage [47]. In a CCI model, hyperthermia increased neutrophil numbers by eightfold [207], reinforced by a prolonged elevation in myeloperoxidase activity in FPI [21]. Spontaneous post-traumatic hyperthermia increased astrocytes and macrophages/microglia within thermoregulatory and circadian nuclei, whereby the degree of hyperthermia correlated with the number of inflammatory cells [192]. In a FPI model delayed hyperthermia also increased BBB permeability [46]. While these findings indicate that hyperthermia influences cerebral neuroinflammation after TBI, more research is warranted to understand its contribution to pathologic outcomes.

Is inflammation after TBI detrimental?

The damaging impact of inflammation on acute TBI is supported by a proportional production of cerebral cytokines, in particular IL-1β and TNF, relative to TBI severity [89]. Both mediators elicit neurotoxic cascades in a synergistic fashion, induce other pro-inflammatory mediators and compromise the BBB [20]. Pharmacological and transgenic animal work unequivocally corroborate TNF harmful roles, but also support its invaluable contribution to long-term recovery [167].

The most informative evidence on the unfavourable role of cytokines implicates IL-β. Systemic delivery of IL-1β in FPI rats amplified the lesion size and worsened behavioural outcome [196]. Conversely, therapeutic neutralisation of IL-1β in focal TBI decreased tissue loss, brain oedema, and cognitive impairment [27], while transgenic overexpression of IL-1ra in astrocytes delayed inflammation and improved recovery after CHI [190]. The natural antagonist of IL-1β, IL-1ra, improved brain damage up to 40% even with delayed intracerebroventricular delivery [195]. Interestingly, when IL-1β antagonists, IL-1ra and soluble IL-1R, were administered centrally, no difference in motor tasks was reported [88]. IL-1ra injected subcutaneously (s.c.) over a week conferred neuroprotection in a model of combined CCI with tibial fracture by reducing cellular inflammation, oedema and neutrophil accumulation [186]. In paediatric

CCI, IL-1ra delivered s.c. improved spatial memory and reduced hippocampal astrogliosis and evoked seizures up to 6-month post-injury [159]. Although not uniform, these studies inspired a phase II clinical trial using human recombinant (hr) IL-1ra (Anakinra) in severe TBI patients [72]. Given s.c. daily for 5 days, hrIL-1ra penetrated the brain and diminished some chemoattractants. A follow-up study, revealed that hrIL1-ra induced an M1 cytokine bias, increasing CCL2, GM-CSF and IL-1β, thus questioning the anti-inflammatory role of IL-1ra [73]. IL-1β is also harmful in diffuse TBI [53]. In TAI mice, IL-1β-antibodies given intraperitoneally 30 min after central FPI reached the brain at therapeutic concentrations by 24 h, improved behavioural and memory function, but did not alter macrophages/microglia activation.

In regard to TNF, treatment with dexabinol, TNF-binding protein and pentoxifillin after CHI improved sensorimotor function [167]. However, gene deletion of TNF or TNF-Rs aggravated brain damage in the post-acute phase compared to a transient benefit seen acutely [150, 183]. The double TNF-lymphotoxin-α KO showed a higher mortality rate immediately after CHI, but no differences in oedema and immunological characteristics [179]. Unsurprisingly, application of one dose dexabinol in severe TBI patients failed to deliver neuroprotection [109].

Post-traumatic neuroinflammation promotes brain recovery

Despite its contribution to secondary brain damage, neuroinflammation plays a beneficial role in recovery by driving processes of regeneration, such as neurogenesis. Neurogenesis is the production of new neurons from neuronal stem/progenitor cells (NPCs), which in the adult mammal brain, including humans, primarily occurs in the hippocampal subgranular zone and the subventricular zone (SVZ) of the lateral ventricles, giving rise to dentate gyrus granule neurons and olfactory bulb interneurons, respectively [185]. Following experimental TBI, the neurogenic process in both regions is stimulated (for recent reviews, see [19, 184]). In the hippocampus, TBI robustly increases NPC proliferation, whereas injury-induced neuronal differentiation and survival of new neurons is far less pronounced [184]. However, importantly, granule neurons produced after TBI are directly associated with spontaneous cognitive recovery [185]. In the SVZ, TBI generally increases proliferation, with a small proportion of new cells undergoing redirected migration towards the site of trauma where they persist for weeks, with the majority acquiring an astrocytic phenotype and few, if any, surviving as new mature neurons [19]. In human TBI, direct evidence for the production of new mature neurons is still lacking; however, the persistence of spontaneous neurogenesis throughout the human lifespan and proof of injury-induced neurogenesis in other neuropathologies, suggests this is worthy of further investigation.

