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The immunological landscape of traumatic brain injury: insights from pathophysiology to experimental models

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Traumatic brain injury (TBI) is a complex, heterogeneous neuropathological disease that continues to be among the prominent causes of mortality and disability around the world. Translational success in TBI has been significant, yet therapies are limited as the intersection of the initial mechanical traumas and secondary neuroinflammatory cascades, which predispose to long-term neurological deficits, is poorly understood. The pathogenesis of TBI is not limited to the primary mechanical injury. The secondary damage, including ischemia, excitotoxicity, oxidative stress, and immune dysfunction, leads to neuronal apoptosis, the breakdown of the blood–brain barrier (BBB), and chronic neuroinflammation. The preclinical controlled cortical impact (CCI) and fluid percussion injury (FPI) TBI models have generated valuable biomechanical data related to TBI-induced immune responses, including microglial priming, astrocyte dysregulation, and peripheral leukocyte recruitment. However, experimental models today are unable to completely replicate the intricate immune cascades in human TBI, particularly delayed and context-specific innate and adaptive immune response activation. Cytokine signaling (IL-1 β , TNF- α , and IL-6), neuroinflammatory amplification through the IL-23/IL-17 pathway, and autoantibody-mediated neurodegeneration are emerging as significant secondary injury mechanisms. Additionally, TBI-induced immunosuppression, which presents as generalized T lymphocyte depletion and aberrant macrophage polarization, enhances the risk of infection and delayed neurological recovery. Emerging immunotherapeutics such as cytokine blockade, complement blockade, and targeted modulation of T lymphocytes have the potential to optimize the post-TBI immune microenvironment for reducing secondary damage. Inclusion of next-generation experimental models combined with secondary injuries, such as hypoxia, polytrauma, and systemic inflammation, is needed to shift towards innovative, biomarker-driven, patient-stratified trials. Thus, integration of immunological phenotyping with translationally relevant models of TBI represents an important cornerstone in the development of targeted therapeutic treatments designed to improve neuroprotection, repair, and long-term functional outcome.

KEYWORDS

traumatic brain injury (TBI), cerebrovascular immunology, immunopathology, controlled cortical impact (CCI), fluid percussion injury (FPI)

Introduction

Traumatic brain injury (TBI) is the leading cause of mortality and morbidity in individuals under the age of 45. This results in substantial economic and societal burdens due to lost productivity and long-term disability (1). Despite contemporary advancements in understanding the pathophysiology of intracranial injuries, the ability to precisely reconstruct the sequence of events leading to trauma and accurately predict injury severity and progression remains a significant challenge (2, 3). The clinical complexity of TBI stems from its heterogeneous nature, involving a dynamic interplay between mechanical damage, secondary biochemical cascades, and a dysregulated immune response. Despite advances in acute care, little is known about the pathophysiological mechanisms that govern long-term recovery and prognosis following traumatic brain injury. Thus, experimental models of TBI serve as a critical tool in elucidating such essential mechanisms, providing insights into neuroinflammatory processes, immune cell recruitment, and secondary injury pathways that shape post-traumatic recovery and therapeutic intervention. The current paper elucidates the immunological landscape of TBI and its integration with experimental models in order to identify potential therapeutic targets that can be translated into clinical practice.

TBI is defined as an injury to the brain caused by an external mechanical force, such as blast waves, crushing forces, impact injuries, projectile penetration, and abrupt acceleration-deceleration forces (3, 4). The proceeding injuries from any combination of the above forces will lead to focal brain damage due to contact phenomena or diffuse brain damage due to acceleration/deceleration inertial phenomenon. Focal brain damage can result in lacerations, contusions, and intracranial hemorrhages, while diffuse brain damage can result in brain swellings and diffuse axonal injuries. However, it is important to note that despite these classifications, TBI is not a single clinical phenomenon but a highly complex disease process with various structural impairments, dysregulated biochemical pathways, altered neuronal function, diminished regulations of cerebral blood flow (CBF), and dysregulated immune metabolism (5).

Neuropathological classification of such injuries is determined by primary and secondary injury insults. Primary insult results from the direct mechanical impact of the damage to the brain immediately following the accident, which can cause instantaneous axonal shearing and hemorrhage, and holds a very small window of therapeutic intervention. Secondary insult results from non-mechanical damage caused by cascades of dysregulated physiological, metabolic, and cellular proceedings that follow the primary insult (6, 7). Secondary insults can lead to cerebral swelling, hypertension, and diffuse and focal hypoxic-ischemic damage. Secondary insults are slow in their clinical manifestations and present a larger window for therapeutic intervention. Furthermore, the mechanism of insults resulting from secondary injuries includes alterations of key biochemical cascades such as homeostatic disturbances in cellular calcium and sodium channels, substantial glutamate excitotoxicity, mitochondrial damage, lipid peroxidation, neuroinflammation, increased generation of free radicals and increased concentration of intracellular free fatty acids, leading to eventual apoptosis and diffuse axonal injury (DAI) (4, 8, 9).

Clinical pathophysiology and management of TBI

Traumatic Brain Injury (TBI) encompasses a spectrum of clinical severity, from mild concussion to profound coma, underpinned by complex neuropathological processes. Clinical presentation varies with the extent of initial mechanical trauma, with severe forms posing a dangerous risk of intracranial hypertension, hypoxemia, and late neurological sequelae. Clinical grading systems cannot, of themselves, explain pathophysiological variation affecting outcome (2, 3).

The trauma happens in two phases: the first insult is due to direct mechanical deformation of brain tissue, and the second phase, from hours to days due to metabolic breakdown, ischemia, excitotoxicity, and immune dysregulation. Ischemia produces lactic acidosis, oxidative stress, and ATP loss, disrupting ionic gradients and activating cascades of cell death. Among the characteristics of secondary injury is abnormal cerebral blood flow (CBF), triphasic in nature and involving hypoperfusion, hyperemia, and delayed hypoperfusion, each contributing in a characteristic fashion to tissue damage and worsening of clinical condition (3, 4).

Treatment of TBI is support-oriented and tiered by severity. Primary prevention, through safety equipment like helmets and seatbelts, is the sole truly effective intervention. Restriction of secondary insult is of urgent priority in the acute setting (4). This includes tight management of intracranial pressure (ICP), maintenance of cerebral perfusion pressure (CPP), and surgery to decompress when necessary. Pharmacologic treatment, such as NMDA-receptor antagonists, calcium channel blockers, and free-radical scavengers, has been studied but has not yet yielded consistent clinical benefit (8, 9). The inability of preclinical potential to be translated clinically emphasizes the need for improved experimental models that more accurately mirror the complex and temporally dynamic nature of human TBI. Table 1 recapitulates a comprehensive pathophysiological summary of traumatic brain injury.

Experimental models of traumatic brain injury

Given the heterogeneous pathophysiology of TBI in the patient population, numerous animal models have been developed over the last several decades that depict clinically relevant features of both focal and diffuse pathophysiologies. Although focal pathologies such as cerebral edema, hematomas, and contusions are well characterized in animal models, their translational value appears variable because clinical TBI often presents with diffuse rather than strictly focal injury patterns (10). Hence, animal models that focus on diffuse pathophysiologies with widespread impact, such as DAI, vascular injury and ischemia, may be more clinically applicable in certain contexts. This paradigm shift is also evident when examining the history of research in animal models of TBI. In contrast to early animal models of TBI that focused exclusively on the biochemical pathophysiology of focal impact injuries, contemporary models focus on the highly elongated molecular and cellular cascades that characterize secondary insult pathophysiology (5, 11).

There are currently four widely utilized animal models used in contemporary TBI research: controlled cortical impact (CCI) injury, fluid percussion injury (FPI), penetrating ballistic-like brain injury

TABLE 1 Comprehensive pathophysiological summary of traumatic brain injury (TBI).

Aspect	Description	Immunological component
Primary injury	Direct mechanical insult causing axonal damage, contusions, and hemorrhage (155).	Limited immune activation initially; rapid release of DAMPs (HMGB1, ATP, S100 β) triggers innate immune responses, including microglial priming (156).
Secondary injury	Progressive biochemical cascades: ischemia, oxidative stress, excitotoxicity (157).	Neuroinflammation propagates via microglial activation, astrogliosis, and sustained cytokine release (IL-1 β , TNF- α , IL-6), leading to prolonged BBB dysfunction (158).
Blood–brain barrier (BBB) disruption	Loss of BBB integrity due to endothelial and astrocytic damage (159).	Recruitment of peripheral immune cells neutrophils, monocytes, T cells through upregulated adhesion molecules (ICAM-1, VCAM-1) and chemokine gradients (CXCL1, MCP-1) (114, 160).
Neuroinflammation	Chronic activation of resident and peripheral immune cells (161).	Dysregulated M1/M2 microglial polarization influences recovery; M1 phenotype sustains injury via ROS and NO, while M2 phenotype promotes tissue repair (162, 163).
Oxidative stress	Excessive ROS, lipid peroxidation, mitochondrial dysfunction (164).	Microglial and neutrophil-derived ROS/NOS contribute to oxidative DNA damage and neuronal apoptosis; Nrf2 dysregulation exacerbates redox imbalance (165, 166).
Cerebral edema	Ionic dysregulation induces cytotoxic and vasogenic swelling (167).	IL-1 β , TNF- α increase endothelial permeability; aquaporin-4 (AQP4) dysregulation on astrocytes contributes to cerebral fluid accumulation and edema progression (159, 168).

(PBBI) and weight-drop impact model. The CCI injury model uses an electromagnetic piston to drive and penetrate a rigid impactor onto exposed dura of known brain regions with a varying gradation of velocity to mimic cortical tissue loss with widespread axonal damage (12, 13). FPI model uses a fluid-filled piston to produce and subsequently inject a pressurized fluid pulse onto an intact dura to cause deformations of brain tissues, with varying degrees of severity, depending on the pulse strength (14, 15). PBBI model uses a projectile transmission of a metal rod with varying degrees of energy to cause a temporary cavity in the brain to induce widespread inflammation, cortical spreading depression and brain swelling (16–19). In weight-drop TBI models, an object of varying weight and height is dropped into gravitational free fall onto an exposed brain skull to cause severe cortical contusions and progressive hemorrhages (20–22). Although each model has unique experimental advantages and limitations in its ability to recapitulate a clinically relevant model of TBI, CCI and FPI tend to yield more consistent injury patterns and can be a useful model to simulate the immune responses seen in human TBI. Accordingly, this review focuses on the role of CCI and FPI models as preclinical therapeutic strategies for the treatment of TBI.

Controlled cortical impact (CCI) injury and fluid percussion injury (FPI) models

The CCI model offers several practical strengths for translational applications. First, CCI can induce widespread diffuse degeneration of cortical and thalamic neurons, comatose states, and BBB dysfunction while controlling for crucial spatiotemporal parameters such as time, velocity and depth of injury across brain regions (14, 23–25). Furthermore, CCI models have been shown to induce cognitive deficits (Morris-water maze test) and emotional and behavioral impairments (forced swim test) that are well-preserved more than 12 months post-TBI injury (26–29). This model allows for the manipulation of velocity and depth of initial impact during the experiment, thereby controlling the severity of such pathophysiological, cognitive and emotional deficits (30, 31). Furthermore, increased gradations of impact velocity correspond to a progressive reduction in cerebral blood flow and elongated elevation of DAI and white matter atrophy. Hence, CCI models allow for collecting and extrapolating post-TBI physiological data in a context similar to ICU and intensive trauma

centers. Because CCI reproduces several pathophysiological and behavioral features seen in human TBI, it may help connect preclinical and clinical work to translate animal models of TBI into novel protocols in clinical care (13, 27, 32, 33).

Furthermore, FPI may provide practical advantages in answering certain translational questions to study severe TBI in humans. The FPI model induces tissue displacements and progressive deformations of grey matter, cerebral edema, and intracranial hemorrhage through rapid injection of the pressurized fluid-filled piston into the epidural space (5, 15, 34). In particular, lateral models of FPI (LFPI) can induce both localized cortical contusions and diffuse neuronal injury across subcortical structures of the hippocampus and thalamus (35). The progressive cell death and DAI in LFPI models will persist up to 1-year post-injury. Furthermore, the LFPI-induced pathophysiological cascade will further progress across vulnerable subcortical regions of the striatum, medial septum and amygdala and cause subsequent cognitive impairments, movement disorders and neurobehavioral dysfunctions that last more than 1-year post injury, similar to the clinical trajectories of human TBI (10, 22, 36, 37).

Although these models have respective features which align with certain clinical contexts, the FPI and CCI models carry important limitations. Whereas moderate and severe cases of human TBI frequently carry skull fractures and substantial contusions across gyri, FPI and CCI models reproduce human TBI without clinically present skull fractures. In addition, clinical TBI is frequently characterized by chronic sleep disorders, vestibular deficits and severe headaches in patients following the injury. Extensive literature of the recent decade has elucidated that sleep–wake dysfunction is one of the most reproducible TBI model sequelae, with phenotypes of hypersomnolence, sleep fragmentation, and disrupted orexin signaling that reflect those seen in human patients. These studies emphasize that no model replicates the whole chronic symptom complex but that convergent animal and human data strongly implicate deranged sleep–wake circuitry as a mechanistic contributor to long-term morbidity after TBI (38–41). Furthermore, investigators have recapitulated isolated features of chronic TBI symptoms using a FPI mouse model to simulate mild TBI. These investigators found mice had difficulty in maintaining wakefulness (42). Stemper et al. (43) used a high-rate rotational acceleration model and showed sustained balance & anxiety-like changes that scaled with duration of acceleration.

