Archives of Anesthesiology and Critical Care (Mar-Apr 2026); 12(2): 169-180.

Available online at http://aacc.tums.ac.ir

Review Article

Role of Inflammation in Secondary Injury Progression after Traumatic Brain Injury and Spinal Cord Injury

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ARTICLE INFO

Article history:
Received 02 June 2025
Revised 23 June 2025
Accepted 08 July 2025

Keywords:
Traumatic brain injury (TBI);
Spinal cord injury (SCI);
Central nervous system (CNS)

ABSTRACT

Trauma to the brain or spinal cord is a type of injury that triggers a cascade of secondary pathophysiological events after the primary mechanical trauma. Neuroinflammation is indeed of foremost importance, acting both as a mediator for tissue repair and an instigator for progressive neurodegeneration. Activated microglia and astrocytes, peripherally derived immune cells infiltrating that site, mediate a complex interaction involving cytokines, oxidative stress, mitochondrial dysfunction, and neurovascular disruption. This early inflammatory signaling helps remove debris and support neuronal regeneration in traumatic brain injury (TBI) and spinal cord injury (SCI). However, when this particular inflammation becomes chronic, it leads to glial damage with aberrant synaptic connections and irreversible harm to neural network circuitry. Mediators, including IL-1β, TNF-α, and the NLRP3 inflammasome, have been identified as promising therapeutic targets; cutting-edge therapies, ranging from small-molecule inhibitors to mitochondrial stabilizers to cell-based interventions, have shown efficacy in preclinical models. Nonetheless, the translation to the clinic has been hindered through shortcomings in classical animal models, failure to integrate biomarker application, and an inability to account for the heterogeneity of human central nervous system (CNS) injury. To bridge this gap, temporally targeted immunomodulation, precision diagnostics, and systems-level approaches will need to align with the molecular pathology involved in disease intervention. Understanding this dual property within post-traumatic inflammation presents an important frontier to develop truly efficacious neuroprotective therapies.

Introduction

Traumatic brain injury (TBI) and spinal cord injury (SCI) are major contributors to global morbidity and mortality, with an estimated 69 million new TBI cases annually and SCI affecting approximately 250,000 to 500,000 individuals worldwide each year [1-2]. TBI is linked to a higher long-term death rate19, 20 than rates for the general population, and it may also raise the long-term risk for cognitive impairment and dementia, stroke [3-4], Parkinsonism [5-7], and epilepsy [8]. These dangers also exist in less severe types of TBI, particularly with repeated trauma [9-12].

Though mechanical injury occurs as a sudden event, and injury damages the initial site immediately, a considerable component of the whole insult accrues progressively by way of complex injury mechanisms, such as neuroinflammation, which plays a critical role both in degenerative and reparative damages [13-14].

After the primary injury, the rupture of the blood-brain barrier, or blood-spinal cord barrier, initiates a highly coordinated inflammatory response in which activity is carried out by the resident glial activation-mainly microglia and astrocytes-during infiltration by peripheral immune cells [13,15-16]. Most of these pro-inflammatory mediators, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), are upregulated and released, thus worsening

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DOI: 10.18502/aacc.v12i2.20957

excitotoxicity, oxidative stress, and neuronal apoptosis [15,17-18].

Like TBI, reactive gliosis is shown concerning morphologic remodeling with concurrent changes in gene expression of astrocytes and microglia that alter synaptic architecture, contribute to glial scar formation, and change neurovascular integrity [16,19]. Also, SCI proves to be an extended neuroimmune reaction modulating axonal regeneration-demyelination and chronic neurodegeneration, which is exhibited by dynamic crosstalk among CNS-residing and infiltrating immune cells [13,20]. In spite of overlapping mechanisms, TBI and SCI display different spatiotemporal inflammatory signaling profiles, with injury-specific and region-specific kinetics, making interpreting individual therapies necessary [17,21].

This article evaluates inferential problems related to inflammation in secondary injury after TBI and SCI. An explanation of major cellular as well as molecular mediators-cytokine networks and glial dynamics to mitochondrial dysfunction and inflammasome activation will identify critical time windows for proper intervention. Eventually, the goal is to use that information in the development of immune modulation therapies to ameliorate progressive neurodegeneration with an emphasis on endogenous repair.