The neurogenic response occurring after TBI is regulated, at least in part, by immune cell activation. Early work found a primarily deleterious role for microglia, in that inhibition of microglial activation with minocycline and indomethacin enhanced hippocampal neurogenesis in models of cranial irradiation, epilepsy and ischemic stroke [16]. However, recent evidence suggests that robustly activated inflammatory microglia are inhibitory, and more mildly activated microglia supportive, and these diverse characteristics may be linked to the soluble factors that are selectively released [52]. For example, in a study of CCI, chronic M1-like microglial activation is reduced in mice undergoing delayed voluntary exercise, leading to elevated levels of hippocampal IL-10, insulin-like growth factor (IGF)-1, CREB and brain-derived neurotrophic factor (BDNF). This change in microglial phenotype was associated with enhanced neurogenesis in the dentate gyrus and improved cognitive function recovery at chronic time points [137].

Astrocytes play a dominant role in maintaining basal neurogenesis [55], through their release of cytokines, chemokines and growth factors. Therefore, astrocytes are likely pivotal in regulating neurogenesis after TBI [55], however, their ability to influence specific stages of injury-induced neurogenesis remains largely unexplored. Interestingly, astrocytes can provide scaffolding to aid migration of neuroblasts from the SVZ towards the site of brain injury [19]. However, hypertrophied astrocytes chronically persisting in the hippocampus may structurally direct the aberrant sprouting of new dentate granule neuron basal dendrites into the hilus [146], potentially contributing to post-traumatic epilepsy.

Further support for a contribution of reactive microglia and astrocytes to neurogenesis is demonstrated by experimental work exploring the role of inflammatory factors. Using primarily cell culture experiments, but also developmental and adult rodent in vivo studies, the specific functions of numerous cytokines, chemokines and growth factors on NPC proliferation, neuroblast migration, survival and maturation of new cells have begun to be elucidated [16, 202]. A recent review [202] has highlighted that generally, cytokines tend to decrease neurogenesis, though with exceptions. TNF, for example, inhibits NPC proliferation and survival. However, while TNF-R1 signalling suppresses NPC proliferation, TNF-R2 increases both NPC proliferation and survival of new neurons. IL-1β decreased NPC proliferation in the hippocampus only, where NPCs express IL-1R1, unlike those of the SVZ. IL-6 also inhibits neurogenesis, while promoting astrocyte differentiation.

Conversely, chemokines largely support neurogenesis. In fact, chemokines are crucial for directing neurogenesis during brain development, and their upregulation following injury may recapitulate these effects, driving NPC proliferation, neuronal differentiation, neuroblast migration and survival of new neurons [16, 202]. Particularly, CXCL12 expressed by activated glia and endothelial cells leads the migration of CXCR4-expressing NPCs from the SVZ to the site of tissue damage, and enhances NPC proliferation, neuroblast motility and survival. Another important chemotactic factor for NPCs is CCL2, with CCL2-dependent migration to the inflammatory site demonstrated following ischemic brain injury in vivo using CCL2- or CCR2 deficient mice.

Chronic neuroinflammation: the culprit of long-term conditions?

Mounting evidence in human and animal studies supports the concept of prolonged neuroinflammation linked to progressive neurodegeneration and onset of a number of medical and psychiatric conditions resulting in chronic symptomatology of TBI (see Table 2, Fig. 4). 1 year after FPI, rats showed marked tissue loss with shrinkage of the hippocampus and ipsilateral cortex coinciding with astrogliosis and neuronal death [175]. In CCI, chronic microglial activation correlated with myelin loss, vascular alterations and microbleeds with vessels surrounded by reactive astrocytes [61]. IgG extravasation in white matter regions suggests that chronic inflammation prolongs BBB leakage.

In both children and adults, T1-weighted MRI and diffusion MRI revealed a progressive brain atrophy up to a year post-TBI [168]. In severe TBI patients, T1-weighted MRI showed a reduction in brain parenchyma by 8.4% at 8 months followed by further atrophy up to 9% at 12 months. Tissue loss correlated with injury severity and outcome [168] affecting specifically white matter regions, indicating axonal vulnerability in chronic TBI.

In TBI patients ongoing elevation of serum TNF, IL-1β, IL-6, IL-8, and IL-10 at 3 months increased the odds of unfavourable outcome at 6–12 months [94]. Chronic neuroinflammation is also supported by evidence of persisting microglial activation lasting up to four decades post-TBI [79]. Active glia located within the shrunken corpus callosum were associated with amyloid precursor protein (APP)-labelled axons for almost two decades. These abnormalities strongly suggest a link between TBI and the onset of dementia as validated in repetitive mild TBI [54]. The opportunity of utilising PET in live patients with the [11C] (R)PK11195 ligand, binding to the TSPO receptor on activated microglia and macrophages, demonstrated a global, chronic immune activation lasting up to 17 years from injury [139].

Epilepsy

Epilepsy occurs with variable incidence after TBI, depending on injury severity, with a higher risk in younger patients [205]. Defined as repetitive post-traumatic seizures greater than 1-week post-injury, post-traumatic epilepsy is a chronic condition that develops over time in a substantial subset of TBI patients. Epilepsy has implications for quality of life including the ability to drive and work independently and is strongly associated with an increased risk of cognitive impairments, anxiety, and depressive disorders [161]. While existing treatments efficaciously reduce acute seizures, they fail to prevent the development of chronic post-traumatic epilepsy or ameliorate the associated comorbidities.

