Chapter

Neuroinflammation in Traumatic Brain Injury

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Abstract

Neuroinflammation following traumatic brain injury (TBI) is an important cause of secondary brain injury that perpetuates the duration and scope of disease after initial impact. This chapter discusses the pathophysiology of acute and chronic neuroinflammation, providing insight into factors that influence the acute clinical course and later functional outcomes. Secondary injury due to neuroinflammation is described by mechanisms of action such as ischemia, neuroexcitotoxicity, oxidative stress, and glymphatic and lymphatic dysfunction. Neurodegenerative sequelae of inflammation, including chronic traumatic encephalopathy, which are important to understand for clinical practice, are detailed by disease type. Prominent research topics of TBI animal models and biomarkers of traumatic neuroinflammation are outlined to provide insight into the advances in TBI research. We then discuss current clinical treatments in TBI and their implications in preventing inflammation. To complete the chapter, recent research models, novel biomarkers, and future research directions aimed at mitigating TBI will be described and will highlight novel therapeutic targets. Understanding the pathophysiology and contributors of neuroinflammation after TBI will aid in future development of prophylaxis strategies, as well as more tailored management and treatment algorithms. This topic chapter is important to both clinicians and basic and translational scientists, with the goal of improving patient outcomes in this common disease.

Keywords: neuroinflammation, traumatic brain injury, inflammatory cytokines, metabolomics and lipidomics, blood-brain barrier, ischemia, neuronal excitotoxicity, chronic traumatic encephalopathy

1. Introduction

Traumatic brain injury (TBI) remains a significant source of morbidity, mortality and increased global healthcare burden and costs. Even among survivors and those classified as having mild TBI, outcomes are often poor [1–3]. This highlights the need for continued research into understanding the pathophysiology of disease and its association with clinical outcomes.

Secondary injury after TBI is exacerbated by several biochemical processes post trauma, including inflammation [4]. Through the neuroinflammatory cascade,

traumatic injuries affect brain structure and function far beyond the acute phase, resulting in heterogeneity of TBI outcomes [5, 6]. Although the primary intent for the inflammatory response is tissue repair, collateral damage can occur if left unregulated and sustained [7]. Animal models have demonstrated that targeting neuroinflammation can alter the biologic process of injury. Unfortunately, effective pharmacological strategies to decrease inflammation in vitro still have not translated into benefit in clinical trials. Continuing research and understanding of neuroinflammation in TBI will provide important guidance into future prognostication methods and therapeutic targets.

2. The pathophysiology of inflammation

While trauma such as blunt force, penetrating injury, or shearing energy, causes the primary injury in TBI, secondary injury can occur in delayed fashion. Pathologic processes that underlie secondary brain injury can persist for days to years after the initial trauma. Neuroinflammation following TBI is a principal driver of secondary injury and is characterized by complex intercellular signaling and profound histochemical changes.

2.1 The acute neuroinflammatory response

Tissue and neuronal injury occurring after trauma activates the release of danger signals. Also known as damage-associated molecular pattern molecules (DAMPs), these trigger an innate immune response and inflammasome activation [6, 8]. Various intracellular molecules can act as DAMPs, including DNA, RNA, high mobility group box 1 (HMGB1), S100 proteins, adenosine triphosphate (ATP), uric acid, lysophospholipids, and lipid peroxidation-derived carbonyl adducts of proteins [9]. Early cytokines are released in damaged tissues within minutes of trauma which typically peak within the first 24 hours [6]. A classic DAMP is HMGB1, which signals through toll-like receptors 2 (TLR-2) and 4 (TLR-4) to increase cytokine production and release [8, 10]. HMGB1, a nuclear protein present in all cell types, attaches onto TLR-4 and activates the NLRP3 inflammasome complex, priming it for further inflammation in response to stressors. The activated inflammasome complex cleaves cytokine precursors such as pro-IL1ß and pro-caspase to create its active metabolite [10].

Responding to early DAMPs release, activated microglia with a pro-inflammatory phenotype release additional cytokines into the extracellular space, potentiating the neuroinflammatory response [3]. Tumor necrosis factor (TNF), and interleukins (ILs) are two primary inflammatory cytokines implicated in neuroinflammation. In animal models, an increase in IL-1β expression is seen as early as 1 hour after trauma [11, 12]. Similarly, increased TNF levels are observed in brain tissue within 17 minutes of injury in a murine model [13]; however, correlation between early cytokine levels and functional outcomes has been conflicting [6]. Studies have not been able to correlate TNF levels with raised ICPs and poor neurological outcomes [14]; TNF levels are also not a good predictor of additional neuronal injury in the immediate hours post injury [15]. Chemokines such as CXCL8 and chemoattractant molecules like CCL2 are observed to be increased in response to cytokines such as IL-1B and TNF, which are elevated after brain injury, and associated with neurological deficit after ischemia [16–19]. Further studies of these cytokines and their role in predicting TBI outcomes are still necessary to elucidate their clinical utility.

Apart from microglia, several other resident central nervous system (CNS) immune cells are capable of expressing cytokines to regulate post-traumatic inflammation. Neutrophils are the earliest and most abundant immune cells to enter the CNS in response to chemokines, with natural killer (NK) cells, dendritic cells and T-lymphocytes also being observed but in less abundance [8, 20]. Matrix metalloproteinases (MMPs) and reactive oxygen species (ROS) are released by neutrophils to promote cellular repair; but, in the acute post-traumatic milieu, these molecules potentiate the breakdown of the blood brain barrier (BBB), promoting migration of immune cells into the CNS, and can lead to delayed secondary hemorrhagic complications after trauma [8, 9]. Within the CNS, astrocyte activity increases within the first few days after injury, undergoing reactive gliosis. Glial fibrillary acidic protein (GFAP) is subsequently upregulated and cytokine production is increased [21]. Highlighting the importance of the inflammatory cascade in mediating secondary brain injury, GFAP levels have been correlated with clinical outcomes in TBI patients [22], and may serve as a biomarker for disease severity.