Global Burden of TBI and SCI

TBI and SCI are global health conditions with lasting considerable impacts on people and communities all over the world [2]. According to a Global Burden of Disease Study, in 2016, the number of prevalent cases of TBI was 55·50 million (53·40–57·62 million) and of SCI was 27·04 million (24·98–30·15 million) [2]. Such injuries have high mortality rates and create serious disability, with the victims normally requiring extended medical care and rehabilitation [22-23].

Men were more than twice as likely as women to have suffered a significant TBI with loss of consciousness, according to a meta-analysis of 15 prevalence studies [24], which included a total sample of 25,134 persons. Young individuals have a higher prevalence; for example, birth-cohort research revealed that over 30% of participants had at least one TBI that required medical attention prior to the age of 25 [25]. It is logical to assume that around half of the world's population has experienced a TBI given the rising prevalence of TBI in the elderly. The findings of a population-based survey conducted in Colorado, USA, using random sampling, which found that 42% of participants had experienced at least one TBI in their lives (36% mild and 6% moderate-to-severe injury), corroborate this conclusion [26]. TBI has a significant long-term effect on health: 3.17 million Americans are thought to have persistent aftereffects of a previous TBI [27]. According to current estimates and forecasts through 2030, TBI ranks among the top three particular neurological conditions that cause neutralizability worldwide [28]. In order to lower this high burden of impairment, coordinated initiatives are needed.

Their load continues to rise, fueled partly by growing age in developed countries, where the leading cause of injury is falls, and increasing traffic injuries in middle- and low-income countries [2,22]. The majority of the injuries are preventable, but poor prevention measures along with delayed interventions aggravate their social and economic load [29].

Therefore, TBI and SCI are not only causes of substantial disability but also a financial cost that is billions annually [22]. For example, TBI alone is estimated to cost the global economy over $400 billion annually [22].

Secondary injury processes following the initial trauma, like neuroinflammation, apoptosis, oxidative stress, and glial scarring, are the cause of the progressive nature of the damage and difficulty in recovery [30-31]. These are not merely downstream effects but are active modulators of tissue degeneration, repair, and function outcomes [20,29].

Microglial activation and macrophage polarization, for instance, play dual roles in the neural tissue repair enhancement and neurodegeneration pathogenesis following CNS trauma [20]. Sustaining M1-like pro-inflammatory states for prolonged durations has been correlated with ongoing neurotoxicity and impaired regeneration [29]. Such a chronic inflammatory environment is predisposed to spread over into the neighboring brain parenchyma and is thought to contribute to progressive atrophy and cognitive deficit well beyond TBI [31-32].

Therefore, awareness of the global burden of TBI and SCI is important not only for developing better clinical treatments but also for enforcing preventive interventions and system redesign [22]. Better understanding of the pathophysiology of secondary injury mechanisms and how they lead to long-term disability is critical to the development of more efficient therapeutic strategies to prevent the long-term impact of these devastating injuries [29,31].

Secondary Injury Cascade

The pathophysiological events after TBI and SCI extend far beyond initial mechanical injury and consist of a series of cellular and molecular events that are temporally and spatially dynamic, commonly termed the secondary injury cascade. This is activated within minutes to hours following the injury and may proceed chronically, furthering neurodegeneration, demyelination, and functional deterioration. The core feature of the process is the breakdown of the blood-brain

barrier and blood-spinal cord barrier, allowing infiltration from peripheral immune mechanisms and exposure of CNS parenchyma to serum-derived cytotoxic substances, thereby intensifying local inflammation. The hallmark event of the secondary injury response is activation of microglia and macrophages (derived from infiltrating monocytes) within a few hours to a few days after the injury and polarization of the two populations to an M1-like, neurotoxic state or an M2-like, neuroprotective state. Prolonged M1 activation induces a microenvironment filled with sustained release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and reactive species, including ROS and nitrogen species, driving inflammation, inducing oxidative stress, mitochondrial dysfunction, and excitotoxicity. NADPH oxidase-2 (NOX2) upregulates many other enzymes, driving redox imbalance and lipid peroxidation, which ultimately leads to progressive apoptosis and necroptosis of neurons and oligodendrocytes.