Contemporary animal models of TBI, including FPI and CCI models, often omit secondary insults, which can complicate extrapolation to heterogeneous clinical populations (12, 44–46). Hence, prioritizing models that include secondary neurologic insults are likely to improve translational alignment. For instance, recent studies have devised randomized TBI + Hypoxemia models of diffuse brain injury in which elevated neuroinflammatory markers of TNF α , IL1- β and IL-6 corresponded to the reduced recovery of sensorimotor function 2 weeks post-injury (47–49). In addition, regions of concentrated axonal injury coincided with substantial astrocytosis and microglial activation (49). Such secondary insult experimental models are particularly promising for the clinical population as they are predictive models of treatment response and recovery rate immediately following the injury. Beyond recapitulating mechanical injury, these models have also been instrumental in deciphering the complex immunological landscape following TBI, providing insights into potential therapeutic targets, as explored in the next section. Table 2 elucidates on the emergent experimental models of TBI and their respective immunological insights.

Immunological mechanism of traumatic brain injury

TBI initiates a multi-factorial cascade of immunological events which may serve as a basis for therapeutic target and intervention in future studies (50). Initial mechanical injury to the brain parenchyma leads to disruption of the BBB, which serves as an interface between the central nervous system and peripheral circulation (51). An impaired and permeable BBB is a pathological hallmark which precedes the immune cascade in TBI (52, 53). Immediately following injury, an inflammatory response is generated, which recruits glial cells (macrophages and astrocytes) to the site of injury, followed by

peripheral immune cells, such as monocytes, natural killer cells, dendritic cells and T cells (47, 54). The activation of the immune system and the subsequent cascades are mediated by damage-associated molecular patterns (DAMPs), purinergic signaling, and the secretion of pro-inflammatory cytokines by glial cells and macrophages near the site of injury (55–57). During this time, the dysfunctional BBB also allows for continued trafficking of pro-inflammatory immune cells, leading to chronic neuroinflammation and cell death (58). Therefore, understanding the role of inflammation and its contribution to secondary injury in the brain following TBI could lead to the development of immune modulation therapies that improve long-term outlooks for TBI patients. Furthermore, the biphasic immune response in TBI mirrors the inflammatory dynamics of glioblastoma (59, 60), making TBI a valuable model for profiling GBM immunophenotypes. Insights into cytokine signaling, BBB disruption, and myeloid polarization in TBI may inform precision immunotherapy in GBM, in particular on the role of metabolic orchestrations that tumor cells utilize to instantiate immune evasions, many of which are abundantly present in post-TBI inflammation cascades (61, 62).

Innate immune response

Microglia and astrocytes are the innate immune cell population in the CNS and play critical roles in neuroinflammation and repair following TBI. Microglia are known to disrupt the BBB when activated by NLRP3, a known pro-inflammatory marker (63). While the mechanism of this activation pathway is not fully elucidated, such process is thought to involve the recruitment of CXCR2-containing neutrophils by GDF-15 production (63). Additionally, astrocytes can exhibit neuroprotective and neurotoxic effects that are highly context dependent which allow for modulation of their behavior via inflammation-associated molecules. Astrocytes have impaired glutamate

TABLE 2 Experimental models of TBI and their immunological insights.

Model	Description	Immunological insights	Strengths	Limitations
Controlled cortical impact (CCI) (169)	Electromagnetic piston delivers cortical impact at controlled velocity and depth.	Induces acute cytokine release (TNF- α , IL-1 β), BBB disruption, microglial priming, and delayed complement activation (170).	High reproducibility; well-suited for mechanistic and therapeutic studies.	Does not model diffuse injuries or secondary polytrauma seen in severe TBI.
Fluid percussion injury (FPI) (171)	Fluid pulse on intact dura induces mixed focal and diffuse injury.	Replicates systemic neuroinflammation, neutrophil infiltration, and prolonged astroglial activation (126, 172, 173).	Models diffuse injuries effectively induces persistent neuroinflammation similar to human TBI.	Less control over injury parameters; minimal replication of focal contusions.
Weight-drop model (174)	Free-falling object induces cortical contusions and hemorrhages.	Increases microglial reactivity, BBB permeability, and excitotoxicity (excessive glutamate release) (175, 176).	Simple and cost-effective; replicates severe cortical contusions.	Poor reproducibility; limited utility in modeling secondary systemic insults.
Penetrating ballistic-like brain injury (PBB1) (16)	High-velocity penetration of brain tissue mimics ballistic trauma.	Triggers chronic neuroinflammation and glial scarring (177–179).	Models severe inflammation and persistent immune dysregulation in penetrating injuries.	Highly invasive; difficult to standardize and ethically challenging.
TBI + secondary insults (180)	Combined TBI with hypoxia, hemorrhagic shock, or systemic inflammation.	Enhances IL-6, TNF- α , and MCP-1 signaling, worsening BBB permeability and neuroimmune dysfunction (52, 180).	Clinically relevant; mimics polytrauma conditions seen in severe TBI.	Complex methodologies; limited standardization across research groups.

reuptake abilities following TBI which can lead to excitotoxicity following TBI (64, 65). This mechanism may be in part due to an imbalance of D-serine release between injured neurons and astrocytes at the site of injury (66). Continued excitotoxicity is linked to microglial activation and neuroinflammation via calmodulin-dependent protein kinase (CaMK), cAMP and extracellular signal-regulating kinase (ERK) pathways (67). Astrocytes are also implicated in maintaining the structural integrity of the BBB as they can release signaling molecules to affect BBB permeability. For instance, VEGF and APOE secretion by astrocytes increases leakiness of the BBB (68, 69). In contrast, sonic hedgehog (SHH) genes or secretion of retinoic acid by astrocytes can reduce BBB permeability (70, 71). Transgenic mouse model without astrocytes showed greater cortical degeneration, demonstrating that astrocytes may play a protective role following TBI as their absence in TBI leads to neuronal degeneration and increased inflammation (72). Conversely, astrocyte activation following the circulation of inflammatory microRNAs was associated with pro-inflammatory state of astrocytes and contributes to secondary brain injury (73). Therefore, astrocytes demonstrate both neuroprotective or neurotoxic, which varies highly within the context of their microenvironment.

Populations of innate immune cells, such as neutrophils and monocytes, undergo proliferation in cervical and draining lymph nodes following TBI (74). The entry of these peripheral immune cells is permitted through the functionally disrupted BBB. M1 macrophages, activated by INF- γ and toll-like receptors (TLRs), cause neurotoxicity via inflammation induction whereas M2 macrophages promote axonal repair following TBI (75). Indeed, a high M1/M2 macrophage ratio has been reported to be detrimental to the reduction of inflammation in CNS injuries (76, 77). Furthermore, a study by Makinde et al. (78) found that circulating peripheral monocytes recruit neutrophils into the injured brain, propagating further breakdown of the BBB. In this model, mice were depleted of all peripheral monocytes, but retained microglia, demonstrating that abrogating peripheral monocyte and neutrophil infiltration following TBI could contribute to enhanced survival and cognitive recovery following TBI.

Cytokine and chemokine signaling in TBI

Immediately after TBI (0–6 h), DAMPS released from necrotic neurons engage TLR2/4 on infiltrating neutrophils, upregulating TNF- α and IL-1 β that promotes endothelial adhesion-molecule expression, matrix metalloproteinase release, and rapid phagocytic clearance of myelin and erythrocytic debris (79). However, persistence of a pro-inflammatory milieu beyond 72 h impedes oligodendrocyte progenitor maturation and synaptic pruning, suggesting phase-specific rather than blanket inhibition (80). Additionally, in the acute post-TBI period, levels of IL-1 β are elevated, and neutralizing IL-1 β with a monoclonal antibody has been shown to prevent secondary injury by inhibiting downstream microglial activation (81). Similarly, inhibiting TNF- α with 3,6-dithiothalidomide within 12 h post-TBI improves recovery outcomes in mouse models (82). IL-6, which can serve as a biomarker of inflammatory load in the central nervous system (CNS), is associated with a worse prognosis during the first year after TBI when elevated. IL-17, which plays a role in sustaining inflammation, is linked to secondary brain injury, as its inhibition by IL-23 abrogates neuronal apoptosis and improves neural function. Furthermore, transfection of astrocytes to produce and release IL-2

locally in the brain has demonstrated neuroprotective effects through the recruitment of T regulatory (Treg) cells (83). These findings collectively suggest that inflammation must be carefully modulated after TBI—both insufficient and excessive inflammation can hinder recovery, with prolonged or elevated inflammation leading to secondary injury.

The adaptive immune response in TBI

T helper (Th) cell subsets play distinct roles in modulating neuroinflammation after traumatic brain injury (TBI), with Th1, Th2, and Th17 cells influencing the blood–brain barrier (BBB) and secondary brain injury through different mechanisms. Th1 cells produce pro-inflammatory cytokines (IFN- γ , IL-2 and IL-12) which can cause further harm. One mechanism by which Th1 cells increase neuroinflammation is by permeabilizing the BBB to allow greater uptake of leukocytes, and results in white matter injury (84). In contrast, Th2 presence is associated with anti-inflammatory cytokine release and neuroprotection in TBI (85). Specifically, Th2 inhibits the activation of microglia, and therefore serves to modulate the neuroinflammatory response following initial TBI (86). In addition, Th17 cells secrete IL-17, which is suspected to promote BBB disruption, increase CNS inflammation, and contribute to secondary brain injury through the IL-23, IL-17 axis (87).

Following TBI, B cells become activated and produce autoantibodies. Autoreactive CD19+ B cells increase in number in the spleen and cervical lymph nodes, with peak levels 8–10 days post-injury (88, 89). Autoantibodies are generated against brain-specific proteins, such as GFAP, myelin-associated glycoprotein (MAG) and myelin basic protein (MBP) (89, 90). Zhang et al. (90) found that elevated levels of anti-GFAP are negatively correlated with patient outcomes, demonstrating that Anti-GFAP may be monitored as a biomarker to correlate with long-term neurodegeneration post-TBI. A subset of B-cells, regulatory B-cells (Breg; CD1dhi CD5+), infiltrate perilesional cortex within 12–48 h, secrete IL-10 and IL-35, and suppress microglial NF- κ B activation, thereby limiting reducing nearby axonal degeneration (91, 92). Additionally, persistent anti-MAG IgM autoantibodies are associated with elevated serum neurofilament light concentrations, which suggest an active neurodegeneration process (89). Furthermore, autoantibodies against MBP and phospholipids in CSF are correlated with increased injury severity and vascular complications (93). Notably, the presence of brain-derived antigens in lymphoid tissue was demonstrated to trigger an adaptive autoimmune response and may be associated with patient outcomes (94). Finally, the production of autoantibodies and its associated sequelae can last for many years after the injury and lead to ongoing neuroinflammation and neurodegeneration.

Systemic immune dysregulation following TBI

Systemic inflammation following TBI is a contributor to secondary injury in the CNS. High levels of inflammation during the first 90 days post-injury generally lead to less favorable outcomes when recovery is evaluated at 6 and 12 months following TBI (95–97). The systemic inflammatory response is characterized by immune activity by both CNS and peripheral immune cells. As previously

mentioned, microglia produce inflammatory molecules such as IL-1 β , IL-6, IL-12, NO, or ROS (81, 91, 98–100). In addition to the release of these pro-inflammatory molecules, reactive microglia increase neuroinflammation by exhibiting phagocytic behavior on the astrocytic processes which extend to support the BBB, and thus increase BBB permeability (98). Microglia further sustain neuroinflammation through the recruitment of peripheral macrophages following TBI (99). In contrast, B cells demonstrate a neuroprotective role following TBI by downregulating the number of inflammatory processes occurring in the immune environment following TBI (100). This occurs through B cell secretion of IL-10 and IL-35 anti-inflammatory cytokines (91). Furthermore, B cells produce brain-derived neurotrophic factor (BDNF), which supports neuronal survival and recovery (101).

TBI impairs the function of key immune cells, namely macrophages, neutrophils, NK cells, and T cells, by disrupting immune responses and increasing susceptibility to infections. Notably, macrophages in patients with TBI have impaired phagocytic capabilities as well as impaired activation of NK cells, resulting in increased risk for infection (102, 103). Neutrophils are elevated in the first 48 h following TBI but are hyporesponsive and demonstrate a mitigated ability to phagocytose bacterial infections for up to several weeks following traumatic injury. This impaired immune response is suspected to be in response to neutrophil infiltration of the brain and subsequent preservation of brain tissue through downregulation of phagocytic behavior (104, 105). Additionally, the severity of NK cell depletion is correlated with severity of TBI and can persist for weeks following initial injury (106). Following TBI, the thymus shrinks, which correlates with the decrease in T cell circulation observed following TBI (107, 108). Th1 cells shift towards Th2 phenotype following TBI and the accompanying shift to Th2 cells predisposes patients to higher rates of infection (109). In concordance, PD-1 upregulation, a sign of immune cell exhaustion, is observed in T cells following TBI (110). Figure 1 recapitulates such immunological axis characteristic of traumatic brain injury.