2.2 The role of chronic neuroinflammation in traumatic brain injury pathology

In addition to the acute and subacute post-trauma inflammatory response, TBI survivors are prone to the development of chronic neuroinflammation that persists for years after injury [8, 23–25]. How acute inflammation transitions to a chronic pro-inflammatory state is not fully understood. Mouse models of TBI have shown that cortical inflammation persists even 30 days post injury and is associated with increased microglial activity [26, 27]. In contrast, mice with genetically depleted microglia did not display the same level of inflammatory response as their wild type counterparts, suggesting the central role of microglia in establishing chronic inflammation [28]. Microglial dysfunction and increased white matter phagocytosis is also associated with chronic neuroinflammation in TBI survivors [23]. Imaging studies in rat TBI models have demonstrated a persistent increase in BBB permeability up to 10 months post injury, and an elevation in CD68, a marker for activated microglia and macrophages, in perilesional cortical tissue up to 11 months post injury [29]. These findings suggest that monocyte extravasation from the blood and into the CNS are capable of sustaining chronic inflammation.

Chronic neuroinflammation may also involve activation of systemic inflammation. Effects of post-traumatic microglial activation can also be observed in regions distant to the brain [24, 28]. Macrophage biomarker studies have also shown chronically elevated serum TNF levels after TBI, with increased TNF levels being associated with unfavorable behavioral outcomes [30]. Plasma levels of pro-inflammatory chemokines and cytokines including interferon gamma (IFN-γ), TNF, IL-8, IL-17A, IL-9, eotaxin, macrophage inflammatory protein-1-beta (MIP-1β), and monocyte chemoattractant protein 1 (MCP-1) remain elevated for over 12 months even in patients with mild TBI with normal magnetic resonance imaging (MRI) brain imaging [31]. Chronic inflammation of both the CNS and systemically likely contributes to long-term neuropsychiatric and poor functional outcomes in post-TBI survivors and those with chronic traumatic encephalopathy (CTE). Ongoing research and expert opinion further implicate long-term systemic inflammation as underlying the etiology psychiatric, neurologic, cardiovascular, renal and liver disease, as well as cancer and metabolic syndrome (**Figure 1**) [32, 33].

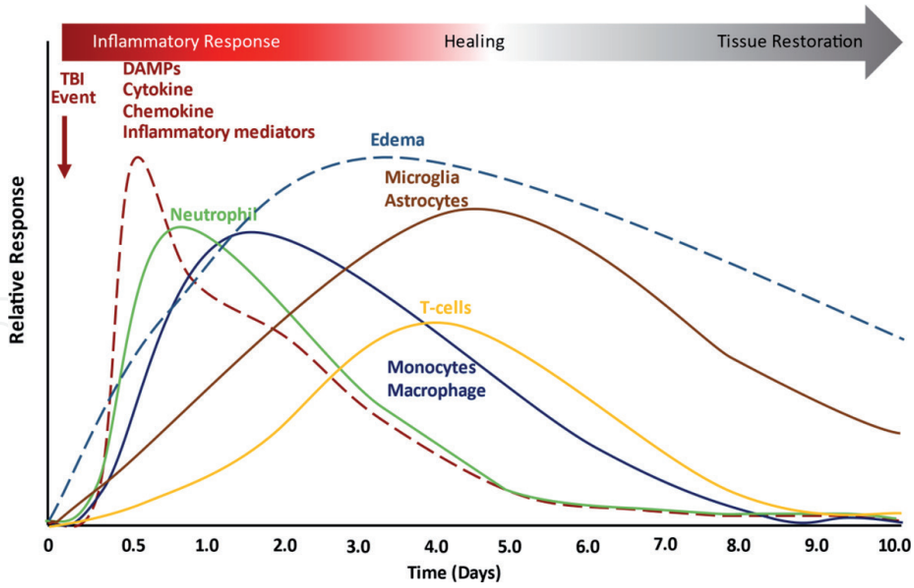

Figure 1.
Timeline of neuroinflammation post-TBI.

3. Mechanisms of secondary brain injury mediated by neuroinflammation

Following TBI, primary injury occurs at the time of trauma as a direct result of the force transferred to the head and brain tissue. This leads to contusion, vascular injury, and axonal shearing. Secondary brain injury results from a complex TBI pathophysiology that leads to extensive and persistent neurologic structural and functional changes. While primary injury is considered irreversible, secondary brain injury is hypothetically preventable. As neuroinflammation is a central mediator of secondary brain injury, it is an important target for research and therapeutic development. Here, we describe primary pathologic processes that are associated with neuroinflammation after TBI.

3.1 Increased blood-brain barrier permeability

The BBB is formed by tightly connected cerebrovascular endothelial cells supported by astrocyte foot processes, pericytes, and basement membrane. It is highly regulated and functions as the interface between peripheral circulation and the CNS. Loss of BBB integrity after brain injury can contribute to neuronal cell death and affect the brain's response to pharmacologic therapy. The underlying structural changes leading to increased BBB permeability following TBI are not fully elucidated. Brain injury has been associated with an increase in the numbers of endothelial caveolae, leading to an increase in transcytosis of plasma proteins and a decrease in the expression of junctional adhesion and tight junction proteins [34, 35]. Under ischemic conditions, BBB integrity may be lost independent of tight junctions and occurs following endothelial swelling and disruption of the basement membrane [36, 37].

The breakdown of the BBB has been strongly linked to inflammation. Within tight junctions, upregulation of vascular endothelial growth factor-A (VEGF-A) from neutrophils and astrocytes act to reduce the expression of tight junction protein claudin-5, leading to BBB leakage [38]. In pro-inflammatory states, activated microglia and recruited neutrophils can sequester in the tissues and elaborate a network of DNA, MMPs, proteases and eicosanoids which is referred to as neutrophil

extracellular traps (a process commonly termed NETosis). NETotic neutrophils release MMPs and neutrophil elastase (NE) that contribute to degradation of the extracellular matrix [39]. In parallel, microglia promote the expression of Aquaporin-4 (AQP-4), contributing to fluid shifts into the CNS [40].