In conjunction with this, in turn, astrogliosis is accompanied by the formation of a dense glial scar rich in chondroitin sulfate proteoglycans (CSPGs), which hinders axonal regeneration and synaptic plasticity. Chronic neuroinflammation also alters the transcriptomic landscape of the injured CNS toward a maladaptive gliotic state associated with synaptic trimming, aberrant connectivity, and long-term behavioral deficits. Subsequently, the major pathways of apoptosis and autophagy further converge in hypoxic and metabolically compromised tissues, adding to cell death and white matter degeneration.

These entangled pathological processes-barrier disruption, neuro-immune dysregulation, glial scar formation, redox imbalance, and programmed cell death-state for the perpetuation of a secondary injury cycle. Interruption of these different mechanisms is a therapeutic goal of great importance to limit lesion expansion and promote neural repair in TBI and SCI.

Blood-Brain-Barrier Damage and Following Consequences

Neuronal death, either rapid or delayed, is an inevitable consequence of the pathogenic processes that follow brain injury. A transcriptional program that causes delayed neuronal death can be started by BBB damage alone [33-34]. Such disturbance may potentially impact the development of long-term TBI problems, including seizures, AD, and cognitive and psychosocial deficits. Notably, loss of neurons may not be the only or even the most significant cause of these illnesses, even though neuronal death is a common characteristic of all these long-term issues [35-36]. Indeed, abnormal neuronal function may be caused by a variety of factors, including tissue remodeling and altered neuronal connectivity, scarring, changes in the composition of extracellular ions, the buildup of toxic substances due to malfunctioning influx-efflux mechanisms, and the extravasation of plasma proteins. Substantial evidence has now been gathered that demonstrates the direct link between long-term brain pathologies and disturbance of the BBB. For patients with TBI, this evidence opens up new possibilities for neuroprotective treatments.

Although the pathophysiological mechanisms behind the development of seizures and epilepsy are still poorly understood, the fact that TBI can cause these difficulties has been acknowledged for several decades [37-38]. Both animal and clinical investigations have established a link between BBB dysfunction and epilepsy, with multiple groups offering proof that BBB rupture is a key initiator of hypersynchronized epileptic activity in the damaged brain. The likelihood of having seizures rises in direct proportion to the severity of TBI [39], and several patient studies have demonstrated that regions of aberrant neuronal activity (as determined by scalp EEG recordings) can spatially overlap with cortical areas with BBB breakdown [40-41]. A study in a mouse model of chronic epilepsy demonstrated a correlation between seizure frequency and the degree of BBB leaking, which is consistent with these findings. According to research conducted on human patients, a significant percentage of post-traumatic seizures occur within the first 24 hours following an injury [42] or within the week that follows [38]. Antiepileptic medications can be administered prophylactically to suppress these occurrences. On the other hand, late-onset seizures, which manifest in the weeks or months after trauma, are typically resistant to antiepileptic medications and are thought to result from local circuit modulation caused by transcriptional alterations and synaptic rewiring. Notably, early astrocyte failure was noted prior to neuronal hypersynchronization in animal trials where the BBB was damaged to create a persistent epileptic focus [43-44]. Following TBI, astrocyte shape and function changes have been extensively documented [45], and both experimental animals and epileptic patients have reported astrocytes' possible involvement in seizure production and epilepsy. [43,46-50]. New research has shown that glial cells in the CNS play new physiological functions, such as regulating synaptic transmission and plasticity [51-52]. Therefore, glial cells may play a significant part in the rearrangement of the neural network, hypersynchronicity, and hyperexcitability that result in seizures and brain dysfunction [44]. The modification of neuronal functions may be due to a number of functional alterations in astrocyte characteristics. Neuronal function may be impacted by decreases in the expression of aquaporin-4 water channels and inwardly rectifying potassium channels, which are thought to be essential for controlling the brain's extracellular potassium ion levels and water content, respectively. Furthermore, since gap

