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Beyond the Impact: Decoding the Inflammatory Cascade in Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is a large-scale health issue which reports high levels of long-term disability and death. Beyond the initial mechanical damage TBI sets in motion a series of secondary injury processes in which neuroinflammation is very much at the core. In this review we look at the patho-physiological processes which follow TBI with a close look at glial cell action, inflammasome signaling, and the chronic inflammatory environment which play a role in the development of long-term neurodegeneration.

After TBI the blood barrier breaks down which in turn allows for peripheral immune cells to enter the central nervous system. Resident microglia and astrocytes become activated which in turn produce a range of pro inflammatory cytokines and reactive oxygen species. This immune response which is at first protective can become dysregulated and may persist over time thus contributing to ongoing neuronal damage and synaptic dysfunction. In the center of this response are inflammasomes which are the NLRP3 inflammasome that play a role in the maturation and release of key pro inflammatory cytokines like IL-1beta and IL-18.

Chronic neuroinflammation in the wake of TBI is reported to play a large role in progressive cognitive decline and in the increase of neurodegenerative diseases such as Alzheimer's and Parkinson's. We present a review of present research related to the cell and molecular bases of inflammation post TBI which also puts into focus the roles of microglia, astrocytes, inflammasomes, and systemic immune responses.

These we have as a base which is then used to put forth new therapeutic approaches which in turn will improve the long-term effects of TBI. We see in chronic neuroinflammation a very promising area for intervention to better the health outcomes in TBI patients and to also in turn reduce the social impact of what is a very complex and at time disabling condition.

Keywords: Traumatic Brain Injury, Neuroinflammation, Inflammasome, Chronic inflammation

Introduction

Traumatic brain injury (TBI) refers to damage to the brain resulting from external mechanical forces such as blunt trauma, blast injuries, or penetrating objects. These injuries disrupt normal brain function and trigger a complex cascade of secondary events, including the breakdown of the blood-brain barrier (BBB), infiltration of peripheral immune cells, and activation of resident glial populations such as astrocytes and microglia. Both the initial mechanical insult and the subsequent inflammatory response contribute significantly to long-term morbidity, mortality, and reduced quality of life in affected individuals [1].

TBI is clinically classified into mild, moderate, and severe categories based on parameters such as the Glasgow Coma Scale (GCS), duration of loss of consciousness (LOC), post-traumatic amnesia (PTA), and neuroimaging findings. Mild TBI is characterized by a GCS of 13–15, LOC under 30 minutes, and PTA lasting less than one day, typically with normal imaging. Moderate TBI includes a GCS of 9–12, LOC lasting 30 minutes to 24 hours, and PTA of 1–7 days. Severe TBI is defined by a GCS score of 3–8, LOC exceeding 24 hours, and PTA longer than 7 days, with neuroimaging findings ranging from normal to severely abnormal.

Epidemiologically, TBI affects an estimated 69 million people worldwide annually, with incidence rates approximately three times higher in low- and middle-income countries compared to high-income nations [2].

TBI-related brain injuries are broadly categorized into primary and secondary injuries. Primary injury occurs now of impact and involves localized tissue damage. Secondary injury evolves over hours to days post-injury and is characterized by widespread neuronal dysfunction caused by mechanisms such as diffuse axonal injury, intracranial edema, excitotoxicity, oxidative stress, and neuroinflammation.

At the cellular and molecular level, traumatic impact triggers the release of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) from injured cells. These molecules activate inflammatory cascades, leading to disruption of CNS homeostasis. Ionic imbalance occurs due to the dysregulated activity of glutamate, a major excitatory neurotransmitter. Neuronal depolarization results in excessive glutamate release, which promotes excitotoxicity and alters ionic gradients—leading to sodium and calcium influx and potassium efflux.

This ionic dysregulation places significant metabolic stress on neurons. ATP-dependent ion pumps, particularly the Na^+/K^+-ATPase, are overactivated to restore homeostasis, resulting in accelerated ATP depletion. Mitochondrial dysfunction ensues as calcium accumulates intracellularly, impairing ATP synthesis and promoting hyper glycolysis and lactate buildup. The combined energy deficit and calcium overload trigger enzymatic pathways that culminate in programmed cell death and further tissue damage [3].

Neuroinflammation and the Role in TBI

The central nervous system (CNS) has historically been regarded as immunologically privileged, with the blood-brain barrier, microglia, and cytokines tightly regulating inflammation. In healthy CNS, resting microglia, characterized by elongated processes, maintaining homeostasis by clearing cellular debris and modulating neuronal connectivity. Following traumatic brain injury (TBI), microglia detect pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) via Toll-like receptors (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptors, adopting an activated, amoeboid morphology to migrate to the injury site. Activated microglia is traditionally categorized into pro-inflammatory M1 and neuroprotective M2 phenotypes, with M1 expressing pro-inflammatory cytokines (e.g., TNF-α) and M2 promoting anti-inflammatory responses and tissue repair via IL-10 secretion.