Once BBB integrity is lost, the influx of peripheral neutrophils, macrophages, natural killer cells, T helper cells, and cytotoxic T cells intended to facilitate tissue repair can sustain neuroinflammation, BBB permeability, and promote secondary brain injury. Elevations of these immune cells and other inflammatory mediators are measurable following human TBI [41, 42]. Extravasation of albumin and other plasma proteins also contribute to the activation of microglia and astrocytes to trigger the release cytokines, chemokines and MMPs [41]. The formation of ROS is associated with MMP activation, resulting in further tissue damage and BBB disruption [43]. Tissue debris from both primary and secondary brain injury contain DNA, RNA, proteins and lipids that can activate TLRs and exacerbate neuroinflammation. These findings highlight the ability of inflammation to be self-propagating and dependent on BBB permeability.

The clinical impact of BBB disruption after TBI is profound. Cerebral edema is the major clinical consequence of BBB dysfunction and occurs due to the increased permeability of the BBB to protein-rich fluid and neuroinflammatory cells into the extracellular space leading to interstitial edema [38]. Cerebral edema is often symptomatic, can lead to increased intracranial pressure and reduced cerebral perfusion and oxygenation, and can be life-threatening when it results in brain compression and herniation.

3.2 Ischemia and tissue hypoxia

Ischemia and hypoxia occur after TBI for several reasons that include intracranial hypertension, reduced cerebral perfusion pressures, and abnormal cerebral autoregulation that result in the inadequate supply of oxygen-rich blood to vulnerable brain regions [44]. Independent of hemodynamics, tissue-mediated clotting and neuroinflammation promote microcirculatory failure and increased ischemic burden that may go clinically unrecognized. Neuroinflammation can directly contribute to microvascular disruption by causing endothelial dysfunction. Functionally, endothelial-dependent vasodilation is diminished after TBI due to impaired nitric oxide (NO) production from uncoupling of endothelial nitric oxide synthase (NOS) [45]. Additionally, reduced capacity for oxygen diffusion due to endothelial cell edema leads to diminished levels of brain oxygen tension in CNS tissue after TBI [46]. Structurally, the activation of MMPs and increased oxidative stress leads to the degradation of vascular basement membrane proteins which results in endothelium instability and loss of cellular integrity [47].

Other factors promote hypoxia and ischemia during neuroinflammation. Neuronal death from cellular hypoxia causes the release of pro-inflammatory cytokines and chemokines. Excess neutrophil activation exacerbates inflammation and competes with neurons for limited oxygen [48]. During NETosis, neutrophil pseudopods that adhere to the endovascular endothelium hinder microcirculatory function and further promote hypoperfusion and neutrophils adherence. Additionally, hypoxic events after TBI induce hypoxia-inducible factor -1a and nuclear factor kappa B (NF-kB) leading to prolongation of neutrophil survival time and activation [49].

The clinical implications of ischemia and tissue hypoxia are significant. A large portion of TBI patients experience ischemic-hypoxic injury [50]; however, the real ischemic burden in TBI is likely underestimated. Anoxic brain injury following TBI is

strongly associated with worse functional outcomes [51]. Ischemic burden, therefore, may be an important intermediate surrogate of disease in TBI research.

3.3 Neuroexcitotoxicity and energy dysfunction

Neuroexcitotoxicity and disrupted energetics after TBI potentiate neuroinflammatory cascades. At injury onset, mechanical stretching of neurons elicits glutamate-independent neuronal activation, inhibiting the magnesium blockade of calcium channels on the cell membrane. In this environment, neurons and glial cells transition into an excessively neuroexcitatory state [52]. Secondary brain injury ensues if reduced cerebral perfusion or ischemia occur in the setting of increased metabolic demand.

Glutamate-dependent pathways are the primary drivers of neuroexcitotoxicity. Glutamate, the most abundant excitatory neurotransmitter of the CNS, contributes to the excitotoxic milieu and is released in large amounts after neuron lysis [8, 53, 54]. Animal models demonstrate an increased extracellular glutamate concentration post-trauma due to altered glutamate transport receptor function and concentration [55, 56]. The acute elevation in glutamate levels overwhelm NMDA and AMPA receptors, exacerbating neuronal injury and death. Ultimately, an influx of calcium into the cell activates apoptosis [57]. Apart from cellular effects, NMDA receptor activation induces inflammatory gene expression. Additionally, TNF and IL-1ß glutamate transporters on astrocytes interfere with glutamate clearance; together, this creates sustained excitotoxicity and inflammation [58].

The post-trauma brain is also affected by disturbed ionic homeostasis and increased energy demands from post-injury repair mechanisms. Microdialysate studies in clinical and experimental TBI models have shown increases in interstitial lactate, adenosine and a concurrent decrease in glucose, consistent with a state of metabolic crisis [59, 60]. Murine TBI models have demonstrated that both acute and delayed changes in energy metabolism occur. Increased glucose consumption and decreased ATP availability were observed on days 1 and 3 post-trauma [61]. Furthermore, mitochondrial fission is disrupted after TBI, contributing to the inability of neurons and glial cells to meet metabolic needs [62].

3.4 Oxidative stress

Oxidative stress describes a state where oxygen-derived free radicals overwhelm the scavenging antioxidant system and is closely related to metabolic dysfunction. Ischemia is an important trigger that promotes anaerobic metabolism and cellular acidosis that activates pH-dependent calcium channels [63]. Decreased cytoplasmic pH triggers increased ROS production which is ultimately involved in lipid peroxidation. Proton extrusion by microglia further exacerbates extracellular acidosis seen in TBI [64].

Post-TBI oxidative stress is regulated by microglia. Following brain injury, microglia activate nicotinamide adenine dinucleotide phosphate oxidase (NOX) and inducible nitric oxide synthase (iNOS). Upregulation of iNOS leads to the production of NO, which when coupled with superoxide, leads to the formation of peroxynitrite. The damaging role of peroxynitrite has been shown indirectly by the ability of peroxynitrite-derived free radical scavengers to attenuate brain injury in TBI [65]. NOX is present in other neuroinflammatory cells such as neutrophils and phagocytic cells, contributing to oxidative stress through the production of superoxide and hydroxyl radicals [66].