Immunology in experimental models of TBI

In order to better understand the underlying pathophysiology and immunological mechanisms of both primary and secondary insults following TBI, experimental models, such as CCI and FPI, have been utilized for their ability to recapitulate the immunological cascades following focal and diffuse TBI.

CCI has been shown to be an effective model for replicating the acute neuroinflammatory cascade following TBI (111, 112). In one study of mice undergoing CCI injury followed by biopsy, seven cytokines were measured, six of which showed significant elevation when compared to naïve controls (113). Following CCI injury, pro-inflammatory cytokines CXCL1, IL-1 β , and IL-6 showed rapid elevation with peak expression at day +1. Three other pro-inflammatory cytokines, IL-12p70, IFN- γ , and IL-10, showed peak expression at day +3. Though not completely mirrored in humans, a number of pro-inflammatory cytokines are preserved in mice and have shown similar temporality and upregulation post-TBI. Elevated serum CXCL1 concentration <24 h post-TBI was positively correlated with TBI severity, and higher levels of CSF IL-6 in the acute phase post-TBI were

associated with worse outcomes as measured by Glasgow Outcome Scale scores at 6 months following injury (114, 115). Another study utilizing cerebral microdialysis paired with arterial and jugular bulb plasma in six TBI patients showed that IL12-p70 and IL-10 peaked more than 3 days following injury, whereas IL-1 β peaked less than 2 days post-injury (116). CCI has been shown to be an effective model for replicating the acute neuroinflammatory cascade following TBICCI has frequently been used to characterize acute neuroinflammatory cascades following TBI. In one study of mice undergoing CCI injury followed by biopsy, seven cytokines were measured, six of which showed significant elevation when compared to naïve controls (113). Following CCI injury, pro-inflammatory cytokines CXCL1, IL-1 β , and IL-6 showed rapid elevation with peak expression at day +1. Three other pro-inflammatory cytokines, IL-12p70, IFN- γ , and IL-10, showed peak expression at day +3. Though not completely mirrored in humans, a number of pro-inflammatory cytokines are preserved in mice and have shown similar temporality and upregulation post-TBI. Elevated serum CXCL1 concentration <24 h post-TBI was positively correlated with TBI severity, and higher levels of CSF IL-6 in the acute phase post-TBI were associated with worse outcomes as measured by Glasgow Outcome Scale scores at 6 months following injury (114, 115). Another study utilizing cerebral microdialysis paired with arterial and jugular bulb plasma in six TBI patients showed that IL12-p70 and IL-10 peaked more than 3 days following injury, whereas IL-1 β peaked less than 2 days post-injury (116).

The chronic inflammatory response following CCI extends well beyond the acute phase, demonstrating persistent neuroinflammation that mirrors human TBI pathology (117–120). In one study of CCI in moderate-level TBI mice, the chronic phase was characterized by progressive expansions of lesion volumes: 287, 309, and 483% increases at 5, 12, and 52 weeks post-TBI, respectively, along with microglial activation persisting up to 1 year post-TBI (121). These findings recapitulate those found in humans, where PET imaging of moderate to severe TBI survivors indicated increased microglial activation up to 17 years post-TBI (122). The extended inflammatory response represents a potential therapeutic window that extends well beyond the traditional acute treatment period, highlighting the importance of understanding and targeting chronic inflammation in TBI treatment strategies.

Despite its control and reproducibility, CCI may not adequately represent diffuse injuries (123). To better simulate these types of injuries, FPI is utilized, which is classified into two categories: midline FPI and lateral FPI. Midline FPI induces diffuse TBI with bilateral structural injury and inflammation while lateral FPI induces both diffuse and focal TBI. In the acute phase, FPI models have demonstrated significant neutrophil infiltration (124, 125). One study analyzed myeloperoxidase (MPO) activity, a specific marker of neutrophils, in rats which underwent trauma via FPI and saw that MPO concentration peaked at 24 h post-trauma (126). In severe TBI human patients, polymorphonuclear neutrophils (PMNs) have shown increased activation and decreased apoptosis, leading to levels up to three times that of controls for the first 24 h following injury (127). Furthermore, FPI models have shown upregulation of the pro-inflammatory cytokines IL-1 β and TNF- α following TBI. In midline FPI, IL-1 β mRNA was significantly upregulated at 24 h

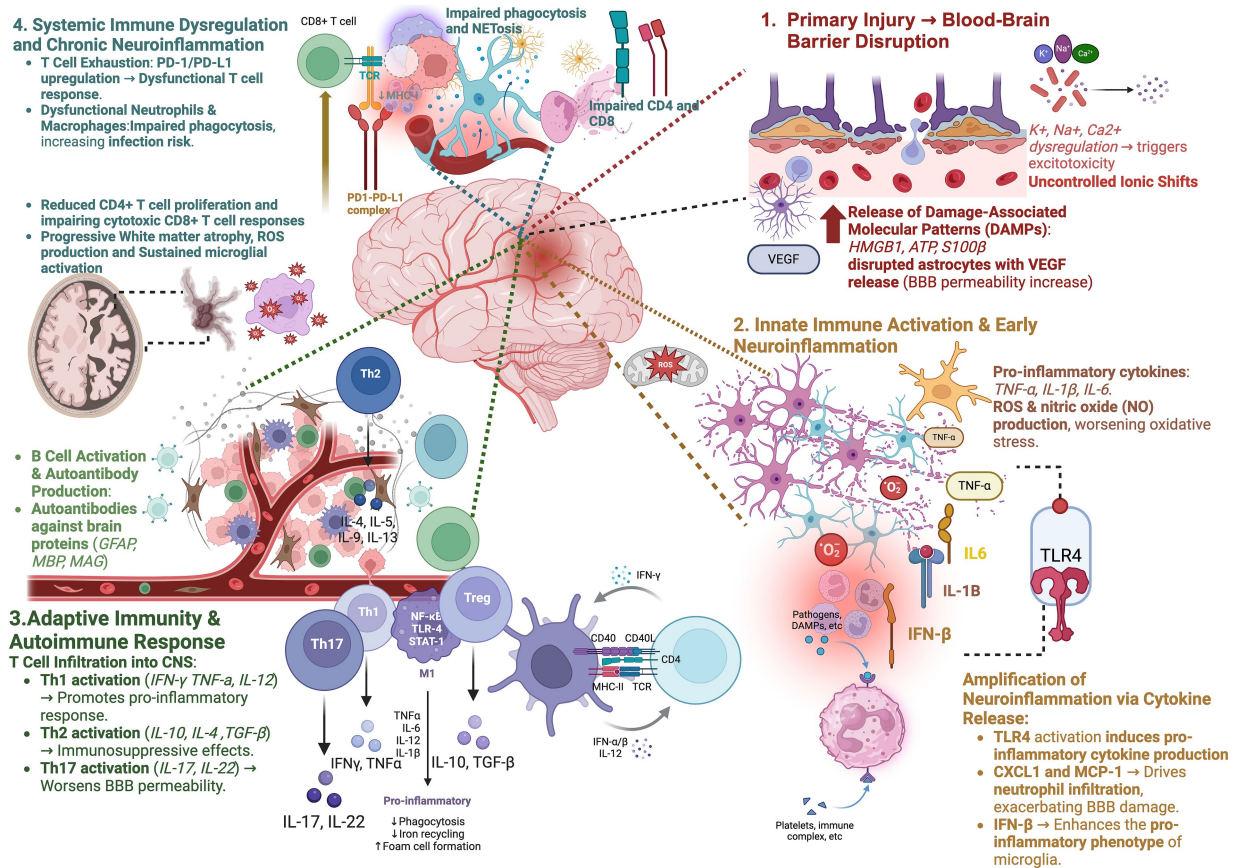


FIGURE 1

The immunological cascade of traumatic brain injury: from acute neuroinflammation to chronic systemic dysregulation and neurodegeneration. Traumatic brain injury (TBI) is characterized by a multistage immune response that ranges from acute neuroinflammation to systemic immune dysregulation and chronic neurodegeneration. Acute BBB breakdown permits damage-associated molecular patterns (DAMPs) to stimulate via TLR4 signaling the activation of microglial cells and the release of pro-inflammatory cytokines (*TNF-α*, *IL-1β*, *IL-6*, *IFN-γ*). This induces peripheral immune infiltration (neutrophils, monocytes, and T cells) and increases the permeability of BBB and the injury of neurons. Th1 and Th17 cells maintain inflammation, CD8+ T cells lead to the death of neurons (granzyme B, perforin) and B cells produce autoantibodies (anti-GFAP, anti-MBP, and anti-MAG), leading to development of autoimmunity of the CNS. Systemically, T cell exhaustion (PD-1/PD-L1) and diminished neutrophil phagocytosis in concert with peripheral inflammation increase responses to opportunistic infections. Chronically, long-term microglial priming, oxidative stress, and damage of blood–brain barrier (BBB) lead to white matter atrophy and synaptic loss, thereby increasing the risks for AD, PD, and chronic traumatic encephalopathy (CTE). This ongoing neuroimmune dysregulation calls for the development of directed immunotherapies to reduce long-term cognitive and functional decline. Figures were created using [BioRender.com](https://www.biorender.com).

post-TBI, and *TNF-α* mRNA was significantly upregulated at 4 and 24 h post-TBI when compared to control mice (128). In brain tissue samples from 21 human TBI patients, both *IL-1β* and *TNF-α* were significantly overexpressed as well, suggesting that FPI captures immunologic responses that resemble clinical TBI in certain respects (129).

Several innate and adaptive pathways differ between rodents and humans. For instance, mice exclusively express the membrane-attack-complex inhibitor, CD59b, exclusively in their testis, as opposed to ubiquitous expression in humans, predisposing mice to heightened complement-mediated inflammation following TBI (130). Furthermore, mouse macrophage and dendritic cells express TLR11/12, absent in humans, which leads to heightened *IFN-γ* secretion (131). Given that this isoform of TLR is not functionally expressed by humans, this contributes an additional immune mechanism of M1 macrophage polarization that differs between mice and humans. In the adaptive compartment, C57BL/6 mice mount a rapid Vβ8.1/8.2 T-cell expansion driving *IL-17* production,

whereas human TCR repertoires show delayed, polyclonal activation (132). These discrepancies may underlie the failure of *IL-17* blockade and complement inhibitors to replicate rodent efficacy in phase II trials.

Given the limitations of traditional models like CCI and FPI in replicating complex secondary injuries such as hypoxia, there has been a shift towards more sophisticated models. These advanced models are designed to include these secondary neurological insults, providing a better model which can recreate the complex realities of human TBI. The TBI + Hypoxia model, in particular, shows notable potential for translational application. A study by Davies and colleagues induced hypoxia in mice 1 day following TBI, and found this led to deficits in memory and learning along with increased astrocytic response when compared to TBI mice which did not undergo hypoxia (133). Other studies incorporating hypoxia as a secondary insult have shown elevated pro-inflammatory cytokines *TNF-α*, *IL-1β* and *IL-6* (134, 135). By incorporating secondary insults into these TBI models, the subsequent

neuroinflammatory cascades more closely resemble human TBI patients, providing a promising direction for clinically translational TBI models. Given the critical role of neuroinflammation in secondary injury, emerging immunomodulatory therapies aim to mitigate these effects, offering new avenues for intervention. Table 3 provides an overview of fundamental mechanisms of resistance in emergent TBI therapeutics.

Targeted immunologic therapy

TBI elicits a complex immunopathological cascade characterized by microglial activation, peripheral leukocyte recruitment, and elevated pro-inflammatory cytokines. Initial neuroprotective responses can transition to detrimental inflammation, exacerbating neuronal damage and impeding recovery. Advances in neuroimmunology have delineated the molecular and cellular mechanisms underpinning post-traumatic neuroinflammation, identifying targeted interventions such as cytokine antagonism, complement inhibition, and T cell modulation. These strategies aim to reduce secondary injury and enhance neurofunctional outcomes in TBI management.

Cytokine modulation has emerged as a potent therapeutic strategy for TBI, targeting the reduction of neuroinflammation and edema through the neutralization of pro-inflammatory cytokines. Among these, interleukin-1 receptor antagonists (IL-1ra) and TNF- α inhibitors have shown significant promise. Inhibition of NLRP3, an upstream inflammasome of IL-1 β , in mice has been shown to attenuate neurological deficits in spatial learning and memory recovery after TBI (136, 137). Furthermore, brain edema and cortical lesion size were significantly reduced following inhibition of NLRP3 in mice. Anakinra, a recombinant form of the human IL-1ra, has been approved in humans for rheumatologic conditions and is now being trialed in humans for TBI (138). Another target for cytokine modulation is TNF- α , and anti-TNF- α agents, such as infliximab, are currently being explored as therapies

for TBI, particularly for their ability to ameliorate endothelial dysfunction in the setting of TBI (139, 140).

Complement inhibition may serve as another potential therapy for TBI, preventing synaptic loss and neurotoxicity. Inhibition of C3 activation has been shown to reduce chronic neuroinflammation and neurodegeneration in mice following CCI (117). C5 deficient mice showed reduced brain lesion size when treated with C1-Inh and CR2-Crry and improved cognitive function following CCI when compared to control mice (141). Currently, anti-C5 antibodies such as eculizumab are being trialed for safety and efficacy in subarachnoid hemorrhage patients, but no trials have been conducted in the setting of patients with TBI (142).