Cytokines released in the brain increase regional hyperexcitability, reducing the threshold of seizures. In turn, epilepsy promotes brain degeneration through cytokine-amplified excitotoxic mechanisms [149]. TNF, IL-6, CAMs and primarily IL-1β, are epileptogenic mediators being both a cause and a consequence of epilepsy [34]. Conversely, seizures induce cytokines and activate microglia [199]. BBB disruption is an additional factor contributing to post-TBI epilepsy, possibly through the extravasation of serum proteins sustaining neuroinflammation and BBB permeability.

The incidence of epilepsy over 42–71 days post-CCI in the adult rodent brain has been reported as 20% in mild and 36% in severe trauma [35, 74], although this incidence may be higher after injury to the developing brain [159]. Mice showed mossy fibre sprouting within the dentate gyrus linked to epileptiform activity in this region. In TBI patients, not only is the IL-1β CSF-serum ratio elevated in those susceptible to epilepsy but also their genetic phenotype may predispose to this condition [44]. Various immunosuppressive drugs have been proposed to prevent the onset of epilepsy [205]. However, Vezzani et al. [199] emphasised the risks of treating epilepsy with anti-inflammatory drugs that may simultaneously hamper the beneficial action of endogenous mediators (e.g., IL-1ra).

Metabolic and neuroendocrine function

Neuroendocrine dysfunction refers to hormone imbalances to the pituitary, hypothalamus, and their axes following TBI [206]. In mild TBI anterior pituitary hormone dysfunction (adrenocorticotropic hormone ACTH, gonadotropin, prolactin, and growth hormone, GH) occurs in 30–80% at 24–36 months, and posterior pituitary dysfunction (oxytocin, vasopressin or antidiuretic hormones) in 4–7% patients at 12 months. These conditions are underdiagnosed but have huge implications for the wellbeing of TBI survivors, which could be easily addressed with replacement therapies [206].

The association between TBI-induced systemic cytokines and hyperadrenergic state as determined via

Table 2 Chronic neuroinflammation may impact on the development of secondary medical conditions after TBI

Condition	Incidence	Cytokines	Cell activation	Pathology	Therapy	References
Epilepsy	4.4–53% in adults 10–20% in children with severe TBI Higher risk in children <5 years and in severe TBI	IL-6, TNF, IL-6, CAMs Elevated IL-1β CSF-serum ratio	Microglia activation, astrogliosis	BBB dysfunction Mossy fibres sprouting in dentate gyrus with epileptiform activity in CCI mice Seizures sustain neuroinflammation Genetic predisposition (IL-1β gene polymorphism)	IL-1 converting enzyme (ICE)-caspase 1 inhibitor IL-1ra, with fluoxetine (serotonin reuptake inhibitor) Indomethacin, (COX-2 inhibitor) Anti-inflammatory treatment controversial	[34, 35, 74, 149, 159, 199, 205]
Metabolic/neuroendocrine dysfunction	Anterior pituitary hormone dysfunction: 30–80% at 24–36 months 4–7% at 12 months	Systemic IL-1β, IL-10, IL-8, CCL2 correlate with epinephrine IL-1β, IL-10, TNF, IL-8, and CCL2, correlate with norepinephrine changes	Unclear	Hypothesis: peripheral cytokines activate the nerve terminals interacting with macrophages, through β-adrenergic receptors	Beta-blockers reduce inflammation and improve outcome in TBI models	[43, 152, 206]
Diabetes	26% patients early/transient 6% patients with persisting diabetes over 6–36 months	CD36 interaction with TLR-4 and -6 expressed on microglia and macrophages		Acceleration/deceleration injury to hypothalamic-pituitary axis post-TBI hypoxia-induced damage	Insulin delivery	[2, 18, 180]
Depression	30% to 50% (moderate, severe TBI) in the first year	IL-1β, IL-6, TNF, IFNγ	Microglial activation in diffuse TBI mice	IL-6 CSF levels correlate with depression severity Cytokine delivery induces depression Acute CSF cytokines as predictors of depression at 6–12 months > TBI Tryptophan metabolism via kynurenine pathway stimulates quinolinic acid excitotoxicity -depression	Minocycline (anti-inflammatory drug) Etanercept (TNF inhibitor) IFNγ -R-deficient mice show reduce depressive behaviours	[37, 57, 81, 176]
CTE	Not known Present in repetitive mild TBI and athletes	IL-1β	Diffuse microgliosis	Hippocampal atrophy Deposition of p-TAU (tauopathy)	Hypothetical therapeutic blockage of TSPO on activated macrophages/microglia	[31, 133]
Alzheimer's disease	Not known	IL-1β, IL-6, TNF, IFNγ, TGFβ	Microglial and astrocyte activation	Accumulation of amyloid plaques, neurofibrillary tangles and tau	Non-steroidal anti-inflammatory drugs, i.e., ibuprofen (COX inhibition)	[8, 78, 80, 101]