ROS will directly target mitochondria, impair ATP synthesis and lead to secondary injury [67]. Additionally, calcium overload in CNS mitochondria will disrupt fusion and fission, two important mechanisms essential in mitochondrial function. This promotes additional free radical formation [68]. Mitochondrial dysfunction due to oxidative stress results in functional impairment and is associated with reduced neuronal repair. Oxidative stress occurs even in mild TBI [69], with ongoing pre-clinical research investigating the effectiveness of anti-oxidant therapy in TBI [70].

3.5 Glymphatic and lymphatic dysfunction

The glymphatic system is a complex transport system that facilitates the exchange of cerebrospinal (CSF) and interstitial fluid by aiding the movement of water, metabolites and immune molecules [71]. Facilitated by AQP-4 channels, glymphatics provide a drainage route for CSF and aid in the surveillance of the CNS by carrying macromolecules and activated antigen-bearing dendritic cells to local lymph nodes where antigens can be presented to activate the adaptive immune response.

TBI and neuroinflammation have been shown to impair glymphatic system drainage. In animal models, TBI dramatically impairs the paravascular influx of CSF MRI tracer, especially in the ipsilateral cortex [72]. A > 25% reduction in glymphatic solute clearance is observed after TBI [73]. Glymphatic function is dependent on AQP-4 channels localized on astrocytes. TBI-induced damage to AQP4 channels contributes glymphatic dysfunction [74]. Re-localization of AQP4 channels away from astrocytic end feet is associated with reduced waste and immune cell clearance [75, 76]. In addition to glymphatics, CNS clearance is also facilitated by lymphatic vessels lining the dura and meningeal vessels. These are rich in T and B cells that readily migrate to injured brain region [77].

Failure of glymphatic and lymphatic function will lead to the accumulation of damage and waste products such as tau, beta-amyloid, pro-inflammatory mediators, and astrocytic proteins [74]. Glial scar formation and reactive astrogliosis may also

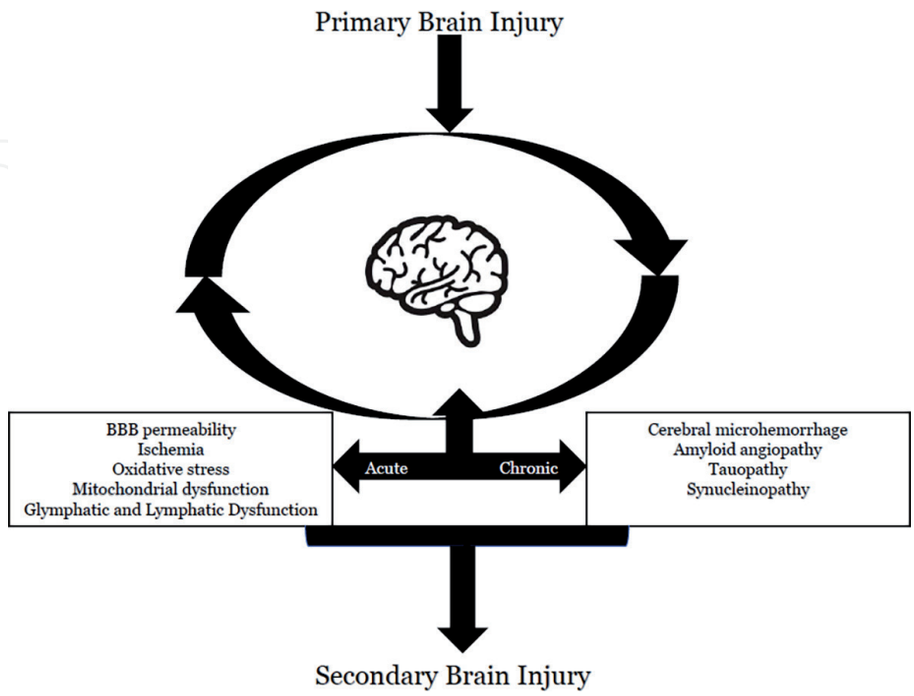

Figure 2.
Conceptual schematic of neuroinflammatory Cascade.

occur [73]. The accumulation of both immune cells and waste products triggers further neuroinflammation by activation of pattern recognition receptors on microglia. These cells and peptides have an important role in the development of neurofibrillary tangle pathology and neurodegeneration in secondary brain injury and the development of CTE (**Figure 2**) [73].

4. Neurodegeneration and long-term sequelae of neuroinflammation

Neurodegeneration and chronic symptomatology occur in survivors of both single and repeated TBI, such as military personnel and contact sport athletes. Progressive symptoms long after trauma has been described as early as the 1920s [78], but the underlying pathogenesis is complex. Recent advances in research implicate chronic inflammation in the development of post-TBI neurodegenerative disease. Autopsy investigation of those who survive >1 year after TBI revealed increased amounts of CNS microglia compared to control tissue [24, 79]. Similarly, positron emission tomography (PET) imaging of professional football players showed greater levels of microglia compared to age-matched controls [80]. Here, we describe distinct pathological and clinical findings that are associated with chronic inflammation following TBI.

4.1 Cerebral microhemorrhage & amyloid angiopathy

The presence of cerebral microhemorrhage is often an indicator of traumatic axonal injury [81, 82]. Older TBI patients are particularly at risk of developing cerebral microbleeds post-TBI due to the senescent BBB having a higher permeability exacerbated by chronic neuroinflammation [83]. Cerebral amyloid angiopathy (CAA) is also a risk factor for microhemorrhage formation, as amyloid accumulation in the vessel walls, especially in the elderly, make them prone to rupture [84, 85]. Apolipoprotein E4 (ApoE4), an important regulator of chronic neuroinflammation, might play a central role. The ApoE4 allele predisposes later development of CAA in TBI survivors [86]. Further study is needed to elucidate the specific mechanism that ApoE4-mediated neuroinflammation results in CAA.