T cell modulation has been seen as another potential therapeutic target for TBI patients. Various T cell subsets, namely V γ 1 and V γ 4 $\gamma\delta$ T cell subsets, play distinct roles in TBI pathophysiology. The former is responsible for activation of microglia and induction of neuroinflammation by secretion of IFN- γ and IL-17, and the latter dampens TBI and maintains microglial homeostasis through TGF- β secretion (143). CD8 + T cells have also been implicated in TBI pathophysiology, causing chronic neurological impairment through increased expression of GrB in activated CD8 + T cells, upregulating the GrB/perforin cytolytic pathway (144). Mice which were pharmacologically depleted of CD8 + T cells showed improved neurological outcomes following CCI.

Other emerging therapies which have shown promise but have not yet progressed to clinical trials include exosome therapy, immune checkpoint inhibitors, and precision immunology approaches. Exosome therapy works by utilizing engineered nanoparticles to deliver anti-inflammatory miRNAs or cytokine inhibitors. In one study of human adipose mesenchymal stem cell-derived exosomes (hADSC-ex) in TBI rats, the exosome therapy facilitated sensorimotor functional recovery, inhibited neuroinflammation, reduced neuronal apoptosis, and promoted hippocampal neurogenesis (145). Immune checkpoint inhibitors, namely the PD-1/PD-L1 pathway, have also been studied for their

TABLE 3 Therapeutic strategies and their challenges.

Therapeutic domain	Current strategies	Emerging approaches	Challenges and limitations
Primary insults	Injury prevention (seatbelts, helmets).	Advanced neuroprotective gear incorporating rotational force dissipation (181).	Limited therapeutic intervention post-impact; relies on behavioral adherence.
Secondary insults	ICP monitoring, CPP optimization, hypothermia therapy.	BBB-permeable neuroprotective agents, biomarker-driven interventions (182).	Heterogeneity of TBI pathology complicates standardized treatment; failure of neuroprotective agents in large-scale trials.
Surgical interventions	Clot evacuation, decompressive craniectomy, CSF drainage.	Minimally invasive procedures, neuroimaging-guided interventions (183, 184).	Risk of infection, exacerbation of neuroinflammation, need for individualized treatment strategies.
Pharmacological interventions	Anticonvulsants, anticoagulants, anti-inflammatory drugs.	Targeted cytokine inhibition, nanoparticle-mediated drug delivery (185, 186).	Poor penetration across the BBB; systemic toxicity concerns.
Experimental models and research	FPI, CCI, TBI + polytrauma models.	Integration of multi-insult models, organoid-based TBI modeling (187, 188).	Limited translational success due to species differences; high experimental costs.

application in TBI. Following surgical brain injury in mice, administration of PD-L1, the ligand for PD-1, significantly reduced cerebral edema, and PD-L1 blockade exacerbated cell death *in vivo* (146). Furthermore, blockade of PD-L1 in post-TBI mice which underwent CCI led to increased cavity size of the injured cortex along with motor and emotion dysfunction, further highlighting that inhibiting T cells through PD-1 interaction may play a protective role in TBI (147). Given the possibility of overactivation of the immune system and subsequent non-specific inflammation, future studies involving immune checkpoint inhibition will need dose-escalation trials to satisfy safety requirements. While PD-1/PD-L1 modulation has been found to be potentially effective at reducing edema and inhibiting T-cell-mediated damage after TBI, the overall risk remains that of immune overdrive within the already inflamed and compromised environment of the CNS (146, 147). Excessive checkpoint blockade can potentially increase BBB disruption, amplify Th1/Th17-mediated cytokine cascades, and induce autoantibody formation against CNS antigens such as GFAP and MBP, thereby accelerating chronic neurodegeneration. Such concerns are further instantiated in GBM, where PD-1 blockade reveals CNS autoimmunity despite therapeutic response in patient populations (60, 148). Thus, new approaches must include biomarker-directed, time-limited checkpoint modulation, possibly in addition to adjuncts such as exosome delivery platforms or microbiome-directed approaches, to maximize the balance between protective immunity and pathologic inflammation.

Gut-brain axis modulation, a precision immunological approach, works by restoring microbiota through probiotics or fecal microbiota transplantation to reduce systemic inflammation and has been explored in mental health, inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis (148–150). Recent efforts have characterized the gut-brain axis as a therapeutic target for TBI as well (151). Table 4 provides an overview of emergent immunotherapeutic strategies in this venture.

Integration with clinical strategies

Integration of these immunological therapies with clinical strategies is essential for clinical relevance in TBI patients. Utilizing immunological biomarkers for patient stratification is one potential avenue by which we can create more targeted immunological therapies to treat TBI patients. Translationally relevant biomarkers must be consistent between CCI rodent models and human TBI patients (43, 123). One study showed correlational similarity between post-TBI rodent and humans for cytokines IL-1 β , IL-6, G-CSF, CCL3, CCL5, and TNF- α , which were also associated with white matter integrity preservation (152). Targeting these specific cytokines may allow for more targeted immunological therapies in the future.

Future immune-based therapies must also complement existing TBI management strategies. Current TBI management focuses on prevention of secondary insults by avoiding hypotension and hypoxia through maintenance of cerebral perfusion pressure and cerebral blood flow. Continual monitoring of intracranial pressure and utilization of bedside maneuvers, hyperosmolar therapy, CSF drainage, pentobarbital coma, and decompressive craniectomy when appropriate are necessary as well (133, 153). Immune-based therapies are focused on reducing neuroinflammation and enhancing functional recovery. This strategy is suited for complementing current therapies focused on therapeutic interventional windows for secondary insults, limiting future complications such as risk of death and long-term neurological and cognitive damage.

Future directions for research and clinical translation

Advancement in TBI research requires closing the translational gap between animal models and human disease. CCI and FPI remain of use but due to their poor ability to emulate diffuse injury, secondary

TABLE 4 Immunological therapeutic targets in TBI.

Target	Mechanism of action	Therapeutic examples	Stage of development	Challenges
Cytokine modulation	Blocks pro-inflammatory cytokines to prevent neuroinflammation.	IL-1 β antagonists (anakinra), TNF- α inhibitors (infliximab) (140, 185).	Preclinical and early-phase trials.	Systemic immunosuppression, narrow therapeutic window.
Microglial polarization	Shifts microglia from M1 (neurotoxic) to M2 (neuroprotective) phenotype.	PPAR- γ agonists (pioglitazone), TGF- β modulators (176, 189, 190).	Preclinical studies.	Risk of impairing microglial surveillance; limited <i>in vivo</i> specificity.
Complement Inhibition	Blocks C3a/C5a signaling to prevent neurotoxicity.	Anti-C5 antibodies (eculizumab) (142, 191).	Early-phase clinical trials.	BBB penetration challenges; increased infection risk.
Chemokine signaling blockade	Inhibits immune cell infiltration by targeting chemokine receptors.	CCR2 inhibitors, CXCR4 antagonists (192, 193).	Preclinical studies.	Risk of off-target immune suppression.
Exosome therapy	Delivers neuroprotective agents via engineered vesicles.	MSC-derived exosomes with ncRNAs modulate neuroinflammation and promote repair (194)	Preclinical research.	Efficiency of BBB crossing; manufacturing scalability.
Gut-brain axis modulation	Alters microbiota composition to regulate systemic inflammation.	Probiotics, fecal microbiota transplantation (FMT) (195, 196).	Early-stage research.	Individual variability in microbiota responses.

insults, and chronic effects (sleep–wake disturbance, vestibular failure, and headache) predictability is compromised. Next-generation models are required to pair TBI with systemic stressors such as hypoxia or polytrauma, use humanized immune systems or brain organoids to address species differences, and standardized injury severities and readouts across laboratories. Essential endpoints to harmonize include blood–brain barrier integrity, cytokine and complement signaling (IL-1 β , TNF- α , IL-6, IL-23/IL-17, C3/C5), immune cell phenotyping, and autoantibody tracking (anti-GFAP, MBP, MAG) that can be directly compared with human biospecimens.

Clinically, enriched longitudinal cohorts supplemented by biomarkers and imaging readouts would need to be developed in order to align immune signatures with recovery trajectories. This platform would permit patient stratification by biomarkers for adaptive trials instead of the one-size-fits-all approach that has unraveled previous therapeutic efforts. Near-term objectives include careful testing of cytokine and inflammasome blockade, complement inhibition, and T-cell modulation, alongside concomitant efforts to confirm pharmacodynamic biomarkers of target engagement. Optimal treatment windows of TBI inflammation must also be addressed by trials given the biphasic development of TBI inflammation.

Other than these main approaches, adjunctive therapies should be examined in well-characterized subgroups. Exosome therapy, modulation of the gut–brain axis, and orexin-targeted therapy for sleep disturbance due to TBI are only a few promising options. Multi-omics and spatial transcriptomics combined with clinical phenotyping will be needed in order to make the leap to precision immunotherapy, as the therapy will be adapted to the individual's specific immune make-up. By combining preclinical rigor with biomarker-informed, mechanism-based clinical trials, the emergent research can shift towards precision therapies that substantially improve long-term neurological and cognitive outcomes.

Concluding remarks

Recent advances in experimental TBI models have enabled more accurate replication of human secondary injury cascades, including dysregulated cerebral blood flow, neuroinflammation, and diffuse axonal injury (154). Unlike earlier models, which emphasized focal insults, new paradigms emphasize the systemic and dynamic nature of secondary damage. Multifactorial models, including the addition of hypotension, radiation, or polytrauma, more closely replicate clinical presentation and may more validly predict treatment response. Immunopathologically, TBI progresses in a biphasic manner: an acute microglial activation, neutrophil invasion, and DAMP-mediated breakdown of the BBB pro-inflammatory process, and a chronic maladaptive immunity subsequently characterized by persistent M1 macrophage activation, oxidative stress, and excitotoxicity. Adaptive immune processes such as Th1/Th17-mediated damage and Th2/Treg-mediated modulation also determine long-term outcome, while autoantibodies to CNS antigens such as GFAP and MBP contribute to progressive neurodegeneration.

Moving forward, precision-targeted immunomodulation offers a compelling therapeutic avenue. IL-1 β , TNF- α , and C5a inhibitors have all shown a potential to reduce secondary injury, and novel approaches, including exosome-mediated cytokine delivery and microbiota modulation, are emerging ventures. The introduction of immunophenotyping and biomarker-based stratification into the clinic

will be instrumental in advancing beyond generalized neuroprotection. Lastly, the integration of multi-omics and spatial transcriptomics with patient-specific immune profiling has the potential to shift the field toward personalized, mechanism-driven therapies that more effectively address the heterogeneity of human TBI.