However, recent studies challenge this binary classification, proposing a spectrum of microglial activation states. For instance, M2 subtypes (M2a, M2b, M2c, M2d) exhibit distinct functions, such as enhanced phagocytosis (M2a), mixed inflammatory activity (M2b), tissue remodeling (M2c), or angiogenesis (M2d). Emerging evidence suggests that microglial identity may be better defined by gene expression profiles or surface markers, particularly in chronic conditions like Alzheimer's disease, where disease-associated microglia (DAM) play a critical role in pathology. This evolving understanding of microglial dynamics underscores the need for refined therapeutic strategies targeting neuroinflammation in TBI [3].

After a trauma the microglia and the astrocytes activate and interact to begin with their inflammatory process. Astrocytes, similarly, to microglia, maintain CNS homeostasis and regulate inflammatory cytokine release regulated by formation of the inflammasome. Astrocytes are the most numerous cell type in the brain and have several roles in maintaining the CNS environment and together with neurons maintain ionic and water balances, control blood flow, form the BBB, and modulate synaptic transmission. Another characteristic astrocyte shared with microglia are their long processes that sample their environments for changes in homeostasis. Astrocytes form complex networks of gap junctions and closely adhere to neurons, and through unique end-feet adhere to blood vessels forming the BBB.

Once homeostasis is disrupted, astrocytes become activated (astrogliosis), which is indicated by an increase of glial fibrillary acidic protein (GFAP), and like microglia, secrete numerous inflammatory products, including cytokines and chemokines such as IL-1β, TNF-α, growth factors and ROS. Factors that stimulate astrogliosis are DAMPs, PAMPs, cytokines from microglia, Aβ from neurons, albumin from BBB disruption, and synaptic glutamate and ATP. In fact, the exact mechanism of astrogliosis is still not fully understood.

Blood brain disruption is another key factor that allows the monocyte entry into the CNS which has a role in inflammation secondary to the injury. Even in mild TBI, where major bleeding is not present, the BBB structure can be damaged or altered both acutely and chronically, even several months and years after the traumatic event as shown in human post-mortem tissue and in preclinical models. The consequences of primary injury on the BBB structure depend on the age, the type, and the severity of the lesion.

The "opening" of the BBB can be seen as early as 3 min after injury in a concussion model. The tight junction protein complex could be altered after TBI. In fact, pial, and intracerebral blood vessels present decreased claudin-5 and occluding expressions soon after injury [4].The mitogen-activated protein kinase 5 (MEK5)/extracellular signal-regulated kinase 5 (ERK5) pathway, a member of the conventional mitogen-activated protein kinase (MAPK) family, modulates inflammation in traumatic brain injury (TBI). Activated by stressors such as cytokines and physical trauma, this pathway involves a cascade where MAPK kinase kinases (MAP3Ks) phosphorylate MAPK kinases

(MAP2Ks), which activate effector MAPKs, including MEK5/ERK5. Once activated, ERK5 translocate to the nucleus, phosphorylating substrates like transcription factors to regulate cell survival, proliferation, and apoptosis.

In TBI, MEK5/ERK5 downregulates pro-inflammatory factors and cell cycle proteins, mitigating microglial polarization and β-cell apoptosis, thus offering a potential therapeutic target for managing neuroinflammation [3].

The assembly of the inflammasome- a multi-protein complex-occurs as a response of the innate immunity. To identify inflammasomes, we utilize their sensor protein, which may have NLR, an absent in melanoma 2 (AIM2) like receptor (ALR), or pyrin. Inflammasomes belonging to the NLR group, which includes NLRP1, NLRP3, and NLRC4, are further categorized based on whether their nucleotide binding regions contain an activation and recruitment domain for caspase (NLRC) or pyrin (NLRP). The inflammasome complex consists of caspase-1 and usually contains an adaptor protein known as apoptosis-associated speck-like protein containing a caspase recruiting domain (ASC). Once the inflammasome is activated, ASC is oligomerized and thus allows pro-caspase-1 to bind to it and become activated. The activation of caspase-1 results in the cleavage and subsequent activation of IL-18 and IL-1β, as well as the formation of a pyroptotic pore via the cleavage of gasdermin-D (GSDMD). Due to this process, pyroptotic cell death and the concomitant release of inflammatory cytokines and the intracellular components occurs [3].