Trauma-induced microhemorrhage and CAA can occur in younger populations, especially with repetitive trauma. In a study of sport-related repetitive head trauma, athletes participating in high-risk sports had increased CAA burden in the frontal and leptomeningeal regions compared to a control population [87]. Microhemorrhage and CAA is seen in TBI survivors in their second and third decades [86, 88]. Since CAA is often a post-mortem diagnosis, the causality of trauma on CAA is still under investigation. Recently, animal models have demonstrated that increased transforming growth factor (TGF-β) expression is associated with the development of CAA after TBI [89].

4.2 Dementia & other neurodegenerative diseases after brain trauma

Early population studies have linked TBI to cognitive decline in both Alzheimer's dementia (AD) and non-Alzheimer's dementia [90–93]. More recent epidemiologic analysis suggests that TBI is significantly associated with dementia, but not AD specifically [90].

Amyloid beta (Aβ) and tau-induced inflammation are important in the pathogenesis of neurodegenerative disease. A rat TBI model demonstrated that progressive atrophy and neuronal cell death continues >1 year after the trauma [94]. PET imaging studies have shown increased Aβ deposition after TBI [95]. Neuroinflammation plays a role in the pathogenesis of tau accumulation [96]. Both acute and chronic activation of the innate immune system exacerbates tau phosphorylation [96–98]. In a rat model of chronic inflammation, implantation of slow-release IL-1β pellets was associated with increased tau phosphorylation [99]. Knocking out receptors that suppress microglial activation results in an enhanced neuroinflammatory response and tau phosphorylation [100]. Conversely, immune suppression is associated with a reduction of p-tau [101]. Anti-inflammatory medications such as infliximab, an TNF-α antagonist, also reduced levels of p-tau in murine models [102]; however, in vitro application of TNF-α and IL-6 did not increase tau levels [103, 104]. Further investigation is needed to better understand the mechanisms by which inflammation after TBI promotes tau pathology.

Parkinson-like symptoms also occur after trauma, suggesting a potential α-synucleinopathy in chronic TBI survivors [105, 106]. Scientific evidence for the importance of α-synuclein pathology is less robust compared to Aβ and tauopathies. Murine models have demonstrated an increase in α-synuclein accumulation in the substantia nigra ipsilateral to the trauma. Furthermore, a notable upregulation of inflammatory cells was observed in the substantia nigra and cerebral peduncles, suggesting that inflammation mediates alpha-synucleinopathies post TBI [105].

4.3 Neuroinflammation in chronic traumatic encephalopathy

Chronic traumatic encephalopathy is a syndrome of neuropsychiatric, cognitive and motor deterioration after repeated exposure to head trauma. Pathologically, CTE is a tauopathy characterized by perivascular accumulation of p-tau in neurons and astrocytes within the cortex [107]. As previously described, neuroinflammation is involved in the formation of p-tau. Immunohistologic analysis of samples from the Boston University-VA Concussion Legacy Foundation Brain Bank showed that a longer history of repeated head injury was associated with increased neuroinflammation [108]. CTE genetic transcripts from brain tissue contain dysregulated neuronal genes that result in inflammatory glial dysfunction. Furthermore, CTE astrocytes express gene transcripts that were associated with neuroinflammation and aging [109]. Autopsy investigation of mild CTE brain tissue revealed increased microglia activation in perivascular regions of subcortical white matter [106, 110, 111]. In vivo diagnostics of National Football League (NFL) athletes utilizing PET imaging revealed an increase in translocator protein expression by activated microglia and reactive astrocytes compared to controls [80, 95]. Further research is needed to elucidate the pathway and time course of inflammation and development of CTE, as well as genetic and epigenetic risk factors that increases the likelihood of CTE after head trauma.

5. Animal models of post-injury neuroinflammation

The initiation and propagation of neuroinflammation is a complex and multifaceted process. Animal models are necessary to study disease mechanisms, identify novel biomarkers, and study the pharmacologic effects of investigational drugs. Given

the current limited treatment options in TBI management, translational research should prioritize research that is validated, feasible and most readily will impact patient care.

5.1 Selection of animals

Several animal models have been used in TBI research. Interspecies differences in cerebral anatomy, complexity, and size are important factors when selecting the model. Animal intelligence varies significantly, although brain size is not correlated with overall intelligence [112]. Most preclinical TBI research is conducted in rodents. Rats and mice are cost-effective, have a large physiological database, permit extensive behavioral testing and have the ability to utilize transgenic animals. A disadvantage is the small lissencephalic brain, characterized by less white matter compared with higher species. In particular, the utilization of genetically engineered mice has aided in the evaluation of key molecules related to microglia activation and neuroinflammation following TBI [26].

More recently, the use of large animals in TBI research has increased. The effect of brain injury on lissencephalic animals as compared to larger ones with gyrencephalic structures differ, at least in part by differences in brain structure and mechanics related to the presence of large gyri [113, 114]. The porcine model has been proposed as an ideal pre-clinical animal model based on feasibility and the anatomic and physiologic similarities to humans in comparison to rodents [115]. This includes cortical structure and proportion of gray-to-white matter that more closely resembles humans [116]. Both mild and more severe TBI can be modeled in the pig.

5.2 Models of injury

Several models of injury have been developed to resemble the pathophysiology of human TBI [113]. The most used ones are the lateral fluid percussion (LFP) model, the controlled cortical impact (CCI) model, the weight drop-impact (WD) model, and the blast model. The chosen mechanism of injury is based on researcher experience and the type of TBI being modeled. Traumatic injury can be delivered over an intact skull to mimic concussion or diffuse injury or delivered to exposed dura to mimic more severe and focal TBI.

The CCI model was first described in the 1980s and is now one of the most used TBI models. It utilizes a pneumatic or electromechanical device with an impactor tip to induce brain displacement. The impact location, velocity, depth, and dwell time can be controlled. Compared to other methods of mechanical injury, namely LFP and WD injury, CCI allows for more control of the force of injury, showing high reproducibility, low animal mortality, and reduced rebound injury [117]. Current CCI rodent models produce the most optimal conditions for understanding the molecular, cellular and biochemical mechanisms of secondary brain injury after focal blunt-force TBI [118].