Table 2 (continued)

Condition	Incidence	Cytokines	Cell activation	Pathology	Therapy	References
PTSD	Most common in the military	Increased blood IL-1β, IL-6, TNF, TNF-RII, CCL2. Reduced anti-inflammatory cytokines IL-4, TGFβ. Cytokines correlate with PTSD severity PTSD models show brain cytokine elevation	Increased pro-inflammatory Th1 and Th17 cells and reduced anti-inflammatory cells Treg	Unclear	IL-1β reduction with inhibition of serotonin transporters SSRIs	[42, 130, 135]

This table summarises the potential role played by protracted neuroinflammation in the onset of the psychiatric, metabolic and endocrine conditions frequently observed weeks to months and years following a TBI. The studies cited here report the presence of elevated cytokines in blood and CSF as well as some pathological features demonstrated in the brain of those sufferers, including the activation of glial cells and the infiltration of immune cells. For each condition, researchers have proposed therapies that may target such pathogenic factors as supported by experimental studies with specific proteins that seem to be uniquely relevant to the development of the disease

catecholamine levels was published recently [43]. In patients with isolated moderate/severe TBI acute plasma levels of IL-1β, IL-10 IL-8, and CCL2 correlated with epinephrine changes. Norepinephrine was also associated with IL-1β, IL-10, TNF, IL-8, and CCL2, suggesting that TBI overstimulates the sympathetic nervous system causing a hyperadrenergic state typical of a stress response. The link between hyperadrenergic state and neuroinflammation remains speculative with the hypothesis that peripheral cytokines activate the nerve terminals interacting with tissue macrophages, possibly through their expression of β-adrenergic receptors. Interestingly, beta-blockers administered in TBI models reduced inflammation and improved outcome [152].

Diabetes mellitus affects up to 26% of patients early after TBI and around 6% with persisting condition [2]. Diabetes not only causes hyperglycaemia, but also hyperlipidaemia. It is speculated that the CD36 receptor (involved in fatty acids uptake), may enhance neuroinflammation, promoting the oxidisation of excessive lipoproteins. CD36 also interacts with TLR-4 and -6, consequently stimulating intracellular responses in macrophages and microglia [18, 180]. Interestingly, amyloid beta (Aβ) and low-density lipoproteins also bind to CD36.

Depression

Depression is one of the most common and durable psychiatric conditions after TBI, whereby inflammation may play a causal role. Cytokines given to healthy volunteers induce depression and have physiological effects on the hypothalamic pituitary-adrenal axis [176]. Some reported acute cytokine production in CSF to predict depression at 6–12 months after TBI [81]. In diffuse TBI mice microglial activation exacerbated with systemic endotoxin challenge amplified depressive symptoms [57]. Moreover, cytokine inhibition with minocycline, etanercept (TNF inhibitor) or the employment of IFNγ-R-KO mice, attenuated depressive behaviours by reducing indoleamine 2,3-dioxygenase (IDO-1) activation [37].

Rather than alterations in serotoninergic neurotransmission, a causative role on depression may rely on the ability of inflammation to alter tryptophan metabolism via the kynurenine pathway by producing excessive amounts of neurotoxins, excitotoxic 3-hydroxy kynurenine and quinolinic acid (QUIN) [37]. In severe TBI patients, QUIN was increasingly elevated in CSF and correlated with unfavourable outcome [215]. The kynurenine pathway depends on TNF and IFNγ, which activate the enzyme IDO-1 required for QUIN production. In post-mortem TBI the upregulation of IFNγ coincided with activated IDO-1 in areas of tissue damage and macrophage activation.