Author contributions

MA: Investigation, Writing – review & editing, Visualization, Writing – original draft. JH: Writing – original draft, Resources, Project administration, Writing – review & editing. JuL: Investigation, Writing – review & editing, Writing – original draft. AR: Writing – original draft, Writing – review & editing. KC: Writing – review & editing, Software, Investigation, Writing – original draft. JaL: Writing – review & editing, Resources, Investigation. LK: Methodology, Writing – review & editing, Resources. RM: Writing – review & editing, Methodology, Resources. JC: Writing – review & editing, Resources, Writing – original draft. ML: Conceptualization, Supervision, Writing – review & editing.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Maas AIR, Menon DK, Manley GT, Abrams M, Åkerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. *Lancet Neurol.* (2022) 21:1004–60. doi: 10.1016/S1474-4422(22)00309-X
2. Finnie JW, Blumbergs PC. Traumatic brain injury. *Vet Pathol.* (2002) 39:679–89. doi: 10.1354/vp.39-6-679
3. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol.* (2008) 7:728–41. doi: 10.1016/S1474-4422(08)70164-9
4. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth.* (2007) 99:4–9. doi: 10.1093/bja/aem131
5. Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. *Nat Rev Neurosci.* (2013) 14:128–42. doi: 10.1038/nrn3407
6. McIntosh TK, Smith DH, Meaney DF, Kotapka MJ, Gennarelli TA, Graham DI. Neuropathological sequelae of traumatic brain injury: relationship to neurochemical and biomechanical mechanisms. *Lab Invest J Tech Methods Pathol.* (1996) 74:315–42.
7. Marshall LF. Head injury: recent past, present, and future. *Neurosurgery.* (2000) 47:546–61. doi: 10.1097/00006123-200009000-00002
8. Baethmann A, Eriskat J, Stoffel M, Chapuis D, Wirth A, Plesnila N. Special aspects of severe head injury: recent developments. *Curr Opin Anaesthesiol.* (1998) 11:193–200. doi: 10.1097/00001503-199804000-00013
9. Nortje J, Menon DK. Traumatic brain injury: physiology, mechanisms, and outcome. *Curr Opin Neurol.* (2004) 17:711–8. doi: 10.1097/00019052-200412000-00011
10. Pierce JE, Smith DH, Trojanowski JQ, McIntosh TK. Enduring cognitive, neurobehavioral and histopathological changes persist for up to one year following severe experimental brain injury in rats. *Neuroscience.* (1998) 87:359–69. doi: 10.1016/s0306-4522(98)00142-0
11. Denny-Brown DE, Russell WR. Experimental concussion: (section of neurology). *Proc R Soc Med.* (1941) 34:691–2. doi: 10.1177/003591574103401102
12. Johnson VE, Meaney DF, Cullen DK, Smith DH. Animal models of traumatic brain injury. *Handb Clin Neurol.* (2015) 127:115–28. doi: 10.1016/B978-0-444-52892-6.00008-8
13. Manley GT, Rosenthal G, Lam M, Morabito D, Yan D, Derugin N, et al. Controlled cortical impact in swine: pathophysiology and biomechanics. *J Neurotrauma.* (2006) 23:128–39. doi: 10.1089/neu.2006.23.128
14. Kabadi SV, Hilton GD, Stoica BA, Zapple DN, Faden AI. Fluid-percussion-induced traumatic brain injury model in rats. *Nat Protoc.* (2010) 5:1552–63. doi: 10.1038/nprot.2010.112
15. Thompson HJ, Lifshitz J, Marklund N, Grady MS, Graham DI, Hovda DA, et al. Lateral fluid percussion brain injury: a 15-year review and evaluation. *J Neurotrauma.* (2005) 22:42–75. doi: 10.1089/neu.2005.22.42
16. Williams AJ, Hartings JA, Lu XCM, Rolli ML, Dave JR, Tortella FC. Characterization of a new rat model of penetrating ballistic brain injury. *J Neurotrauma.* (2005) 22:313–31. doi: 10.1089/neu.2005.22.313
17. Williams AJ, Hartings JA, Lu XCM, Rolli ML, Tortella FC. Penetrating ballistic-like brain injury in the rat: differential time courses of hemorrhage, cell death, inflammation, and remote degeneration. *J Neurotrauma.* (2006) 23:1828–46. doi: 10.1089/neu.2006.23.1828
18. Williams AJ, Ling GSF, Tortella FC. Severity level and injury track determine outcome following a penetrating ballistic-like brain injury in the rat. *Neurosci Lett.* (2006) 408:183–8. doi: 10.1016/j.neulet.2006.08.086
19. Williams AJ, Wei HH, Dave JR, Tortella FC. Acute and delayed neuroinflammatory response following experimental penetrating ballistic brain injury in the rat. *J Neuroinflammation.* (2007) 4:17. doi: 10.1186/1742-2094-4-17
20. Dail WG, Feeney DM, Murray HM, Linn RT, Boyeson MG. Responses to cortical injury: II. Widespread depression of the activity of an enzyme in cortex remote from a focal injury. *Brain Res.* (1981) 211:79–89. doi: 10.1016/0006-8993(81)90068-8
21. Feeney DM, Boyeson MG, Linn RT, Murray HM, Dail WG. Responses to cortical injury: I. Methodology and local effects of contusions in the rat. *Brain Res.* (1981) 211:67–77. doi: 10.1016/0006-8993(81)90067-6
22. Morales DM, Marklund N, Lebold D, Thompson HJ, Pitkanen A, Maxwell WL, et al. Experimental models of traumatic brain injury: do we really need to build a better mousetrap? *Neuroscience.* (2005) 136:971–89. doi: 10.1016/j.neuroscience.2005.08.030
23. Smith DH, Soares HD, Pierce JS, Perlman KG, Saatman KE, Meaney DF, et al. A model of parasagittal controlled cortical impact in the mouse: cognitive and histopathologic effects. *J Neurotrauma.* (1995) 12:169–78. doi: 10.1089/neu.1995.12.169
24. Hall ED, Sullivan PG, Gibson TR, Pavel KM, Thompson BM, Scheff SW. Spatial and temporal characteristics of neurodegeneration after controlled cortical impact in mice: more than a focal brain injury. *J Neurotrauma.* (2005) 22:252–65. doi: 10.1089/neu.2005.22.252
25. Mao H, Zhang L, Yang KH, King AI. Application of a finite element model of the brain to study traumatic brain injury mechanisms in the rat. *Stapp Car Crash J.* (2006) 50:583–600. doi: 10.4271/2006-22-0022
26. Fox GB, Fan L, Levasseur RA, Faden AI. Sustained sensory/motor and cognitive deficits with neuronal apoptosis following controlled cortical impact brain injury in the mouse. *J Neurotrauma.* (1998) 15:599–614. doi: 10.1089/neu.1998.15.599
27. Dixon CE, Kochanek PM, Yan HQ, Schiding JK, Griffith RG, Baum E, et al. One-year study of spatial memory performance, brain morphology, and cholinergic markers after moderate controlled cortical impact in rats. *J Neurotrauma.* (1999) 16:109–22. doi: 10.1089/neu.1999.16.109
28. Dixon CE, Kraus MF, Kline AE, Ma X, Yan HQ, Griffith RG, et al. Amantadine improves water maze performance without affecting motor behavior following traumatic brain injury in rats. *Restor Neurol Neurosci.* (1999) 14:285–94. doi: 10.3233/RNN-1999-00099
29. Washington PM, Forcelli PA, Wilkins T, Zapple DN, Parsadanian M, Burns MP. The effect of injury severity on behavior: a phenotypic study of cognitive and emotional deficits after mild, moderate, and severe controlled cortical impact injury in mice. *J Neurotrauma.* (2012) 29:2283–96. doi: 10.1089/neu.2012.2456
30. Goodman JC, Cherian L, Bryan RMJ, Robertson CS. Lateral cortical impact injury in rats: pathologic effects of varying cortical compression and impact velocity. *J Neurotrauma.* (1994) 11:587–97. doi: 10.1089/neu.1994.11.587
31. Saatman KE, Feeko KJ, Pape RL, Raghupathi R. Differential behavioral and histopathological responses to graded cortical impact injury in mice. *J Neurotrauma.* (2006) 23:1241–53. doi: 10.1089/neu.2006.23.1241
32. Alessandri B, Heimann A, Filippi R, Kopacz L, Kempinski O. Moderate controlled cortical contusion in pigs: effects on multi-parametric neuromonitoring and clinical relevance. *J Neurotrauma.* (2003) 20:1293–305. doi: 10.1089/089771503322686094
33. Kochanek PM, Hendrich KS, Dixon CE, Schiding JK, Williams DS, Ho C. Cerebral blood flow at one year after controlled cortical impact in rats: assessment by magnetic resonance imaging. *J Neurotrauma.* (2002) 19:1029–37. doi: 10.1089/089771502760341947
34. Graham DI, McIntosh TK, Maxwell WL, Nicoll JA. Recent advances in neurotrauma. *J Neuropathol Exp Neurol.* (2000) 59:641–51. doi: 10.1093/jnen/59.8.641
35. Hicks R, Soares H, Smith D, McIntosh T. Temporal and spatial characterization of neuronal injury following lateral fluid-percussion brain injury in the rat. *Acta Neuropathol.* (1996) 91:236–46. doi: 10.1007/s004010050421
36. Bramlett HM, Dietrich WD. Quantitative structural changes in white and gray matter 1 year following traumatic brain injury in rats. *Acta Neuropathol.* (2002) 103:607–14. doi: 10.1007/s00401-001-0510-8
37. Liu YR, Cardamone L, Hogan RE, Gregoire MC, Williams JP, Hicks RJ, et al. Progressive metabolic and structural cerebral perturbations after traumatic brain injury: an in vivo imaging study in the rat. *J Nucl Med.* (2010) 51:1788–95. doi: 10.2967/jnumed.110.078626
38. Lew HL, Poole JH, Guillory SB, Salerno RM, Leskin G, Sigford B. Persistent problems after traumatic brain injury: the need for long-term follow-up and coordinated care. *J Rehabil Res Dev.* (2006) 43:vii–x. doi: 10.1682/jrrd.2006.05.0054
39. Rowe RK, Harrison JL, O'Hara BF, Lifshitz J. Diffuse brain injury does not affect chronic sleep patterns in the mouse. *Brain Inj.* (2014) 28:504–10. doi: 10.3109/02699052.2014.888768
40. Sharp DJ, Scott G, Leech R. Network dysfunction after traumatic brain injury. *Nat Rev Neurol.* (2014) 10:156–66. doi: 10.1038/nrnneurol.2014.15
41. Sandsmark DK, Elliott JE, Lim MM. Sleep-Wake disturbances after traumatic brain injury: synthesis of human and animal studies. *Sleep.* (2017) 40:zsx044. doi: 10.1093/sleep/zsx044
42. Lim MM, Elkind J, Xiong G, Galante R, Zhu J, Zhang L, et al. Dietary therapy mitigates sleep deficits caused by mild traumatic brain injury. *Sci Transl Med.* (2013) 5:215ra173. doi: 10.1126/scitranslmed.3007092
43. Stemper BD, Shah AS, Pintar FA, McCrea M, Kurpad SN, Glavaski-Joksimovic A, et al. Head rotational acceleration characteristics influence behavioral and diffusion tensor imaging outcomes following concussion. *Ann Biomed Eng.* (2015) 43:1071–88. doi: 10.1007/s10439-014-1171-9
44. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma.* (1993) 34:216–22. doi: 10.1097/00005373-199302000-00006
45. Dennis AM, Haselkorn ML, Vagni VA, Garman RH, Janesko-Feldman K, Bayir H, et al. Hemorrhagic shock after experimental traumatic brain injury in mice: effect on neuronal death. *J Neurotrauma.* (2009) 26:889–99. doi: 10.1089/neu.2008.0512
46. Simon DW, Vagni VM, Kochanek PM, Clark RSB. Combined Neurotrauma Models: Experimental Models Combining Traumatic Brain Injury and Secondary Insults. *Methods Mol Biol.* (2016) 1462:393–411. doi: 10.1007/978-1-4939-3816-2_22
47. Soliman E, Gudenschwager Basso EK, Ju J, Willison A, Theus MH. Skull bone marrow-derived immune cells infiltrate the injured cerebral cortex and exhibit anti-inflammatory properties. *Brain Behav Immun.* (2025) 123:244–53. doi: 10.1016/j.bbi.2024.09.023
48. Goodman MD, Makley AT, Huber NL, Clarke CN, Friend LAW, Schuster RM, et al. Hypobaric hypoxia exacerbates the neuroinflammatory response to traumatic brain injury. *J Surg Res.* (2011) 165:30–7. doi: 10.1016/j.jss.2010.05.055
49. Yan EB, Hellewell SC, Bellander BM, Agyapomaa DA, Morganti-Kossmann MC. Post-traumatic hypoxia exacerbates neurological deficit, neuroinflammation and

cerebral metabolism in rats with diffuse traumatic brain injury. *J Neuroinflammation*. (2011) 8:147. doi: 10.1186/1742-2094-8-147

50. Tang J, Kang Y, Zhou Y, Shang N, Li X, Wang H, et al. TIMP2 ameliorates blood-brain barrier disruption in traumatic brain injury by inhibiting Src-dependent VE-cadherin internalization. *J Clin Invest*. (2024) 134:e164199. doi: 10.1172/JCI164199

51. Hay JR, Johnson VE, Young AMH, Smith DH, Stewart W. Blood-brain barrier disruption is an early event that may persist for many years after traumatic brain injury in humans. *J Neuropathol Exp Neurol*. (2015) 74:1147–57. doi: 10.1097/NEN.0000000000000261

52. Simon DW, McGeachy MJ, Bayir H, Clark RSB, Loane DJ, Kochanek PM. The far-reaching scope of neuroinflammation after traumatic brain injury. *Nat Rev Neurol*. (2017) 13:171–91. doi: 10.1038/nrneurol.2017.13

53. Price L, Wilson C, Grant G. Blood–brain barrier pathophysiology following traumatic brain injury In: Translational research in traumatic brain injury. Boca Raton, FL: CRC Press/Taylor and Francis Group (2016)

54. Toutouji A, Krieg C, Borucki DM, Mandava M, Guglietta S, Tomlinson S. Mass cytometric analysis of the immune cell landscape after traumatic brain injury elucidates the role of complement and complement receptors in neurologic outcomes. *Acta Neuropathol Commun*. (2023) 11:92. doi: 10.1186/s40478-023-01583-0

55. Liesz A, Dalpke A, Mracsko E, Antoine DJ, Roth S, Zhou W, et al. DAMP signaling is a key pathway inducing immune modulation after brain injury. *J Neurosci*. (2015) 35:583–98. doi: 10.1523/JNEUROSCI.2439-14.2015

56. Choo AM, Miller WJ, Chen YC, Nibley P, Patel TP, Goletiani C, et al. Antagonism of purinergic signalling improves recovery from traumatic brain injury. *Brain*. (2013) 136:65–80. doi: 10.1093/brain/awt286

57. Thelin EP, Hall CE, Gupta K, Carpenter KLH, Chandran S, Hutchinson PJ, et al. Elucidating pro-inflammatory cytokine responses after traumatic brain injury in a human stem cell model. *J Neurotrauma*. (2018) 35:341–52. doi: 10.1089/neu.2017.5155

58. Mouzon BC, Bachmeier C, Ferro A, Ojo JO, Crynen G, Acker CM, et al. Chronic neuropathological and neurobehavioral changes in a repetitive mild traumatic brain injury model. *Ann Neurol*. (2014) 75:241–54. doi: 10.1002/ana.24064

59. Abikenari MA, Enayati I, Fountain DM, Leite MI. Navigating glioblastoma therapy: a narrative review of emerging immunotherapeutics and small-molecule inhibitors. *Microbes Immun*. (2024) 5075. doi: 10.36922/mi.5075