junction proteins (connexins) create useful channels between cells that are crucial for the spatial buffering of ions and small molecules (such as potassium ions), a decrease in their expression may also play a part. Numerous pro- and anti-inflammatory chemicals that may be either pro- or anti-epileptogenic are produced by astrocytes. Therefore, the observed rise in glial cell cytokine production may have an impact on neuronal activity. Last but not least, deficiencies in these processes may impact neuronal function because certain glial cells play a critical role in the uptake and metabolism of glutamate (certain glial cells contain glutamatergic receptors and have the ability to release glutamate). In fact, it appears that altered (or activated) astrocytes impact extracellular glutamate levels by reducing their capacity to absorb and process this neurotransmitter [53]. Although several experimental and theoretical models indicate a key function for the maintenance of potassium homeostasis, it is still unknown to what degree each of the putative pathways mentioned above is essential to neural activity. Long-lasting focused increases in BBB permeability have been linked to 89 aberrant focal rhythmogenesis and seizures in individuals who have had TBI, which have been reported years after the initial damage [40,54]. As a result, while a temporal overlap between BBB damage and seizure activity has been identified in the clinical context, a causal association has not yet been established. However, data from experimental animals has repeatedly demonstrated that seizures can be easily started if the BBB is disrupted [33,43,49,55-57]. Additionally, several patients with primary CNS cancer who received chemotherapy that made use of mannitol, a well-known BBB opener, to optimize drug transport experienced focal motor seizures, according to Marchi and colleagues [58], Serum S100β levels, a sign of BBB disruption, were found to be strongly correlated with the onset of immediate focal seizures. Furthermore, after carotid surgery, Ivens et al. (2019) reported protracted seizures in individuals with hyperperfusion syndrome whose blood-brain barrier was impaired [18].

Noble and Wrathall first reported injury-induced alterations in permeability to horseradish peroxidase (HRP) using a rat model of spinal contusion injury [59]. They discovered that the degree of injury affected HRP extravasation; a light injury caused focused extravasation in the gray matter of the spine, but a severe injury affected both the gray and white matter. Within a day, HRP extravasation reached its maximum, and the barrier closed after 14 days. In SCI mice, Whetstone et al. reported comparable alterations in acute permeability, followed by a subsequent increase in permeability 3–7 days after the injury [60]. It is interesting to note that this secondary alteration occurs at the same time when blood monocytes invade the damaged spinal cord. In SCI rats, alterations in microvascular permeability in the spinal cord white matter have been linked to microglia activation [61]. Although the BBB is first disrupted by mechanical pressures, inflammatory mediators surely have an impact on subsequent alterations in endothelial function, such as the preservation of blood-to-tissue transfer.

Vascular permeability can be increased by the proinflammatory cytokines TNFα and IL-1β, which are up-regulated right after injury [62]. Reactive oxygen species, kinins, histamines, nitric oxide, and elastase are among the various vasoactive chemicals that are generated by glia and leukocytes and may also be involved [63-69]. Additionally, neutrophils and endothelia create matrix metalloproteinase (MMP)-9, which promotes leukocyte diapedesis and may operate as a vascular permeabilizing agent [70]. These findings suggest that controlling inflammatory cells and the chemicals they release may control pathological changes in blood-brain barrier function. On the other hand, if neuroinflammation is adequately managed, its vasoactive characteristics may be used to help carry medications to the brain or spinal cord that has sustained persistent damage [13].

Key Inflammatory Mediators and Pathways

The inflammatory processes occur subsequent to TBI and SCI as very complex phenomena, involving a plethora of molecular and cellular events that determine further damage and repair processes to the injured area. Prominent among these inflammatory mediators are cytokines and chemokines, together with various signaling pathways that would be better characterized as orchestrators of this response, ultimately determining the balance that tilts either way between neurodegeneration and some prospects for salvage [18,71]. About the very early moments following an injury, the activation of resident glial cells, especially the microglia and astrocytes, represents an immediate and critical constitutive feature of this inflammatory process. Microglia function as the primary responders to the signal, undergoing phenotypic changes and releasing pro-inflammatory cytokines in a cascade-like manner, such as IL-1β, TNF-α, and IL-6, all of which in turn mediate neuroinflammation and contribute to the secondary injury cascade [18,72].