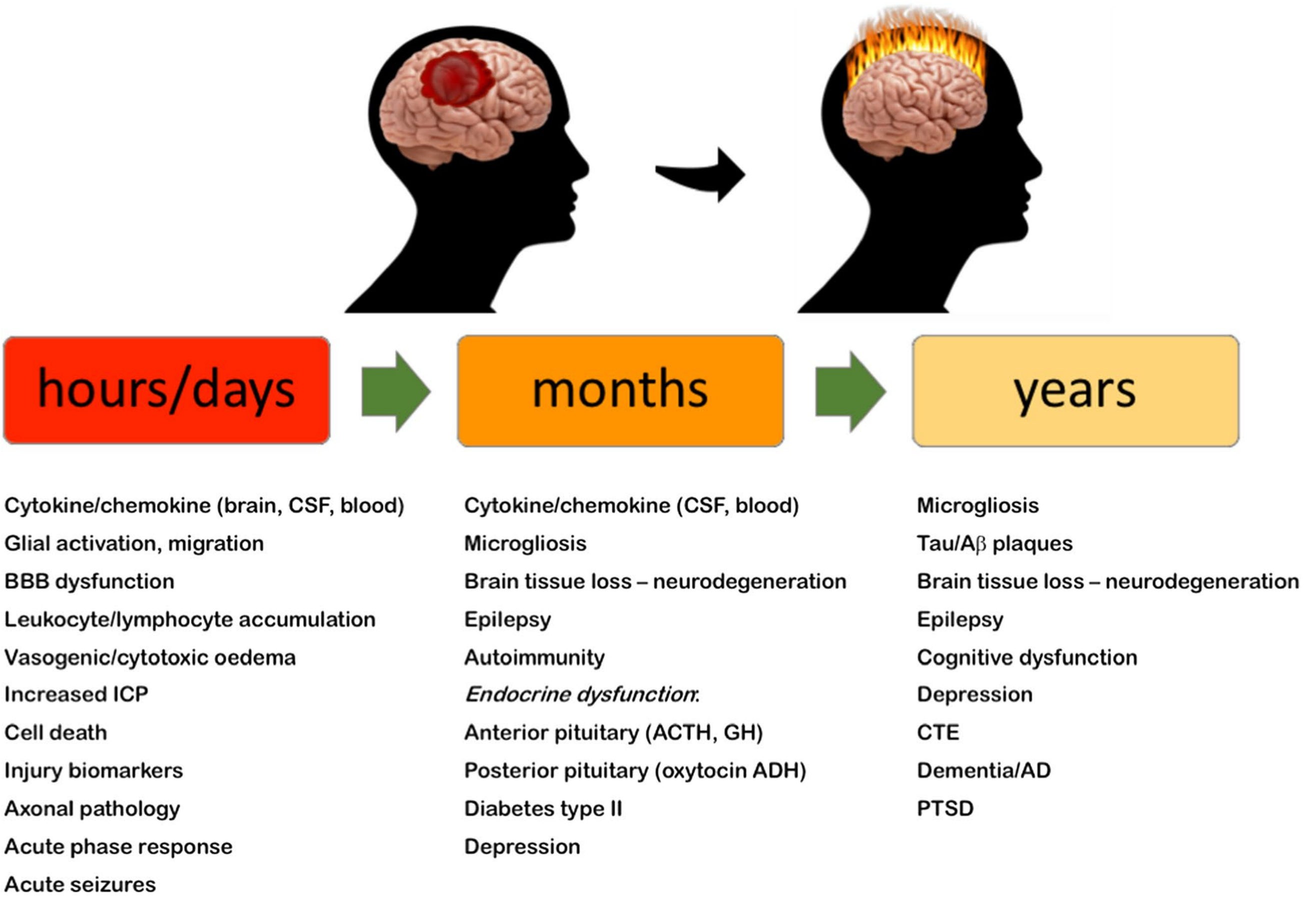

Fig. 4 Sustained cerebral inflammation contributes to chronic TBI conditions. This diagram summarises the multitude of medical conditions that arise acutely and progress in the months and years following brain trauma, including the mild form of injury. Much attention is currently given to these long-term conditions that severely affect the quality of life of patients, potentially leading to morbidity, depression, dementia, and suicide

Chronic traumatic encephalopathy

The term chronic traumatic encephalopathy (CTE) was coined in 2005 based on post-mortem brain neurodegenerative changes of a football player who presented with various neurological changes [133]. A hallmark of CTE is widespread microgliosis. Using a new TSPO marker, 11C-DPA-713, Coughlin et al. [31] reported prolonged brain inflammation in 11 former NFL players with neuropsychiatric changes. Increased TSPO may play a role in chronic inflammation, cytokine production to award the proposition of TSPO as an anti-inflammatory therapeutic target [31]. The authors also described increased deposition in phosphorylated Tau (tauopathy). Tauopathy, is thought to stimulate further inflammation and sustain chronic neurotoxic processes. The degree of tau deposits correlated with severe cognitive impairment, behavioural changes and dementia [113].

Alzheimer's disease

TBI is a recognised risk-factor for the development of dementia including Alzheimer's Disease (AD), however, epidemiological studies have not yet reached a consensus [78, 101]. β-Amyloid and Tau are hypothesised to cause neurodegeneration in AD and are also present in TBI brain. This link is difficult to reproduce in rodents; although there is APP deposition/accumulation, the plaques are absent [78]. The role of chronic inflammation post-TBI in the development of AD remains unclear, but sufficient evidence shows that TBI, and predominantly repetitive TBI are associated with dementia. A study on 2500 retired footballers found a fivefold increase in mild cognitive impairment and a threefold increase in memory deficit with an earlier onset of AD [63]. Accumulation of amyloid deposits was present in 30% of patients, most distinctively in younger individuals dying acutely [143]. In chronic TBI these plaques consist of immune-stimulating proteins, primarily Aβ42, neurofibrillary tangles and Tau, typical features of AD [80].

Interestingly, while adaptive microglia are beneficial by phagocytosing amyloid plaques, innate activated microglia seem to facilitate the formation of Aβ plaques [8]. Aβ also promotes cytokine synthesis. Johnson et al. suggest that the rapid Aβ plaque formation seen in TBI ensues from the accumulation of APP, a characteristic of axonal pathology, and the unbalanced equilibrium between Aβ formation and catabolism.