60. Abikenari M, Schonfeld E, Choi J, Kim LH, Lim M. Revisiting glioblastoma classification through an immunological lens: a narrative review. *Glioma*. (2024) 7:3–9. doi: 10.4103/glioma.glioma_4_24

61. Oft HC, Simon DW, Sun D. New insights into metabolism dysregulation after TBI. *J Neuroinflammation*. (2024) 21:184 2024 Jul 29. doi: 10.1186/s12974-024-03177-6

62. Medikonda R, Abikenari M, Schonfeld E, Lim M. The metabolic orchestration of immune evasion in glioblastoma: from molecular perspectives to therapeutic vulnerabilities. *Cancers*. (2025) 17:1881. doi: 10.3390/cancers17111881

63. Yoon SH, Kim CY, Lee E, Lee C, Lee KS, Lee J, et al. Microglial NLRP3-gasdermin D activation impairs blood-brain barrier integrity through interleukin-1 β -independent neutrophil chemotaxis upon peripheral inflammation in mice. *Nat Commun*. (2025) 16:699. doi: 10.1038/s41467-025-56097-1

64. Yi JH, Pow DV, Hazell AS. Early loss of the glutamate transporter splice-variant GLT-1v in rat cerebral cortex following lateral fluid-percussion injury. *Glia*. (2005) 49:121–33. doi: 10.1002/glia.20099

65. van Landeghem FKH, Weiss T, Oehmichen M, von Deimling A. Decreased expression of glutamate transporters in astrocytes after human traumatic brain injury. *J Neurotrauma*. (2006) 23:1518–28. doi: 10.1089/neu.2006.23.1518

66. Perez EJ, Tapanes SA, Loris ZB, Balu DT, Sick TJ, Coyle JT, et al. Enhanced astrocytic D-serine underlies synaptic damage after traumatic brain injury. *J Clin Invest*. (2017) 127:3114–25. doi: 10.1172/JCI92300

67. Zhang X, Wang D, Zhang B, Zhu J, Zhou Z, Cui L. Regulation of microglia by glutamate and its signal pathway in neurodegenerative diseases. *Drug Discov Today*. (2020) 25:1074–85. doi: 10.1016/j.drudis.2020.04.001

68. Argaw AT, Asp L, Zhang J, Navrazhina K, Pham T, Mariani JN, et al. Astrocyte-derived VEGF-A drives blood-brain barrier disruption in CNS inflammatory disease. *J Clin Invest*. (2012) 122:2454–68. doi: 10.1172/JCI60842

69. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, et al. Apolipoprotein E controls cerebrovascular integrity via cyclophilin a. *Nature*. (2012) 485:512–6. doi: 10.1038/nature11087

70. Xing G, Zhao T, Zhang X, Li H, Li X, Cui P, et al. Astrocytic sonic hedgehog alleviates intracerebral hemorrhagic brain injury via modulation of blood-brain barrier integrity. *Front Cell Neurosci*. (2020) 14:575690. doi: 10.3389/fncel.2020.575690

71. Mizze MR, Nijland PG, van der Pol SMA, Drexhage JAR, van het Hof B, Mebius R, et al. Astrocyte-derived retinoic acid: a novel regulator of blood-brain barrier function in multiple sclerosis. *Acta Neuropathol (Berl)*. (2014) 128:691–703. doi: 10.1007/s00401-014-1335-6

72. Myer DJ, Gurkoff GG, Lee SM, Hovda DA, Sofroniew MV. Essential protective roles of reactive astrocytes in traumatic brain injury. *Brain*. (2006) 129:2761–72. doi: 10.1093/brain/awl165

73. Korotkov A, Puhakka N, Gupta SD, Vuokila N, Broekaart DWM, Anink JJ, et al. Increased expression of miR142 and miR155 in glial and immune cells after traumatic

brain injury may contribute to neuroinflammation via astrocyte activation. *Brain Pathol*. (2020) 30:897–912. doi: 10.1111/bpa.12865

74. Jin X, Ishii H, Bai Z, Itokazu T, Yamashita T. Temporal changes in cell marker expression and cellular infiltration in a controlled cortical impact model in adult male C57BL/6 mice. *PLoS One*. (2012) 7:e41892. doi: 10.1371/journal.pone.0041892

75. Zhang J, Li Y, Duan Z, Kang J, Chen K, Li G, et al. The effects of the M2a macrophage-induced axonal regeneration of neurons by arginase 1. *Biosci Rep*. (2020) 40:BSR20193031. doi: 10.1042/BSR20193031

76. Kigerl KA, Gensel JC, Ankeny DP, Alexander JK, Donnelly DJ, Popovich PG. Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. *J Neurosci*. (2009) 29:13435–44. doi: 10.1523/JNEUROSCI.3257-09.2009

77. Hsieh CL, Kim CC, Ryba BE, Niemi EC, Bando JK, Locksley RM, et al. Traumatic brain injury induces macrophage subsets in the brain. *Eur J Immunol*. (2013) 43:2010–22. doi: 10.1002/eji.201243084

78. Makinde HM, Cuda CM, Just TB, Perlman HR, Schwulst SJ. Nonclassical monocytes mediate secondary injury, neurocognitive outcome, and neutrophil infiltration after traumatic brain injury. *J Immunol*. (2017) 199:3583–91. doi: 10.4049/jimmunol.1700896

79. Vaibhav K, Braun M, Alverson K, Khodadadi H, Kutiyanawalla A, Ward A, et al. Neutrophil extracellular traps exacerbate neurological deficits after traumatic brain injury. *Sci Adv*. (2020) 6:eaa8847. doi: 10.1126/sciadv.aax8847

80. French HM, Reid M, Mamontov P, Simmons RA, Grinspan JB. Oxidative stress disrupts oligodendrocyte maturation. *J Neurosci Res*. (2009) 87:3076–87. doi: 10.1002/jnr.22139

81. Ozen I, Ruscher K, Nilsson R, Flygt J, Clausen F, Marklund N. Interleukin-1 Beta neutralization attenuates traumatic brain injury-induced microglia activation and neuronal changes in the Globus Pallidus. *Int J Mol Sci*. (2020) 21:387. doi: 10.3390/ijms21020387

82. Baratz R, Tweedie D, Wang JY, Rubovitch V, Luo W, Hoffer BJ, et al. Transiently lowering tumor necrosis factor- α synthesis ameliorates neuronal cell loss and cognitive impairments induced by minimal traumatic brain injury in mice. *J Neuroinflammation*. (2015) 12:45. doi: 10.1186/s12974-015-0237-4

83. Yshii L, Pasciuto E, Bielefeld P, Mascali L, Lemaitre P, Marino M, et al. Astrocyte-targeted gene delivery of interleukin 2 specifically increases brain-resident regulatory T cell numbers and protects against pathological neuroinflammation. *Nat Immunol*. (2022) 23:878–91. doi: 10.1038/s41590-022-01208-z

84. Sen T, Saha P, Gupta R, Foley LM, Jiang T, Abakumova OS, et al. Aberrant ER stress induced neuronal-IFN β elicits white matter injury due to microglial activation and T-cell infiltration after TBI. *J Neurosci*. (2020) 40:424–46. doi: 10.1523/JNEUROSCI.0718-19.2019

85. Xiong X, Barreto GE, Xu L, Ouyang YB, Xie X, Giffard RG. Increased brain injury and worsened neurological outcome in interleukin-4 knockout mice after transient focal cerebral ischemia. *Stroke*. (2011) 42:2026–32. doi: 10.1161/STROKEAHA.110.593772

86. Gimsa U, Wolf SA, Haas D, Bechmann I, Nitsch R. Th2 cells support intrinsic anti-inflammatory properties of the brain. *J Neuroimmunol*. (2001) 119:73–80. doi: 10.1016/S0165-5728(01)00343-5

87. Li T, Zhang YM, Han D, Hua R, Guo BN, Hu SQ, et al. Involvement of IL-17 in secondary brain injury after a traumatic brain injury in rats. *NeuroMolecular Med*. (2017) 19:541–54. doi: 10.1007/s12017-017-8468-4

88. Newell-Rogers MK, Duong A, Nazarali R, Tobin RP, Rogers SK, Shapiro LA. Unilateral cervical Vagotomy modulates immune cell profiles and the response to a traumatic brain injury. *Int J Mol Sci*. (2022) 23:9851. doi: 10.3390/ijms23179851

89. Needham EJ, Stoevesandt O, Thelin EP, Zetterberg H, Zanier ER, Al Nimer F, et al. Complex autoantibody responses occur following moderate to severe traumatic brain injury. *J Immunol*. (2020):20161786. doi: 10.1101/2020.07.24.20161786

90. Zhang Z, Zoltewicz JS, Mondello S, Newsom KJ, Yang Z, Yang B, et al. Human traumatic brain injury induces autoantibody response against glial fibrillary acidic protein and its breakdown products. *PLoS One*. (2014) 9:e92698. doi: 10.1371/journal.pone.0092698

91. Dwyer LJ, Maheshwari S, Levy E, Poznansky MC, Whalen MJ, Sirbulescu RF. B cell treatment promotes a neuroprotective microenvironment after traumatic brain injury through reciprocal immunomodulation with infiltrating peripheral myeloid cells. *J Neuroinflammation*. (2023) 20:133. doi: 10.1186/s12974-023-02812-y

92. Wang RX, Yu CR, Dambuza IM, Mahdi RM, Dolinska MB, Sergeev YV, et al. Interleukin-35 induces regulatory B cells that suppress CNS autoimmune disease. *Nat Med*. (2014) 20:633–41. doi: 10.1038/nm.3554

93. Kobeissy F, Moshourab RA. Autoantibodies in CNS trauma and neuropsychiatric disorders: a new generation of biomarkers In: FH Kobeissy, editor. Brain Neurotrauma: Molecular, neuropsychological, and rehabilitation aspects. Boca Raton, FL: CRC Press/Taylor & Francis (2015)

94. Planas AM, Gómez-Choco M, Urrea X, Gorina R, Caballero M, Chamorro Á. Brain-derived antigens in lymphoid tissue of patients with acute stroke. *J Immunol*. (2012) 188:2156–63. doi: 10.4049/jimmunol.1102289

95. Xu W, Yue S, Wang P, Wen B, Zhang X. Systemic inflammation in traumatic brain injury predicts poor cognitive function. *Immun Inflamm Dis*. (2022) 10:e577. doi: 10.1002/iid3.577