As these inflammatory mediators traverse throughout the injured CNS, they provoke additional cellular responses, like the recruitment of peripheral immune cells like macrophages, neutrophils, and lymphocytes. The secretion of chemotactic cytokines such as CCL2 and CXCL10 further intensifies the recruitment of these immune cells that mediate further neurodegeneration by releasing OS, NO, and excitatory amino acids [20,73]. The BBB becomes compromised, and the entry of these

peripheral immune cells into the parenchyma takes place, thereby engaging with reactive astrocytes and microglia and furthering neuronal injury and debilitating regenerative potential [18-19]. Interestingly, while neuroinflammation considerably contributes to tissue damage, it also aids in repair during tissue healing [71,74]. Repair processes include synaptic remodeling, neurogenesis, and angiogenesis.

The timing of inflammatory changes is critical for any CNS insults and their outcomes. Early on, pro-inflammatory cytokines ought to be signaling to help remove debris and assist in tissue repair, but if these cytokines signal for too long, injury arises. Long-term activation of such interferes with axon regeneration through promoting glial scarring, which in turn releases inhibitory extracellular matrix molecules such as CSPGs [18,75]. Pro-inflammatory signaling enters into the picture in SCI, whereby prolonged duration contributes to the establishment of a hostile environment for regeneration [19-20]. The chronicity of activation of the NLRP3 inflammasome in microglia and astrocytes serves to amplify this inflammatory response, which exacerbates chronic neurodegeneration and associated functional loss, grading out into months or years after the initial insult [18,71]. In the later stages of injury, anti-inflammatory mediators such as IL-10, TGF-β, and IL-4 are released, attempting to counterbalance the inflammatory response and promote tissue repair [19,72]. However, this reparative response is often insufficient to fully repair the damage, particularly in the presence of persistent glial activation and continued release of neurotoxic mediators. The failure to resolve inflammation effectively thus becomes a significant determinant of long-term neurological dysfunction following both TBI and SCI [18-19]. Apart from cytokines, a number of other chemicals may also be helpful as indicators of brain damage. For instance, GFAP expression is regulated by IL-6's stimulation of the JAK/STAT pathway. It is commonly known that after TBI, there is an increase in serum GFAP expression [76-77]. Serum GFAP levels have been demonstrated to predict mortality and outcome in patients with severe TBI [78-81]. In more recent times, it has been discovered that GFAP-BDPs in the serum of mild and moderate TBI patients within four hours of damage correlate with injury severity (GCS) and may be linked to CT lesions [82]. According to a recent study, outcome prediction could be significantly improved by integrating the IMPACT Outcome Calculator with measures of GFAP in serum and CSF [83]. Furthermore, CSF was used to evaluate the expression of II-spectrin breakdown product 145 (SBDP145), which showed a significant correlation with 6-month mortality [83]. In a different study, SBDPs in the CSF of patients with severe TBI were assessed at the time of admission and then every 6 hours for a maximum of 7 days [84]. It was demonstrated that there was a substantial association between SBDP145 and injury severity (as determined by GCS), in addition to the fact that all TBI patients had higher expression of SBDPs than controls. Additionally, patients who passed away had noticeably greater levels of SBDP145 and SBDP120, indicating that these markers could be able to predict mortality [84]. Microtubule-associated proteins (MAP-2), which are neuronal-specific proteins present in dendrites, are another indicator of note [85]. MAP-2 expression is lost from damaged brain regions, according to laboratory research in models of ischemia and traumatic injury. Shortly after injury, elevations in MAP-2 expression can be seen in serum [86-88]. More recently, it has been demonstrated that serum MAP-2 expression is still elevated six months following severe traumatic brain injury. Additionally, it was discovered that non-vegetative state patients have higher serum MAP-2 expression than vegetative state patients, which is correlated with better outcome (GOSE) [89]. Accordingly, elevated blood MAP-2 expression may indicate the development of improved cognitive function in individuals with severe TBI, and MAP-2 may have utility as a marker for outcome prediction. Last but not least, the inflammasome may offer us helpful biomarkers of brain injury since it produces mature IL-1 and IL-18. In a recent study, 23 patients with moderate or severe TBI had their CSF taken, and the amount of inflammasome proteins was assessed [90]. TBI patients' CSF had higher levels of caspase-1, Nacht leucine-rich-repeat protein-1 (NALP-1), and apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) than did controls. Additionally, there was a strong correlation between all three proteins and the outcome (GOS at 5 months; [90].) Although brain injury has received nearly all of the attention in the development of biomarkers for CNS injury, markers for SCI are also desperately needed. After SCI, MRI is not necessarily the most accurate technique to anticipate results, but it can be utilized to identify lesions, bleeding, and transactions. Although neurological evaluation cannot be administered within the first crucial hours following an injury, it has been demonstrated to be predictive of prognosis [91]. Clinicians may be able to determine the optimal course of treatment and establish earlier prognoses with the help of biomarkers for SCI. There has been very little research done on SCI biomarkers, and it has mostly concentrated on S100B and NSE. According to laboratory studies, the CSF exhibits higher levels of S100B, NSE, and neurofilament protein (NFL) expression [92-94]. Animals undergoing an experimental SCI show a comparable rise in serum [94-96]. These findings provide some indication that the NSE and S100B are capable of differentiating various damage severities. In a rat weight-drop model of SCI, it was demonstrated that both NSE