Post-traumatic stress disorder

Much research efforts focus on understanding post-traumatic stress disorder (PTSD), a frequent illness in the military. In a military cohort, elevated plasma TNF and IL-6 were only found in TBI individuals and were greater in the high-PTSD group [42]. Interestingly, blood concentrations of TNF-RII were significantly higher in PTSD military, also associated with reduced hippocampal volume, corroborating the hypothetical influence of inflammation on a number of post-TBI conditions [130]. A meta-analysis identified IL-1β, IL-6 and IFNγ associated with disease severity and duration [135]. Knowing that PTSD doubles the chances of mortality in the military and that a quarter of those deployed will sustain TBI or PTSD, it becomes a critical issue to address therapeutically in chronic TBI [42].

Genetic variance determines the extent of inflammatory response and outcome

The prognosis of brain injury relies on genetic and external factors. The individual immune response elicited by head trauma varies significantly. A potential negative influence on the pathophysiology of neurotrauma was ascribed to TNF, IL-1β, APO-E4, NOS3, and BDNF [7, 38]. Clinical studies report large ranges of cytokine concentrations in CSF and blood that reflect both, the unique patterns and severity of brain damage, but also the intrinsic genetic variability.

Analysis of single nucleotide polymorphisms (SNPs) in a cohort of > 1000 TBI patients has linked the presence of two cytokine alleles with poor outcome at 6 months. Among the cytokines evaluated, the study found that carriers of two alleles for TNF-308 SNP, located in the TNF promoter gene, were more likely to have an unfavourable outcome compared to non-carriers [203]. Expectedly, two TNF-308 alleles enhance TNF transcription and production [209]. Also, the TNF-308 allele is located to the HLA-A1-B8-DR3-DQ2 haplotype, which increases the risk for autoimmunity. Higher levels of TNF have been detected in the CSF of AD patients as well as post-mortem brain tissue in early AD onset [223]. Thus, amplified cytokine responses may play a pivotal role in post-TBI dementias.

Rather than influencing outcome, IL-1β may impact on the clinical evolution post-TBI. Allele 2 (IL-1RN*2) of the IL-1RN gene coding for the antagonising receptor of IL-1β, IL-1ra is of particular importance since IL-RN*2 carriers with TBI have higher concentrations of IL-1β and IL-1Ra in plasma (but reduced IL-1ra in local tissues), which defines a pro-inflammatory phenotype. Homozygotes for IL-1RN*2 have a lower production of icIL-1Ra1, which may reduce the benefit of opposing the detrimental action IL-1β [66]. IL-1RN allele 2 also carriers a higher risk for cerebral haemorrhages mediated by IL-1ra on vascular wall integrity, a fact supported by IL-1ra-KO mice having premature death and exaggerated perivascular inflammation [128]. IL-1β gene polymorphism may also have an impact on epilepsy [205]. Patients with heterozygous CT alleles of the rs1143634 genotype have an earlier onset of seizures [44]. Consistently, acute levels of serum IL-1β correlated with higher mortality after TBI.

IL-6 gene polymorphism of the promoter region including the 174C/G and IL-6-572G/C variants may influence outcome in severe TBI, whereby the G allele and the GG genotype specifically were associated with higher survival rate [36]. G alleles seem to generate a higher synthesis of circulating IL-6. This relationship fits well with a report correlating higher IL-6 with favourable outcome and IL-6 neurotrophic properties [172]. Consistently, others reported that the -174 C allele correlated with lower IL-6 in blood samples [114].

Age and sex influence the neuroinflammatory response after TBI

A number of variables can influence an individual's inflammatory response after TBI, including biological sex and age at the time of injury. Sex and age disparities in the incidence and clinical outcomes of TBI have been widely reported in patient populations, albeit with often conflicting and controversial findings [17, 178].

During embryonic and early post-natal development, microglia are being increasingly recognised for their sexually dimorphic distribution and function in the immature brain [17]. At adulthood, microglia vary in quantity and phenotype between male and female rodents, in many brain regions [97], and in vitro studies have demonstrated that male and female microglia exhibit differential responses to cytokine stimulation [129]. While these data support the plausible hypothesis that microglia would respond to injury in a sex-specific manner, few studies have empirically addressed this. Some reports have failed to detect any sex-dependent effects [12, 62], or indeed, observed an increased cytokine response to experimental TBI in females [5]. However, in general, females show a degree of neuroprotection compared to males in pathological and functional outcomes after experimental brain injuries, including the extent of neuroinflammation [9, 28, 198], and the extent of myeloid cell infiltration and microglial activation [49]. For example, Villapol and colleagues reported a strikingly divergent inflammatory response depending on sex, whereby pro-inflammatory cytokine release and glial cell activation were faster and more pronounced in males after moderate-to-severe CCI [200]. Recently, sex differences in the cerebral vascular response to experimental TBI, associated with differences in microglia activation and blood–brain barrier changes, have also been reported [82].