The WD and LFP models are also used to study neuroinflammation. In WD injury, a fixed amount of weight is dropped from a set height onto either exposed dura or closed skull. The closed-head model can be utilized to cause diffuse neuronal injury and has been shown to result in elevation of apoptotic and neuroinflammatory markers. The LFP model was first established in rabbit and cat models but has since been adapted for rodents. It involves the generation of a fluid pulse that impacts against an exposed dural surface of the brain and produces more diffuse injury compared to CCI. Reproducibility requires extensive preparation and model experience to minimize injury variability. The blast model mimics the injuries commonly encountered in

war. The force is produced by utilizing shockwave tubes or open field detonation. This model has been utilized to study CTE and its associated neuroinflammation [119].

6. Biomarkers of neuroinflammation

Plasma biomarkers of post-TBI inflammation are commonly used in translational research given their accessibility, the ability to serially sample, the presence of validated assays for detection, and the ability to form large biorepositories and databases. Brain tissue and CSF biosamples can be difficult to obtain but may offer a more accurate picture of the local environment. There has been growing interest in identifying and validating in vivo markers of neuroinflammation with special focus on using functional MRI and PET to measure intermediate biomarkers of disease.

The number of biomarkers of neuroinflammation studied is rapidly increasing [26]. No gold standard biomarker has been established. Understanding the mechanisms of expression of these markers will advance our understanding of TBI and help develop future therapeutics targeting the acute and chronic consequences of neuroinflammation. Here, we aim to introduce biomarkers of importance and emerging interest in the field of post-TBI neuroinflammation and discuss potential limitations.

6.1 Peptide biomarkers

Peptide cytokines are the most used biomarkers of inflammation. In the acute period, TBI induces damage to the cellular membrane, leading to the release of DAMPs and upregulation of TNF-α and other cytokines from microglia and astrocytes. Historically, the cytokines most studied include INF-γ and several ILs. There are important limitations to consider when using cytokine biomarkers. Changes in cytokine expression can be non-specific, and their relationship with clinical outcomes is variable. TNF-α is generally considered a pro-inflammatory cytokine associated with detrimental effects in TBI [120, 121]; however, studies have suggested that it also has an anti-inflammatory component that promotes motor recovery after TBI [122]. Several studies have found limited correlation between ILs such as IL-1β and IL-6 and outcome in human TBI [123, 124]. Chemokines, generated by activated microglia and astrocytes to recruit peripheral immune cells to the site of injury, can also be assayed from biofluids. The CCL and CXCL subclasses of chemokines have been most extensively characterized in animal models of post-TBI inflammation [26]. The expression of cytokines and chemokines is regulated several ways; therefore, measurements may provide a general description of the inflammatory response post-TBI but might lack the specificity in describing specific biochemical pathways or differentiating between CNS and systemic inflammation.

More novel peptide biomarkers of interest include neurotransmitter levels and protein aggregates. Post-TBI, a large increase in the release of extracellular glutamate and other amino acids can be studied. Glutamate is an excitatory amino acid that can lead to toxic effects via activation of different receptors such as N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA) [53, 54]. In clinical research, glutamate can be measured longitudinally using bedside microdialysis techniques [125]. Protein aggregates such as Aβ, tau and α-synuclein are challenging to measure. Historically, they have been limited to post-mortem analysis; however, recent advances in PET imaging have allowed in vivo assessment of tau burden [126].

6.2 Glial and immune cells

Microglial activation and neutrophil recruitment and activation have been of principle interest in post-TBI neuroinflammation research. Common immunohistochemical measures of microglial activation include Iba-1 and CD68 and downstream markers such as TLRs and NF-kβ [26, 127]; however, flow cytometry-based analysis of microglia remains the gold standard. The identification of translocator protein 18 kDa (TSPO), located on the mitochondrial membrane of microglia, has allowed the development of radioligands with PET visualization of activated microglia in vivo [128].

Activated neutrophils and NETosis are measured commonly by TLR4 expression, CitH3 localization, and DNase-I expression, which acts to degrade neutrophil-derived extracellular traps [129]. Measures of endothelial adhesion molecules including selectins, vascular cell adhesion molecules (VCAMs), and intercellular adhesion molecules (ICAMs) provide an indirect measurement of peripheral immune cell recruitment across the BBB. Antibodies against several of these adhesion molecules have been developed and utilized for in vivo visualization by MRI but is mostly validated in ischemic stroke models [130–132]. The longitudinal study of glial and immune cell phenotypes in chronic post-TBI inflammation may further demonstrate their importance mediating long-term morbidity after brain injury.

6.3 Omics-based biomarkers

Multi-omics, including genomics, proteomics, metabolomics and lipidomics can be used to characterize the complex chemical pathways involved in TBI pathogenesis for use in prediction models and drug development. Genetic analysis can elucidate the genetic influence on post-TBI outcomes and would allow precision treatment based on genetic traits. In analysis of a large biologic database, genetic modules that showed greatest change in expression were primarily associated with neurodevelopment and immune inflammation [133]. As previously discussed, the ApoE-4 allele is also of special interest in the field of chronic TBI-induced inflammation. ApoE protein is a mediator of cholesterol and lipid transport in the brain and has been shown to attenuate glial activation and CNS inflammatory responses. In experimental models, a small peptide of ApoE [133–149] was shown to significantly improve histological and functional outcomes following TBI [134].