and S100B expression correlated with the severity of the injury [94]. However, a related study was unable to identify a variation in the expression of the serum CSF NSE across different levels of graded damage [96].

Human research on SCI biomarkers has concentrated on identifying ischemic injury in patients having surgery for thoracoabdominal aortic aneurism [97-100]. Other studies have examined S100B or NSE following surgery for spinal epidural empyema [101], lumbar disk herniation [102], or paresis brought on by spinal metastases [103]. Regarding the usefulness of S100B or NSE as indicators of ischemia injury, the data from these investigations is not conclusive. Although multiple studies have documented elevated expression of these biomarkers, nothing is known about the relationship between this and the results. Longer durations of higher serum S100B were associated with a worse outcome in cases of spinal epidural empyema or paresis caused by spinal metastases [101,103]. Finally, biomarkers for traumatic SCI in humans have been evaluated in two trials. Although both markers were elevated in the first measurement of GFAP and NFL expression in the cerebrospinal fluid of individuals with traumatic SCI, no statistical analysis was conducted, and only six patients were included [104]. The second study assessed the protein expression of IL-6, IL-8, MCP-1, S100B, and GFAP using CSF from 27 patients with complete or incomplete SCI [105].

Acute Response and Chronic Consequences

Neuroinflammation that happens during TBI and SCI serves opposing purposes; on the one hand, it induces neuroprotective mechanisms, and on the other hand, it triggers processes resulting in secondary injury [13,16]. During the acute injury phase, inflammation becomes a consequence of rapid resident glial cell activation, particularly with the microglia and astrocytes responding within minutes of mechanical insult [15,29]. Such damage begins to be detected via pattern recognition receptors (PRRs) that act upon damage-associated molecular patterns (DAMPs), which include nucleotides such as ATP, proteins such as HMGB1, and the fragments of extracellular matrix components, leading to the activation of the nuclear factor-κB (NF-κB) signaling pathway and the transcription of pro-inflammatory mediators including TNF-α, IL-1β, and IL-6 [14,17]. This initial response promotes the phagocytosis of debris, and this inflammatory response attracts peripheral immune cells while stimulating neurotrophic factors exerting transient effects such as BDNF and GDNF for neuronal survival and axonal sprouting via chemokine gradients (e.g., CCL2, CXCL10) [13]. This time window for advantageous intervention is quite narrow, and rapid mismanagement of the inflammatory environment will lead to a chronic pathological state [20,29].