Such sex-based differences are largely attributed to the sex steroids oestrogen and progesterone, which have a broad spectrum of effects on hormone receptors and downstream signalling, oxidative stress, glial reactivity, cerebral blood flow and metabolism, and excitotoxicity [178]. Regarding the inflammatory response, oestrogen and progesterone attenuate microglial activation as well as pro-inflammatory cytokine release [11]. Unfortunately, application of these findings in the form of hormonal-based therapies have had limited success in TBI clinical trials.

There are also reports of age-specific differences in the inflammatory response after TBI. It is now well-established that resident microglia are phenotypically distinct in the immature brain compared to the adult, displaying a unique combination of pro- and anti-inflammatory activation markers simultaneously during normal development [97]. Conversely, changes in homeostatic microglial function are observed during normal aging, whereby the immune system shifts to a chronic, mild inflammatory state associated with altered morphology, reduced motility, and increased levels of pro-inflammatory cytokines [129].

As expected, experimental TBI in older animals predisposes to an exacerbated inflammatory response, involving increased accumulation of peripheral macrophages [117], chronically activated microglial/macrophage phenotypes [93], and elevated pro-inflammatory cytokine release [193]. In contrast, a blunted, delayed infiltration of CD3 + T cells was observed in old (21 months) mice compared to young adult (2-months-old) mice [193].

The inflammatory response after TBI in the immature brain appears to be more complex, and dependent on developmental age. In the neonatal brain, traumatic injuries induce a marked suppression of cytokine signalling [187]. Neonatal neutrophils do not extravasate from blood vessels as readily as adult cells do, such that their accumulation is reduced in the neonatal brain after hypoxic-ischemic injury compared to the adult [98]. Further, non-classical pathways of complement activation are not yet fully mature by term, which may have widespread age-dependent effects on the inflammatory response [98]. In contrast, in rodents of 2–3 weeks of age, approximating 2–4 years of age in humans [154], the brain becomes predisposed to enhanced inflammation. Exposure to IL-1β results in a more robust response at this age compared to in adult rodents, including the degree of BBB breakdown and neutrophil infiltration [4]. This increased susceptibility to a neuroinflammation has been demonstrated in experimental TBI, whereby 3-week old mice exhibited more robust neutrophil recruitment into the injured cortex compared to adults [26]. This acute response was associated with progressive neuropathology over subsequent weeks post-injury, and appears to be mediated in part by the neutrophil protease elastase [160]. Increasing evidence also indicates age-dependent differences in the inflammatory response to TBI in patients. For example, children younger than 4 years of age at the time of a severe TBI had significantly higher CSF levels of soluble IL-2Rα and ferritin compared to children older than four [125].

In summary, while evidence is mounting that biological sex and age can greatly impact on neuroimmunological activity, additional studies are needed to fully understand how these variables influence secondary inflammatory mechanisms after injury, and in turn, how these mechanisms shape functional outcomes. Therapeutic interventions targeting the inflammatory response after TBI should consider both sex and age differences as significant contributing factors.

Therapeutic modulation of cerebral inflammation after TBI

While immunomodulation is a logical therapeutic strategy, the multifaceted and often beneficial role of inflammation after TBI suggests that treatment must be carefully designed. The CRASH trial has demonstrated that nonspecific, high-dose immune suppression is detrimental [144], and thus consideration must be given not only to the therapeutic target, but also to the timing, duration and dosage of treatment. Here, we present an overview of selected anti-inflammatory therapeutic agents and strategies showing promise in both preclinical and clinical scenarios.

Progesterone

In the early 1990s researchers observed sex-specific differences in post-TBI outcomes, with beneficial effects in females attributed to the hormones progesterone and oestrogen. Subsequent experiments revealed improved outcomes in male rodents with peri-injury administration of progesterone [147], highlighting its utility as a neuroprotective agent. Progesterone downregulates the production of IL-1β and TNF in TBI models [68], with a potential mechanism via reduction of complement factor C3 [197]. Progesterone also inhibits microglial activation and microglial TNF production [50]. Despite this promising preclinical evidence, neither of the phase III clinical trials of progesterone (ProTECT, SyNAPSe) met their clinical benchmarks of improved GOSE at 6 months [173, 212]. Further studies are warranted, with additional consideration for patient characteristics, injury subtypes and complicating secondary insults.

Statins

Statins are a group of lipid-lowering drugs with extensive immunomodulatory and anti-inflammatory properties. Treatment with atorvastatin at 1 mg/kg/day acutely following CCI reduced neuronal cell death, invasion of T cells, neutrophils and natural kill (NK) cells as well as the production of cytokines and chemokines [213]. This was coupled with attenuated microglial/macrophage activation. Similarly, simvastatin administered 24-h post-CCI decreased microglial and astrocyte activation, including a reduction in IL-1β levels but no changes in IL-6 or TNF [99]. However, timing and concentration of statins play a significant role in the outcomes post-TBI. When atorvastatin was administered at 5 or 10 mg/kg/day similar efficacy was reported as 1 mg/kg/day [213]. In models of intracerebral haemorrhage higher does or delayed treatment has found to be ineffective or even deleterious [163]. Statin therapy in TBI is extensively reviewed in [208].