Lipid biomarker analysis might hold several advantages over proteomics and peptide biomarkers in TBI. Limitations of proteomics include a bias towards highly abundant proteins, difficulty in measuring protein aggregates, and challenges in using plasma samples to assay proteins generated in the CNS [135]. In comparison, lipids are abundant in the CNS and cross the BBB by active transport. Bioactive lipids that mediate inflammation are of particular interest due to their role in both pro-inflammatory cell signaling and resolution of inflammation. Omega-3 polyunsaturated fatty acids (ω-3 PUFAs), including eicosatetraenoic acid and docosahexaenoic acid, are active compounds with anti-neuroinflammatory properties. In pro-inflammatory states, they are metabolized by lipoxygenases (e.g. 15-LOX and 5-LOX) to specialized pro-resolving lipid mediators (SPMs) such as resolvins, protectins, and maresins. In experimental models, ω-3 PUFAs act as a neuroprotectant in TBI by modulating neuroinflammation through SIRT1 mediated deacetylation of the HMGB1/NF-kb pathway [136]. A greater understanding of the biologic actions of SPMs and other

lipid signaling molecules, and the mechanisms of lipid metabolism dysregulation related to TBI would identify novel therapeutic targets.

7. Current therapies with anti-inflammatory properties

Attenuating neuroinflammation following TBI has been a treatment target for several decades to generally mixed results. Certain current standard treatments potentially work through anti-inflammatory pathways, while neuroinflammation remains a focus for novel therapeutic development.

7.1 Steroidal and non-steroidal anti-inflammatory drugs

Steroids are not routinely used in the management of TBI. They were initially investigated for their potential to decrease neuroinflammation and intracranial pressure in severe TBI. Several randomized trials were conducted with conflicting results. The CRASH trial, a randomized placebo-controlled multicentric trial evaluated the use of high dose methylprednisolone after TBI. Interim analysis of the first 10,008 patients demonstrated increased mortality in patients receiving steroids, resulting in early study closure [137]. The mechanisms of harm are not fully understood; however, there is little interest in a future study of the effect of high-dose steroids in TBI.

The use of non-steroidal anti-inflammatory drugs (NSAIDs), such as COX-1 and COX-2 inhibitors ibuprofen and indomethacin, have shown varied results in pre-clinical studies. Although a strong anti-inflammatory action is observed if dosed shortly before or after injury, clinical effect has not been demonstrated [138]. Ibuprofen can cross the BBB and localize in injured tissues and has been studied as an anti-inflammatory agent in post-TBI stem cell grafting [139]. In a rat model of TBI, extended use of high dose ibuprofen significantly worsened neurocognitive outcomes [140]. Indomethacin administration is associated with reduced intracranial pressure secondary to reduced CBF [141], however, it has limited therapeutic potential due to its inability to cross the BBB [142]. Additional concerns over bleeding due to inhibition of platelet cyclooxygenase further limit their use acutely after TBI.

Minocycline, a second-generation tetracycline antibiotic, has been extensively studied in TBI due to its anti-inflammatory, neuroprotective and anti-apoptotic properties [143]. In a murine model, minocycline administration resulted in marked reductions of activated microglia and decreased tissue IL-1B levels [144]. In a gerbil model, when administered shortly after ischemia, minocycline was neuroprotective against brain ischemia by preventing activation of microglia and the appearance of NADPH reactive cells [145]. A clinical trial of 15 patients, performed to assess the safety and feasibility of minocycline showed that it was safe for moderate-to-severe TBI with a potential effect on clinical outcomes [146]; however, long-term use may be associated with gastrointestinal and neurologic adverse events [147]. The current use of minocycline is limited due to the lack of large longitudinal clinical evidence to support its use for TBI-related neuroinflammation.

7.2 Anti-epileptic drugs

Seizures are a common consequence of TBI. Their occurrence is associated with worse functional outcomes and if uncontrolled, can contribute to long-term

neurodegeneration [148]. Neuroinflammation has been proposed as a mechanistic cause of seizures post-TBI. Pro-inflammatory cytokines like TNF-α and IL-1β can lead to hyperexcitability through their action on glutamate and NMDA receptors, increasing susceptibility to seizures [149]. Classical anti-epileptics such as phenytoin and benzodiazepines have not been shown to reduce the risk of developing late post-traumatic epilepsy but rather decrease the early post-traumatic seizures occurring within the first 7 days [150]. Whether anti-epileptic drugs are generally pro-inflammatory or anti-inflammatory is still not verified. Levetiracetam interestingly has been found to mediate its anti-epileptogenic effects, at least partially, through modulation of inflammation in seizing brain regions. This was demonstrated by the reduction of reactive gliosis and IL-1β following administration of levetiracetam in epileptic animals [151]. In comparison, an in vitro model of epilepsy showed increased microglial activation in cultures treated with valproic acid when compared to carbamazepine, gabapentin, and phenytoin [152].

7.3 Hyperosmolar fluids

Hyperosmolar therapy is widely used to treat TBI-related cerebral edema and elevated intracranial pressure. The early action is primarily due to the creation of an osmotic gradient that draws interstitial fluid from the brain tissue into the intravascular space. Hyperosmolar therapies, typically hypertonic saline or mannitol, have been investigated for their anti-inflammatory properties. In a rat model of intracerebral hemorrhage, hyperosmolar fluid reduced microglial activation and promoted phagocytic anti-inflammatory M2-like phenotype in perihematomal and contralateral tissues [153]. In a clinical study of 65 patients with severe TBI, hypertonic saline was found to attenuate expression of pro-inflammatory cytokines such as TNF-α and IL-10 [154]. Additionally, hyperosmolar therapy was found to downregulate AQP-4 expression in perivascular astrocytes [155]. These findings add further support to hyperosmolar therapy for their neuroinflammatory modulation.

In clinical practice, bolus doses of hyperosmolar therapy are standard of care for clinical or radiographic cerebral herniation; however, the use of continuous hypertonic saline infusion after TBI remains controversial with a recent randomized controlled trial showing no benefit of this therapy on 6-month functional outcomes [156]. Further study is needed to determine the anti-inflammatory properties of hyperosmolar therapy, and which patients are most likely to benefit from treatment.