96. Kumar RG, Boles JA, Wagner AK. Chronic inflammation after severe traumatic brain injury: characterization and associations with outcome at 6 and 12 months postinjury. *J Head Trauma Rehabil.* (2015) 30:369–81. doi: 10.1097/HTR.0000000000000067
97. Samanta RJ, Chiollaz AC, Needham E, Yue JK, Helmy A, Zanier ER, et al. Parsimonious immune-response endotypes and global outcome in patients with traumatic brain injury. *EBioMedicine.* (2024) 108:105310. doi: 10.1016/j.ebiom.2024.105310
98. Haruwaka K, Ikegami A, Tachibana Y, Ohno N, Konishi H, Hashimoto A, et al. Dual microglia effects on blood brain barrier permeability induced by systemic inflammation. *Nat Commun.* (2019) 10:5816. doi: 10.1038/s41467-019-13812-z
99. Hazelton I, Yates A, Dale A, Roodselaar J, Akbar N, Ruitenberg MJ, et al. Exacerbation of acute traumatic brain injury by circulating extracellular vesicles. *J Neurotrauma.* (2018) 35:639–51. doi: 10.1089/neu.2017.5049
100. Sirlulescu RF, Chung JY, Edmiston WJ, Poznansky SA, Poznansky MC, Whalen MJ. Intraparenchymal application of mature B lymphocytes improves structural and functional outcome after contusion traumatic brain injury. *J Neurotrauma.* (2019) 36:2579–89. doi: 10.1089/neu.2018.6368
101. Korley FK, Diaz-Arrastia R, Wu AHB, Yue JK, Manley GT, Sair HI, et al. Circulating brain-derived neurotrophic factor has diagnostic and prognostic value in traumatic brain injury. *J Neurotrauma.* (2016) 33:215–25. doi: 10.1089/neu.2015.3949
102. Chou A, Krukowski K, Morganti JM, Riparip LK, Rosi S. Persistent infiltration and impaired response of peripherally-derived monocytes after traumatic brain injury in the aged brain. *Int J Mol Sci.* (2018) 19:1616. doi: 10.3390/ijms19061616
103. Roquilly A, David G, Cinotti R, Vourc'h M, Morin H, Rozec B, et al. Role of IL-12 in overcoming the low responsiveness of NK cells to missing self after traumatic brain injury. *Clin Immunol.* (2017) 177:87–94. doi: 10.1016/j.clim.2015.08.006
104. Rhind SG, Crnko NT, Baker AJ, Morrison LJ, Shek PN, Scarpelini S, et al. Prehospital resuscitation with hypertonic saline-dextran modulates inflammatory, coagulation and endothelial activation marker profiles in severe traumatic brain injured patients. *J Neuroinflammation.* (2010) 7:5. doi: 10.1186/1742-2094-7-5
105. Liao Y, Liu P, Guo F, Zhang ZY, Zhang Z. Oxidative burst of circulating neutrophils following traumatic brain injury in human. *PLoS One.* (2013) 8:e68963. doi: 10.1371/journal.pone.0068963
106. Kong XD, Bai S, Chen X, Wei HJ, Jin WN, Li MS, et al. Alterations of natural killer cells in traumatic brain injury. *Neurosci Bull.* (2014) 30:903–12. doi: 10.1007/s12264-014-1481-9
107. Schwulst SJ, Trahanas DM, Saber R, Perlman H. Traumatic brain injury-induced alterations in peripheral immunity. *J Trauma Acute Care Surg.* (2013) 75:780–8. doi: 10.1097/TA.0b013e318299616a
108. Mazzeo AT, Kunene NK, Gilman CB, Hamm RJ, Hafez N, Bullock MR. Severe human traumatic brain injury, but not Cyclosporin A treatment, depresses activated T lymphocytes early after injury. *J Neurotrauma.* (2006) 23:962–75. doi: 10.1089/neu.2006.23.962
109. Wang Z, Chen G. Immune regulation in neurovascular units after traumatic brain injury. *Neurobiol Dis.* (2023) 179:106060. doi: 10.1016/j.nbd.2023.106060
110. Yang Y, Ye Y, Chen C, Kong C, Su X, Zhang X, et al. Acute traumatic brain injury induces CD4+ and CD8+ T cell functional impairment by upregulating the expression of PD-1 via the activated sympathetic nervous system. *Neuroimmunomodulation.* (2019) 26:43–57. doi: 10.1159/000495465
111. Al-Khateeb ZF, Boumenar H, Adebimpe J, Shekerzade S, Henson SM, Tremoleda JL, et al. The cellular senescence response and neuroinflammation in juvenile mice following controlled cortical impact and repetitive mild traumatic brain injury. *Exp Neurol.* (2024) 374:114714. doi: 10.1016/j.expneurol.2024.114714
112. Guber IG, Russell AL, Shick TJ, Vagni VA, Carlson JC, Kochanek PM, et al. Exploratory assessment of the effect of systemic administration of soluble glycoprotein 130 on cognitive performance and chemokine levels in a mouse model of experimental traumatic brain injury. *J Neuroinflammation.* (2024) 21:149. doi: 10.1186/s12974-024-03129-0
113. Lagraoui M, Latoche JR, Cartwright NG, Sukumar G, Dalgard CL, Schaefer BC. Controlled cortical impact and craniotomy induce strikingly similar profiles of inflammatory gene expression, but with distinct kinetics. *Front Neurol.* (2012) 3:155. doi: 10.3389/fneur.2012.00155
114. Chen Y, Wang Y, Xu J, Hou T, Zhu J, Jiang Y, et al. Multiplex assessment of serum chemokines CCL2, CCL5, CXCL1, CXCL10, and CXCL13 following traumatic brain injury. *Inflammation.* (2023) 46:244–55. doi: 10.1007/s10753-022-01729-7
115. Kumar RG, Diamond ML, Boles JA, Berger RP, Tisherman SA, Kochanek PM, et al. Acute CSF interleukin-6 trajectories after TBI: associations with neuroinflammation, polytrauma, and outcome. *Brain Behav Immun.* (2015) 45:253–62. doi: 10.1016/j.bbi.2014.12.021
116. Helmy A, Carpenter KLH, Menon DK, Pickard JD, Hutchinson PJA. The cytokine response to human traumatic brain injury: temporal profiles and evidence for cerebral parenchymal production. *J Cereb Blood Flow Metab.* (2011) 31:658–70. doi: 10.1038/jcbfm.2010.142
117. Alawieh A, Langley EF, Weber S, Adkins D, Tomlinson S. Identifying the role of complement in triggering neuroinflammation after traumatic brain injury. *J Neurosci.* (2018) 38:2519–32. doi: 10.1523/JNEUROSCI.2197-17.2018
118. Witcher KG, Bray CE, Chunchai T, Zhao F, O'Neil SM, Gordillo AJ, et al. Traumatic brain injury causes chronic cortical inflammation and neuronal dysfunction mediated by microglia. *J Neurosci.* (2021) 41:1597–616. doi: 10.1523/JNEUROSCI.2469-20.2020
119. Toutonji A, Mandava M, Guglietta S, Tomlinson S. Chronic complement dysregulation drives neuroinflammation after traumatic brain injury: a transcriptomic study. *Acta Neuropathol Commun.* (2021) 9:126. doi: 10.1186/s40478-021-01226-2
120. Ritzel RM, Doran SJ, Barrett JP, Henry RJ, Ma EL, Faden AI, et al. Chronic alterations in systemic immune function after traumatic brain injury. *J Neurotrauma.* (2018) 35:1419–36. doi: 10.1089/neu.2017.5399
121. Loane DJ, Kumar A, Stoica BA, Cabatbat R, Faden AI. Progressive neurodegeneration after experimental brain trauma: association with chronic microglial activation. *J Neuropathol Exp Neurol.* (2014) 73:14–29. doi: 10.1097/NEN.0000000000000021
122. Ramlackhansingh AF, Brooks DJ, Greenwood RJ, Bose SK, Turkheimer FE, Kinnunen KM, et al. Inflammation after trauma: microglial activation and traumatic brain injury. *Ann Neurol.* (2011) 70:374–83. doi: 10.1002/ana.22455
123. Deshetty UM, Periyasamy P. Potential biomarkers in experimental animal models for traumatic brain injury. *J Clin Med.* (2023) 12:3923. doi: 10.3390/jcm12123923
124. Humphries DC, O'Neill S, Scholefield E, Dorward DA, Mackinnon AC, Rossi AG, et al. Cerebral concussion primes the lungs for subsequent neutrophil-mediated injury. *Crit Care Med.* (2018) 46:e937–44. doi: 10.1097/CCM.00000000000003270
125. Li L, Peng R, Wang C, Chen X, Gheyret D, Guan S, et al. B2 integrin regulates neutrophil trans endothelial migration following traumatic brain injury. *Cell Commun Signal.* (2025) 23:70. doi: 10.1186/s12964-025-02071-9
126. Keeling KL, Hicks RR, Mahesh J, Billings BB, Kotwal GJ. Local neutrophil influx following lateral fluid-percussion brain injury in rats is associated with accumulation of complement activation fragments of the third component (C3) of the complement system. *J Neuroimmunol.* (2000) 105:20–30. doi: 10.1016/s0165-5728(00)00183-1
127. Junger WG, Rhind SG, Rizoli SB, Cuschieri J, Baker AJ, Shek PN, et al. Pre-hospital hypertonic saline resuscitation attenuates the activation and promotes apoptosis of neutrophils in patients with severe traumatic brain injury. *Shock Augusta Ga.* (2013) 40:366–74. doi: 10.1097/SHK.0000000000000038
128. Witcher KG, Dziabis JE, Bray CE, Gordillo AJ, Kumar JE, Eiferman DS, et al. Comparison between midline and lateral fluid percussion injury in mice reveals prolonged but divergent cortical neuroinflammation. *Brain Res.* (2020) 1746:146987. doi: 10.1016/j.brainres.2020.146987
129. Frugier T, Morganti-Kossmann MC, O'Reilly D, McLean CA. In situ detection of inflammatory mediators in post mortem human brain tissue after traumatic injury. *J Neurotrauma.* (2010) 27:497–507. doi: 10.1089/neu.2009.1120
130. Qin X, Miwa T, Aktas H, Gao M, Lee C, Qian YM, et al. Genomic structure, functional comparison, and tissue distribution of mouse Cd59a and Cd59b. *Mamm Genome.* (2001) 12:582–9. doi: 10.1007/s00335-001-2060-8
131. Koblansky AA, Jankovic D, Oh H, Hienny S, Sungnak W, Mathur R, et al. Recognition of profilin by toll-like receptor 12 is critical for host resistance to *Toxoplasma gondii*. *Immunity.* (2013) 38:119–30. doi: 10.1016/j.immuni.2012.09.016
132. Szabo PA, Goswami A, Mazzuca DM, Kim K, O'Gorman DB, Hess DA, et al. Rapid and rigorous IL-17A production by a distinct subpopulation of effector memory T lymphocytes constitutes a novel mechanism of toxic shock syndrome immunopathology. *J Immunol.* (2017) 198:2805–18. doi: 10.4049/jimmunol.1601366
133. Davies M, Jacobs A, Brody DL, Friess SH. Delayed hypoxemia after traumatic brain injury exacerbates long-term behavioral deficits. *J Neurotrauma.* (2018) 35:790–801. doi: 10.1089/neu.2017.5354
134. Oh SK, Park HJ, Yu GG, Jeong SH, Lee SW, Kim H. Secondary hypoxic ischemia alters neurobehavioral outcomes, neuroinflammation, and oxidative stress in mice exposed to controlled cortical impact. *Clin Exp Emerg Med.* (2021) 8:216–28. doi: 10.15441/ceem.20.124
135. Price AD, Baucom MR, Becker ER, Archdeacon CM, Smith MP, Caskey C, et al. Systemic inflammatory effect of Hypobaric during aeromedical evacuation after porcine traumatic brain injury. *J Am Coll Surg.* (2024) 239:430–42. doi: 10.1097/XCS.0000000000001119
136. Yan C, Yan H, Mao J, Liu Y, Xu L, Zhao H, et al. Neuroprotective effect of Oridonin on traumatic brain injury via inhibiting NLRP3 inflammasome in experimental mice. *Front Neurosci.* (2020) 14:14. doi: 10.3389/fnins.2020.557170
137. Xu X, Yin D, Ren H, Gao W, Li F, Sun D, et al. Selective NLRP3 inflammasome inhibitor reduces neuroinflammation and improves long-term neurological outcomes in a murine model of traumatic brain injury. *Neurobiol Dis.* (2018) 117:15–27. doi: 10.1016/j.nbd.2018.05.016
138. Lassarén P, Lindblad C, Frostell A, Carpenter KLH, Guilfoyle MR, Hutchinson PJA, et al. Systemic inflammation alters the neuroinflammatory response: a prospective clinical trial in traumatic brain injury. *J Neuroinflammation.* (2021) 18:221. doi: 10.1186/s12974-021-02264-2
139. Benhamou Y, Miranda S, Armengol G, Harouki N, Drouot L, Zahr N, et al. Infliximab improves endothelial dysfunction in a mouse model of antiphospholipid syndrome: role of reduced oxidative stress. *Vasc Pharmacol.* (2015) 71:93–101. doi: 10.1016/j.vph.2015.03.014