Erythropoietin

The multifunctional agent EPO has substantial effects on the inflammatory response after TBI, by decreasing acute production of IL-1β, TNF, ICAM-1 and CCL-2 [104, 225] and reducing recruitment of neutrophils and microglia [225]. We demonstrated EPO neuroprotection in experimental diffuse TBI via abrogation of acute IL-1β production with concomitant reduction of macrophage/microglial recruitment, however, this was only observed when a hypoxic insult was superimposed, suggesting that EPO may be most beneficial in a combined TBI-hypoxic injury [70]. Phase III clinical trials of EPO in TBI have thus far been largely unsuccessful: the trial of Robertson and colleagues revealed no differences in 6-month GOSE in severe TBI patients [145], while the EPO-TBI trial of moderate-to-severe TBI had a similar finding, with no reduction in patients with unfavourable GOSE [127]. However, two recent post hoc analyses of the EPO-TBI data found that EPO reduced mortality in patients with extracranial injuries [174], and to reduce mortality when administered on a frequent schedule [102]. Both these trials faced certain limitations, which may have influenced outcome, particularly with respect to timing and doses of EPO [104]. This is underscored by a smaller study in severe TBI patients, in which EPO had a beneficial effect on 3-month GOS and reduced serum biomarkers when administered on a more rigorous dosing schedule [102].

Minocycline

Minocycline is an antibiotic originally developed for the treatment of bacterial meningitis displaying anti-inflammatory properties, making it an ideal candidate for treatment of TBI. Following CCI in adult rats minocycline improved functional outcome and increased myelination of white matter tracts [64]. In paediatric CCI rats minocycline altered microglial activation delivered selective thalamic neuroprotection [170]; this was, however, associated with delayed functional recovery. In mice subjected to CHI, minocycline decreased lesion volume, improved neurological outcome in the first day following injury, but this was not maintained to day 4 [15]. When the study was extended to 6 weeks, and the subsequent doses halved, minocycline successfully reduced microglial activation and promoted early neurogenesis that was sustained [126]. More recent studies have reported sex variances of minocycline treatment post-CCI [189]. Differences in IL-6 seem to be sex-dependent rather than minocycline-dependent. While IL-1β expression was reduced with minocycline, TNF remained unaffected. These results suggest greater attention to sex differences needs to be considered when assessing therapeutics.

Hypothermia

Therapeutic hypothermia employs the principle that by lowering body temperature metabolic demands are reduced. Controversy exists within the literature regarding the use of hypothermia following TBI [164]. Metabolic-targeted therapeutic hypothermia significantly reduced mortality in severe TBI patients [56]. Hypothermia in a FPI model decreased inflammasome signalling [194], while in CCI rats, hypothermia induced 2- or 4-h post-injury was associated with improved neurological outcomes, reduced oedema and inflammation [224]. However, the best effects were achieved with hypothermia induced 15-min post-injury, suggesting an "ideal" time window for therapeutic hypothermia, which may not be feasible in the clinic.

Heparinoids

Heparin is an anticoagulant used to prevent venous thromboembolism as part of TBI management. However, in addition to these effects, heparinoids, including unfractionated heparin (UFH) and low molecular weight heparin (LMWH), have anti-inflammatory actions in peripheral diseases, which include inhibition of leukocyte rolling and neutrophil accumulation [219]. Similarly, in TBI, treatment with UFH or

LMWH in preclinical models decreased cyclooxygenase-2 activity, reduced leukocyte sequestration in the injured tissue and decreased cerebral oedema [100, 122]. Furthermore, in severe TBI patients, early administration of heparin within 3-day post-TBI was associated with slower progression of brain damage seen on CT scans [86]. Despite these promising findings, in the clinical setting treatment with heparinoids is often delayed or withheld due to an increased risk of cerebrovascular haemorrhage. Treatment with a low-anticoagulant desulfated heparin was recently explored to determine whether the modified heparins could maintain anti-inflammatory properties [123]. Nagata and colleagues found that following experimental TBI, 2,3-O desulfated heparin reduced cerebral leukocyte recruitment, microvascular permeability and oedema, potentially contributing to neurological recovery, suggesting that low-anticoagulant heparins may be a promising new therapy for TBI patients.

Conclusion

In this article we have provided a comprehensive up-to-date review of the complexity of the inflammatory responses ensuing in the acute and chronic stages following TBI. Often considered as a whole phenomenon, this review highlights the distinct and intricate pathways characterising humoral and cellular immunoactivation in experimental and clinical settings. Research progress in this area is developing rapidly, often breaking the dogmas that were defined decades earlier. Understanding further such processes will help designing suitable therapies to neutralise the pathological consequences of neuroinflammation and simultaneously harness those properties that promote repair and regeneration with the much-needed ultimate goal of improving patients' outcomes.

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