In subacute and chronic progression, sustained pro-inflammatory activation, underpinned largely by classically activated (M1-like) microglia and infiltrating monocytes, amplifies oxidative and nitrosative stress, leading to excitotoxicity and mitochondrial dysfunction [31,74]. Chronic production of IL-1β, TNF-α, and ROS further augments neuronal and oligodendroglia apoptosis while disrupting the synaptic homeostasis, causing impairment of dendritic spine formation and inhibition of remyelination [29,32]. Glial scar formation due to hypertrophic astrocytes and extracellular matrix remodeling serve on one hand, to limit the propagation of the lesion; on the other hand, the inhibitory proteins deposited in the CSPGs also act as barriers against axonal regeneration [75]. Importantly, maladaptive inflammation is thus further propagated by feedback loops involving activation of the inflammasome (e.g., NLRP3) and changes in cytokine receptor signaling, causing chronic atrophy of white matter and long-term neurobehavioral consequences [13,31]. This chronic phase may last for months to years, with some evidence of ongoing microglial activation and increased expression of cytokines observable in both animal models of TBI and SCI, as well as in human postmortem studies [23,32]. Thus, inflammation in CNS trauma is a two-edged sword: once critical for debris clearance and regenerative priming, it becomes pathological when prolonged or dysregulated. A refined understanding of the spatiotemporal immune dynamics would be pivotal in the immunomodulatory strategy to preserve reparative elements.

Mitochondrial Damage Fuels Inflammation

Regulators of the neuroinflammatory response become more and more important and encompass a larger territory than those earlier understood to be trauma-specific. Calcium overload and glutamate excitotoxicity are the two major mitochondrial insults. The post-traumatic mitochondrial insults, by way of release, include mitochondrial damage-associated molecular patterns (mtDAMPs), including mitochondrial DNA (mtDNA), N-formyl peptides, ATP, and cardiolipin [19,74]. These mtDAMPs trigger sterile inflammation initiation and sustain it through recognition by pattern recognition receptors (PRRs) such as Toll-like receptor 9 (TLR9), NLRP3, and the cGAS–STING pathway [18,71]. As a concomitant, mitochondrial dysfunction leads to increased reactive species generation, which damages vital macromolecules and, on the other hand, works as secondary signaling messengers to amplify NF-κB and MAPK pathways in both microglia and astrocytes [29,74]. This pro-inflammatory signaling cascade drives the transcription of genes encoding cytokines, including TNF-α, IL-1β, and IL-6, which, in turn, cause further mitochondrial depolarization, mPTP opening, and

caspase activation, inducing a vicious feed-forward loop of mitochondrial and inflammatory dysfunction [19,71].

During the trauma in the CNS, strong activation of the NLRP3 inflammasome, another intracellular sensor of mtROS and oxidized mtDNA, occurred, and caspase-1 was cleaved, alongside the maturation of IL-1β and IL-18, both very neurotoxic and capable of exacerbating blood-brain barrier disruption [18,71]. In addition, mitophagy failure to clear oxidatively damaged mitochondria under circumstances of chronic inflammation and aging causes the accumulation of dysfunctional mitochondria and persistent cytokine release [73-74]. Mitochondrial impairment alters astrocytic function. Oxidative stress-induced astrocytes show morphological reactivity and enhanced glycolytic metabolism, resulting in lactate accumulation followed by further neuronal injury around the perilesional zone [19]. These astrocytic transitions reinforce the neurotoxic microenvironment by promoting glial scar formation while further inhibiting synaptic plasticity [75].

Bridging the Translational Divide in Neurotrauma Research: Challenges and Emerging Solutions

Neuroprotection and anti-inflammation therapy trials seemed successful, although there has never been a visible transitory shift in the quite well-established preclinical data into clinical practice following TBI or SCI. These translational bridges are a combination of biological, methodological, and logistical challenges, which may weaken the generalizability and reproducibility of experimental findings. This circumstance is mostly caused by a mismatch found between preclinical models and human pathology. Rodent models, which are essential for mechanistic discovery, are not similar to the complex, often heterogeneous, polyphasic injury types, as in human CNS trauma; e.g., most models are young and healthy, genetically homogeneous animals showing controlled injury, while the clinical population mostly has patients who are aged, with polytrauma and comorbidity such as diabetes, hypertension, or prior neurodegeneration [73-74]. Most standardized disease models-inducing controlled cortical impact or contusion-based SCI-rarely, simulate the heterogeneous injury mechanisms experienced clinically (e.g., diffuse axonal injury, hemorrhagic lesions) [18,71]. The absence of sufficient temporal and spatial resolution is another barrier to describing injury evolution and treatment response. The majority of acute or subacute outcome assessments are gross anatomic or locomotor ones, whereas long-term cognitive, behavioral, and electrophysiological deficits, which predominate in man, are studied relatively rarely [32,73]. Their absence of blinded randomization and small sample size maximize the disbenefits' effect on reproducibility and statistical power, and both factors, therefore, add to the heightened failure rate observed in late-phase clinical trials. Moreover, species differences in PK/PD and limited CNS penetration by many therapeutic agents aggravate the problem of translatability. An animal drug that shows efficacy in the rodent organism may be poorly bioavailable and rapidly metabolized, or it may simply fail to cross the human BBB or blood-spinal cord barrier efficiently [18,71]. In addition to these complexities regarding routes and methods of delivery, the timing for infusion of therapeutic drugs also remains one of those variables often optimized within animal studies but impractical or delayed in real-world trauma settings.