7.4 Tranexamic acid

Tranexamic acid (TXA) is a lysine analogue that is widely studied as an antifibrinolytic in life-threatening hemorrhage. In TBI, TXA is more widely accepted and used based on recent clinical trial data. The CRASH 3 trial demonstrated that TXA reduces head injury-related deaths without increasing the thrombotic risk [157]. TXA has been shown to have both pro-inflammatory and anti-inflammatory effects in the surgical literature [158, 159]. In animal models, it inhibits plasmin which normally activates the migration of macrophages through modulation of BBB integrity by degrading laminin, fibronectin, and collagen [160]. Specifically in models of TBI, early TXA has been shown to reduce TBI-induced coagulopathy. Reduced bleeding and blood products in the CNS might limit pro-inflammatory triggering. TXA may generally suppress circulating immune cells; however, measurable reductions in anti-inflammatory markers were not observed in a mouse model of TBI [161]. Although

TXA is approved to be safe and well-studied in TBI, its full impact on neuroinflammation has not been validated.

7.5 Hypothermia

Hypothermia has been investigated in several acute neurological conditions. In TBI, humoral and cellular neuroinflammation is temperature-dependent. In preclinical trials, hypothermia has been shown to decrease free radicals, TNF-α mRNA levels, and BBB permeability [162]. Several clinical trials of hypothermia have been done in TBI, with overall low-quality evidence. A meta-analysis in 2014 suggested a possible trend towards reduced rates of death, vegetative state, and disability with hypothermia [163]; however, the report was inconclusive. Larger clinical trials are needed to assess the efficacy and safety of hypothermia in reducing neuroinflammation in TBI and improving clinical outcomes.

8. Future research directions

Advances in novel therapies that target neuroinflammation after TBI has been limited by an incomplete understanding of the pathologic mechanisms of disease. Translational and clinical research is needed to further identify both modifiable and non-modifiable factors that influence the inflammatory response, and how acute neuroinflammation after brain injury transitions to a chronic inflammatory state. Characterizing both acute and chronic processes will lead to biomarker discovery and support the development of novel therapeutic agents aimed at improving long-term patient outcomes.

8.1 Determining how biologic factors modify the inflammatory response post-injury

Non-modifiable biologic factors such as age, sex, and ethnicity likely influence the post-TBI inflammatory response. A better understanding of these effects will improve patient-tailored treatments. In animal models, age appears to exacerbate inflammatory-mediated secondary brain injury. In comparison to younger animals, aged rodents show higher mortality after CCI, more pronounced brain edema formation, and worse neurobehavioral scores [164]. This was associated with an early rise of inflammatory markers in aged animals compared to the delayed response observed in younger mice. Peripherally derived CCR2(+) macrophages accumulate in greater amounts in aged brains after TBI compared to young animals and likely mediate the enhanced neuroinflammatory response associated with age [165]; however, the role of other immune cells has been suggested [166]. Ketone metabolism, which improves energetics and reduces inflammation, is reduced in older age [167, 168]. Additional research is necessary to fully describe the age-dependent effects of TBI and how age influences the efficacy of candidate drugs.

Although the majority of TBI occurs in males, sex-based differences in TBI pathophysiology and outcomes should be understood. Elevations in endogenous sex hormones, specifically progesterone and allopregnanolone, have been demonstrated to have anti-inflammatory and neuroprotective properties [169]. Sex steroids are also known to regulate astrogliosis and microglia activation and may account for sex differences [170]. Investigational drugs, including steroids, likely have differential impact

in men and women, highlighting the need to study efficacy in diverse patient populations. Although many identified differences in physiology between sexes exist, the literature of the impact of sex on functional outcomes after TBI is conflicting [171].

8.2 Important research questions for novel therapeutic approaches

Despite the large body of anti-inflammatory drugs studied in both preclinical and clinical research [172], their standard use in human TBI has not yet been supported by high-quality evidence. Many important questions remain, including the identification of drugs that should be prioritized for clinical trials. Candidate drugs or anti-inflammatory drug classes may not be mutually exclusive and could have a synergistic effect when used together. In animal models, combination of progesterone and vitamin D, fresh frozen plasma and valproic acid, and C3a and C5a receptor blockers demonstrated greater anti-inflammatory and neuroprotective effects then when used individually [173–175]. The optimal timing and duration of potential treatments are also unknown. Given both the acute and chronic inflammatory phases of TBI contribute to functional outcomes, future study is needed to determine the utility of anti-inflammatory drugs administered beyond the acute phase.

Both short and long-term outcome measures are necessary to establish the efficacy of novel therapies. In pre-clinical research, measures of inflammatory cytokines are insufficient to characterize the complex pathogenesis of TBI. Of emerging interest, use of "omics" that encompass genomics, proteomics, metabolomics and lipidomics will provide a comprehensive picture of the molecular pathways leading to secondary brain injury and would allow for precision medicine [176]. Given the chronic morbidity in TBI survivors, the use of long-term outcomes, including biomarkers of neurodegeneration and neurocognitive and functional outcomes are needed in both animal models and clinical trials. Demonstrating reduced mortality in TBI can be difficult, especially in moderate-to-severe TBI where outcomes are generally poor, while alternative outcome measures described may be more sensitive and meaningful.

TBI is a ubiquitous disease impacting all ages, genders, racial, socioeconomic and geographic backgrounds. Preferred drug therapies should be safe, feasible and effective across mixed patient populations and medical environments. Behavioral modifications may play a role in attenuating sequelae of neuroinflammation. Complementary therapies such as meditation and massage may reduce inflammation [177], while dietary changes can also impact chronic inflammation [178, 179]. Ultimately, a multi-disciplinary and systems-based approach to TBI is needed to further our understanding of this challenging disease and promote the development of novel treatment approaches.

8.3 Conclusion

In conclusion, post-TBI neuroinflammation is a complex blend of processes that is involved in acute and chronic brain injury. Although it is intended to promote repair, ongoing neuroinflammation can impede recovery. The inflammatory cascade in TBI affects the CNS milieu and brain functions long after the initial traumatic phase. Although pre-clinical research suggests that treating neuroinflammation as a therapeutic target may be beneficial, clinical trials have not yielded measurable benefits. Understanding the intricacy of these processes will assist clinicians and scientists in creating an individualistic approach to monitor and limit inflammation after TBI with the goal to reduce secondary brain injury, enhance neurological repair, and improve patient outcomes.

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