140. Zhou Y, Fan R, Botchway BOA, Zhang Y, Liu X. Infliximab can improve traumatic brain injury by suppressing the tumor necrosis factor alpha pathway. *Mol Neurobiol.* (2021) 58:2803–11. doi: 10.1007/s12035-021-02293-1
141. Chen M, Edwards SR, Maskey D, Woodruff TM, Tomlinson S, Reutens D. Complement component 5 (C5) deficiency improves cognitive outcome after traumatic brain injury and enhances treatment effects of complement inhibitors C1-Inh and CR2-Crry in a mouse model. *Neurotrauma Rep.* (2023) 4:663–81. doi: 10.1089/neur.2023.0024
142. Koopman I, Tack RW, Wunderink HF, Bruns AH, van der Schaaf IC, Cianci D, et al. Safety and pharmacodynamic efficacy of eculizumab in aneurysmal subarachnoid hemorrhage (CLASH): a phase 2a randomized clinical trial. *Eur Stroke J.* (2023) 8:1097–106. doi: 10.1177/23969873231194123
143. Abou-El-Hassan H, Rezende RM, Izzy S, Gabriely G, Yahya T, Tatematsu BK, et al. Vγ1 and Vγ4 gamma-delta T cells play opposing roles in the immunopathology of traumatic brain injury in males. *Nat Commun.* (2023) 14:4286. doi: 10.1038/s41467-023-39857-9
144. Daglas M, Draxler DF, Ho H, McCutcheon F, Galle A, Au AE, et al. Activated CD8+ T cells cause long-term neurological impairment after traumatic brain injury in mice. *Cell Rep.* (2019) 29:1178–1191.e6. doi: 10.1016/j.celrep.2019.09.046
145. Chen Y, Li J, Ma B, Li N, Wang S, Sun Z, et al. MSC-derived exosomes promote recovery from traumatic brain injury via microglia/macrophages in rat. *Aging.* (2020) 12:18274–96. doi: 10.18632/aging.103692
146. Chen Q, Xu L, Du T, Hou Y, Fan W, Wu Q, et al. Enhanced expression of PD-L1 on microglia after surgical brain injury exerts self-protection from inflammation and promotes neurological repair. *Neurochem Res.* (2019) 44:2470–81. doi: 10.1007/s11064-019-02864-8
147. Gao X, Li W, Syed F, Yuan F, Li P, Yu Q. PD-L1 signaling in reactive astrocytes counteracts neuroinflammation and ameliorates neuronal damage after traumatic brain injury. *J Neuroinflammation.* (2022) 19:43. doi: 10.1186/s12974-022-02398-x
148. Abikenari M, Liu J, Ha JH, Annagiri S, Himic V, Medikonda R, et al. Emerging trends in cell-based therapies: contemporary advances and ethical considerations in translational neurosurgical oncology. *J Neuro-Oncol.* (2025) 175:1–20. doi: 10.1007/s11060-025-05170-2
149. Yang R, Chen Z, Cai J. Fecal microbiota transplantation: emerging applications in autoimmune diseases. *J Autoimmun.* (2023) 141:103038. doi: 10.1016/j.jaut.2023.103038
150. Bistas KG, Tabet JP. The benefits of prebiotics and probiotics on mental health. *Cureus.* (2023) 15:e43217. doi: 10.7759/cureus.43217
151. George AK, Behera J, Homme RP, Tyagi N, Tyagi SC, Singh M. Rebuilding microbiome for mitigating traumatic brain injury: importance of restructuring the gut-microbiome-brain axis. *Mol Neurobiol.* (2021) 58:3614–27. doi: 10.1007/s12035-021-02357-2
152. Xuan ToMohamed A, Cumming P, Nasrallah FA. Diffusion tensor imaging and plasma immunological biomarker panel in a rat traumatic brain injury (TBI) model and in human clinical TBI. *Front Immunol.* (2023) 14:1293471. doi: 10.3389/fimmu.2023.1293471
153. Vella MA, Crandall ML, Patel MB. Acute Management of Traumatic Brain Injury. *Surg Clin North Am.* (2017) 97:1015–30. doi: 10.1016/j.suc.2017.06.003
154. Abikenari MA (2024). Experimental models of traumatic brain injury: Controlled cortical impact and fluid percussion injury models and secondary neurologic insults as predictive models in treatment strategy. OSF Preprints. Available online at: https://osf.io/preprints/osf/ds36x_v1 (Accessed July 25, 2024).
155. Thapa K, Khan H, Singh TG, Kaur A. Traumatic brain injury: mechanistic insight on pathophysiology and potential therapeutic targets. *J Mol Neurosci.* (2021) 71:1725–42. doi: 10.1007/s12031-021-01841-7
156. Vourc'h M, Roquilly A, Asehnoune K. Trauma-induced damage-associated molecular patterns-mediated remote organ injury and immunosuppression in the acutely ill patient. *Front Immunol.* (2018) 9:1330. doi: 10.3389/fimmu.2018.01330
157. Wagner AK, Bayir H, Ren D, Puccio A, Zafonte RD, Kochanek PM. Relationships between cerebrospinal fluid markers of excitotoxicity, ischemia, and oxidative damage after severe TBI: the impact of gender, age, and hypothermia. *J Neurotrauma.* (2004) 21:125–36. doi: 10.1089/089771504322778596
158. Kostyunina OV, Komolotsev IG, Timokhova AV, Belikova AA, Balan SI, Gulyaeva NV. Biomarkers of brain cell-specific immune mechanisms and their translational potential: state of the evidence for traumatic brain injury. *Neurochem J.* (2024) 18:752–62. doi: 10.1134/S1819712424700557
159. Chodobski A, Zink BJ, Szmydynger-Chodobska J. Blood-brain barrier pathophysiology in traumatic brain injury. *Transl Stroke Res.* (2011) 2:492–516. doi: 10.1007/s12975-011-0125-x
160. Stanimirovic DB, Wong J, Shapiro A, Durkin JP. Increase in surface expression of ICAM-1, VCAM-1 and E-selectin in human cerebrovascular endothelial cells subjected to ischemia-like insults. *Acta Neurochir Suppl.* (1997) 70:12–6. doi: 10.1007/978-3-7091-6837-0_4
161. Bouras M, Asehnoune K, Roquilly A. Immune modulation after traumatic brain injury. *Front Med.* (2022) 9:995044. doi: 10.3389/fmed.2022.995044
162. Wu H, Zheng J, Xu S, Fang Y, Wu Y, Zeng J, et al. Mer regulates microglial/macrophage M1/M2 polarization and alleviates neuroinflammation following traumatic brain injury. *J Neuroinflammation.* (2021) 18:2. doi: 10.1186/s12974-020-02041-7
163. Xu H, Wang Z, Li J, Wu H, Peng Y, Fan L, et al. The polarization states of microglia in TBI: a new paradigm for pharmacological intervention. *Neural Plast.* (2017) 2017:1–11. doi: 10.1155/2017/5405104
164. Khatiri N, Thakur M, Pareek V, Kumar S, Sharma S, Datusalia AK. Oxidative stress: major threat in traumatic brain injury. *CNS Neurol Disord Drug Targets.* (2018) 17:689–95. doi: 10.2174/1871527317666180627120501
165. Smith AN, Shaughnessy M, Collier S, Hopkins D, Byrnes KR. Therapeutic targeting of microglia mediated oxidative stress after neurotrauma. *Front Med.* (2022) 9:1034692. doi: 10.3389/fmed.2022.1034692
166. Lu XY, Wang HD, Xu JG, Ding K, Li T. Deletion of Nrf2 exacerbates oxidative stress after traumatic brain injury in mice. *Cell Mol Neurobiol.* (2015) 35:713–21. doi: 10.1007/s10571-015-0167-9
167. Cardona-Collazos S, Gonzalez WD, Pabon-Tsakamoto P, Gao GY, Younsi A, Paiva WS, et al. Cerebral edema in traumatic brain injury. *Biomedicine.* (2025) 13:1728. doi: 10.3390/biomedicine13071728
168. Czyżewski W, Litak J, Sobstyl J, Mandat T, Torres K, Staśkiewicz G. Aquaporins: gatekeepers of fluid dynamics in traumatic brain injury. *Int J Mol Sci.* (2024) 25:6553. doi: 10.3390/ijms25126553
169. Osier N, Dixon CE. The controlled cortical impact model of experimental brain trauma: Overview, research applications, and protocol. *Methods Mol Biol.* (2016) 1462:177–92. doi: 10.1007/978-1-4939-3816-2_11
170. Dalgard CL, Cole JT, Kean WS, Lucky JJ, Sukumar G, McMullen DC, et al. The cytokine temporal profile in rat cortex after controlled cortical impact. *Front Mol Neurosci.* (2012) 5:6. doi: 10.3389/fnmol.2012.00006
171. Mao H, Lu L, Bian K, Clausen F, Colgan N, Gilchrist M. Biomechanical analysis of fluid percussion model of brain injury. *J Biomech.* (2018) 77:228–32. doi: 10.1016/j.jbiomech.2018.07.004
172. Newell EA, Todd BP, Luo Z, Evans LP, Ferguson PJ, Bassuk AG. A mouse model for juvenile, lateral fluid percussion brain injury reveals sex-dependent differences in Neuroinflammation and functional recovery. *J Neurotrauma.* (2020) 37:635–46. doi: 10.1089/neu.2019.6675
173. Ekmark-Lewén S, Flygt J, Kiwanuka O, Meyerson BJ, Lewén A, Hillered L, et al. Traumatic axonal injury in the mouse is accompanied by a dynamic inflammatory response, astroglial reactivity and complex behavioral changes. *J Neuroinflammation.* (2013) 10:44. doi: 10.1186/1742-2094-10-44
174. Khalin I, Jamari NLA, Razak NBA, Jamari NL, Razak NB, Hasain ZB, et al. A mouse model of weight-drop closed head injury: emphasis on cognitive and neurological deficiency. *Neural Regen Res.* (2016) 11:630–5. doi: 10.4103/1673-5374.180749
175. Baracaldo-Santamaría D, Ariza-Salamanca DF, Corrales-Hernández MG, Pachón-Londoño MJ, Hernandez-Duarte I, Calderon-Ospina CA. Revisiting Excitotoxicity in traumatic brain injury: from bench to bedside. *Pharmaceutics.* (2022) 14:152. doi: 10.3390/pharmaceutics14010152
176. Yi HJ, Lee JE, Lee DH, Kim YI, Cho CB, Kim IS, et al. The role of NLRP3 in traumatic brain injury and its regulation by pioglitazone. *J Neurosurg.* (2020) 133:1083–91. doi: 10.3171/2019.6.JNS1954
177. Bhattacharyya S, Zhang X, Feferman L, Johnson D, Tortella FC, Guizzetti M, et al. Decline in arylsulfatase B and increase in chondroitin 4-sulfotransferase combine to increase chondroitin 4-sulfate in traumatic brain injury. *J Neurochem.* (2015) 134:728–39. doi: 10.1111/jnc.13156
178. Shear DA, Lu XCM, Pedersen R, Wei G, Chen Z, Davis A, et al. Severity profile of penetrating ballistic-like brain injury on neurofunctional outcome, blood-brain barrier permeability, and brain edema formation. *J Neurotrauma.* (2011) 28:2185–95. doi: 10.1089/neu.2011.1916
179. Davis AR, Shear DA, Chen Z, Lu XCM, Tortella FC. A comparison of two cognitive test paradigms in a penetrating brain injury model. *J Neurosci Methods.* (2010) 189:84–7. doi: 10.1016/j.jneumeth.2010.03.012
180. Lazaridis C, Rusin CG, Robertson CS. Secondary brain injury: predicting and preventing insults. *Neuropharmacology.* (2019) 145:145–52. doi: 10.1016/j.neuropharm.2018.06.005
181. Abayazid F, Ding K, Zimmerman K, Stigson H, Ghajari M. A new assessment of bicycle helmets: the brain injury mitigation effects of new technologies in oblique impacts. *Ann Biomed Eng.* (2021) 49:2716–33. doi: 10.1007/s10439-021-02785-0
182. Guo P, Jin Z, Wang J, Sang A, Wu H. Irisin rescues blood-brain barrier permeability following traumatic brain injury and contributes to the neuroprotection of exercise in traumatic brain injury. *Oxidative Med Cell Longev.* (2021) 2021:1118981. doi: 10.1155/2021/1118981
183. Buccilli B, Alan A, Aljeradat BG, Shahzad A, Almealawy YF, Chisvo NS, et al. Neuroprotection: surgical approaches in traumatic brain injury. *Surg Neurol Int.* (2024) 15:23. doi: 10.25259/SNI_774_2023
184. Pujari R, Hutchinson PJ, Kolias AG. Surgical management of traumatic brain injury. *J Neurosurg Sci.* (2018) 62:584–92. doi: 10.23736/S0390-5616.18.04533-2
185. Lindblad C, Rostami E, Helmy A. Interleukin-1 receptor antagonist as therapy for traumatic brain injury. *Neurotherapeutics.* (2023) 20:1508–28. doi: 10.1007/s13311-023-01421-0
186. Mohammed FS, Omay SB, Sheth KN, Zhou J. Nanoparticle-based drug delivery for the treatment of traumatic brain injury. *Expert Opin Drug Deliv.* (2023) 20:55–73. doi: 10.1080/17425247.2023.2152001

187. Ramirez S, Mukherjee A, Sepulveda S, Becerra-Calixto A, Bravo-Vasquez N, Gherardelli C, et al. Modeling traumatic brain injury in human cerebral organoids. *Cells*. (2021) 10:2683. doi: 10.3390/cells10102683
188. Lai JD, Berlind JE, Fricklas G, Lie C, Urenda JP, Lam K, et al. KCNJ2 inhibition mitigates mechanical injury in a human brain organoid model of traumatic brain injury. *Cell Stem Cell*. (2024) 31:519–536.e8. doi: 10.1016/j.stem.2024.03.004
189. Zamanian MY, Taheri N, Opulencia MJC, Bokov DO, Abdullaev SY, Gholamrezaipour M, et al. Neuroprotective and anti-inflammatory effects of pioglitazone on traumatic brain injury. *Mediat Inflamm*. (2022) 2022:1–10. doi: 10.1155/2022/9860855
190. Manaenko A, Lekic T, Barnhart M, Hartman R, Zhang JH. Inhibition of transforming growth factor- β attenuates brain injury and neurological deficits in a rat model of germinal matrix hemorrhage. *Stroke*. (2014) 45:828–34. doi: 10.1161/STROKEAHA.113.003754
191. Roselli F, Karasu E, Volpe C, Huber-Lang M. Medusa's head: the complement system in traumatic brain and spinal cord injury. *J Neurotrauma*. (2018) 35:226–40. doi: 10.1089/neu.2017.5168
192. Somebang K, Rudolph J, Imhof I, Li L, Niemi EC, Shigenaga J, et al. CCR2 deficiency alters activation of microglia subsets in traumatic brain injury. *Cell Rep*. (2021) 36:109727. doi: 10.1016/j.celrep.2021.109727
193. Friedman-Levi Y, Liraz-Zaltsman S, Shemesh C, Rosenblatt K, Kesner EL, Gincberg G, et al. Pharmacological blockers of CCR5 and CXCR4 improve recovery after traumatic brain injury. *Exp Neurol*. (2021) 338:113604. doi: 10.1016/j.expneurol.2021.113604
194. Beylerli O, Tamrazov R, Gareev I, Ilyasova T, Shumadalova A, Bai Y, et al. Role of exosomal ncRNAs in traumatic brain injury. *Non-Coding RNA Res*. (2023) 8:686–92. doi: 10.1016/j.ncrna.2023.10.004
195. Pagkou D, Kogias E, Foroglou N, Kotzampassi K. Probiotics in traumatic brain injury: new insights into mechanisms and future perspectives. *J Clin Med*. (2024) 13:4546. doi: 10.3390/jcm13154546
196. Hu X, Jin H, Yuan S, Ye T, Chen Z, Kong Y, et al. Fecal microbiota transplantation inhibited neuroinflammation of traumatic brain injury in mice via regulating the gut-brain axis. *Front Cell Infect Microbiol*. (2023) 13:1254610. doi: 10.3389/fcimb.2023.1254610