Emerging solutions are currently in development to address these challenges. Further development using large animal models such as pigs and other non-human primates, which will closely approach humans in brain size, white-to-gray matter ratios, and immune responses, will further improve translational relevance. In this direction, multi-omics approaches (transcriptomics, proteomics, and metabolomics) are advancing in parallel to allow a detailed characterization of injury-induced changes at the molecular level and patient-specific identification of inflammatory signatures that inform personalized interventions [29,74].

In addition, the clinical trial design with biomarkers is gaining ground. Quantification of cytokines (including IL-6, S100B, and GFAP) from cerebrospinal fluid or blood, coupled with advanced imaging methods (for example, TSPO-PET, DTI-MRI), provides real-time monitoring of neuroinflammation, blood-brain barrier integrity, and integrity of the white matter to permit better patient stratification and adaptive trial methods [18,71]. Artificial intelligence and machine learning are also being leveraged to create disease trajectory models, predict treatment responsiveness, and optimize therapeutic windows. Consensus guidelines for preclinical rigor and reproducibility, such as the ARRIVE and STAIR recommendations, have been developed to increase methodological transparency and promote cross-laboratory standardization. Collaborative multicenter preclinical consortia are being established that exact a trial-like structure in order to validate therapeutic efficacy across models, species, and research settings.

In conclusion, bridging the translational divide in neurotrauma research will rest on a multifaceted systems approach to incorporate more representative animal models, long-term and molecular outcome measures, precision medicine tools, and collaborative infrastructure. Only by this convergence shall experimental neurotherapeutics really enjoy the promise in the clinic.

Conclusion

One important and complex mechanism in the pathophysiology of secondary injury after SCI and TBI is neuroinflammation. The inflammatory response is a complicated cascade that includes the activation of local glial cells (microglia and astrocytes) and the invasion of peripheral immune cells. It is brought on by the breakdown of the BBB, or blood-spinal cord barrier. Even though acute neuroinflammation is essential for protecting neurons by clearing debris and providing trophic support, its persistence after the acute phase worsens damage to neurons and glia, leading to oxidative stress, mitochondrial dysfunction, glial scarring, and neurodegeneration. The dual nature of immune responses inside the CNS, where early pro-inflammatory signaling aids in healing but chronic inflammation causes irreparable damage, is highlighted by the function of neuroinflammation in TBI and SCI. Important molecular mediators have been found to be key players in the damage cascade, including ROS, cytokines (e.g., IL-1β, TNF-α, IL-6), and activation of inflammasomes (e.g., NLRP3). Neuroinflammation's temporal dynamics, which range from the acute, reparative phase to the chronic, degenerative phase, call for precise therapeutic approaches that are adapted to the particular inflammatory pathways and timing of the condition. It has been difficult to translate these discoveries into clinical therapies, even though significant progress has been made in understanding the molecular and cellular underpinnings of post-traumatic inflammation. Preclinical models have shown the effectiveness of current therapy approaches that target inflammatory mediators, such as NLRP3 inflammasome blockers (e.g., MCC950), TNF-α inhibitors (e.g., etanercept), and IL-1β inhibitors (e.g., anakinra). However, the limitations of preclinical models that are unable to recreate the complexity and variety of human injuries, especially with regard to long-term functional results, have hindered their clinical translation. Furthermore, the development of universally successful medicines is complicated by difficulties in patient categorization and the underrepresentation of comorbidities, such as age-related neurodegeneration.

Acknowledgment

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, for their support and cooperation.

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