Chronic Inflammation

The T Cells possess an important role in chronic traumatic brain injuries. In the referenced study, it was determined in an experiment between two groups of mice the impact of these cells on neuronal loss, motor function, and fear memory. Genetic T cell deletion mice (which lack T Cells) and Wildtype mice were taken in comparison. After three months of TBI-Injury, controlled cortical impact assessing behavioral, histological, and immune system response results were recorded. Neuronal loss can be reduced in absence of T Cells as it is the case in T Cell deletion mice. However, lack of T cells led to alteration of freezing time in fear memory test. It causes changes in fear memory processing.

It changed the injured brain´s response from conditioning fear to contextual fear because the fear was tested on 2 days in a row and the freezing time on the second day was longer. Despite unchanged lesion volume in both groups, the absence of T lymphocytes reduces monocytic infiltration into the brain 3 months after TBI. So, we can see that chronic neuroinflammation is T Cell dependent post TBI. Furthermore, the activation markers MHCII and IFNγ were reduced in monocytes in T Cell deletion mice. This is the case for Microglial due to lower levels of CD204 as well. As a result, absence of T cells shows a reduced activation of monocytes and microglial which is beneficial for reducing the chronic neuroinflammation post TBI [5].

Alzheimer´s disease shares many characteristics with TBI, including neuronal loss, chronic inflammation, structural damage and behavioral impairments. Additionally, they have many pro-inflammatory pathways in common, such as NLRP1, NLRP3, AIM2, ASC speck activity, cytokine release, proptosis, and chronic microglia activation, promoting neuronal loss. This loss releases damage-associated molecular patterns (DAMPs) which initiate a cycle of chronic inflammation and inflammasome activation enhancing neuronal degeneration further. Alzheimer's disease is influenced by genes strongly. However, TBI relies on environmental factors. TBI conducts to the aggregation of Aβ and tau proteins due to decreasing of their glymphatic and lymphatic clearance. TBI facilitates the occurrence of AD onset by 4 - 10 years in predetermined people. Therefore, inhibition of inflammatory cells, like microglia and astrocytes, can play a crucial role in reducing the risk of AD post-TBI. In TBI, the location and the severity of the injury have a decisive role in determining the damage degree. Nevertheless, TBI is a risk factor in developing AD, but it does not ensure the onset of the disease [6].

Factors prior to TBI can have an impact on the recovery process, such as stress. Weight loss of 9 – 10 % post-TBI in mice was measured. Stress had no effect on it because the same outcome was observed in the control group. Furthermore, the spatial learning process with prior stress exposure was examined. During the first days of post-TBI, stress exposure impaired the spatial learning process. Nevertheless, this finding was determined to be transient because the testing of stress exposure on chronic neuroinflammation 30 days post-TBI showed improvement and was at the same level as without pre-stress exposure. Stress exposure plays a negative and prolonged role in hypothalamic-pituitary-adrenal axis activity. It elevated the neuroinflammatory markers like IL-1β, IL-6, TNF-α, and MCP-1 levels. This leads to prolonged recovery and amplified inflammation response which affects the cognitive deficits correspondingly [7].

The Effects of Hypobaric (HB) exposure was measured in many tests to examine its negative impact on post-TBI injuries in secondary neuroinflammatory mechanisms. Morris Water Waze test determines the negative changes that occur at the level of cognitive impairments especially in memory and spatial learning post-TBI injury. It worsens the ability for spatial search strategies and increases the inefficient looping behavior within 6 - 72 hours of post TBI.

Besides, depressive-like behaviors are elevated at 6 hours post-TBI as shown in the forced swim test. Additionally, it leads to increased neuronal loss in hippocampus, especially in the CA1, CA2/3, and dentate gyrus regions because HB exposure reinforces microglial activation and astrocyte reactivity in the injured cortex up to 30 days post-TBI. This causes worsening of cognitive deficits. On the other hand, HB exposure does not show significant change of motor recovery and does not show worsening of lesion volume after mild TBI, as demonstrated by the Cavalieri method of unbiased stereology [8]. Another study also exhibited the same outcome in the hypobaric exposure led to the neuroinflammation, associated cell death and the cell cycle activation. Treatment with cell cycle inhibitor CR8 can mitigate these negative effects remarkably [9].

TBI can cause cognitive, motor, or mood neuropsychiatric deficits acutely after injury and can develop chronically. This occurs due to the upregulation of pro-inflammatory cytokines / chemokines like (IL-1b, CCL2, TNF alpha) which leads to neuroin-

flammation because of microglial activation. This can endure for long time post-TBI. The study provided an example about the presence of CD68+ microglia after one year of controlled cortical impact injury. Frequently injuring the head of mice shows elevated levels of microglia and astrocytes which indicate the white matter damage.

It aligns with hippocampal-dependent learning deficits 12 – 18 months post injury [10]. However, microglial priming lasted with high activity 30 days post-TBI. The results of the experiments demonstrated impairment in anterograde learning which was not present on day 7 post-TBI. In the mentioned experiment, the study highlighted the worsening of the cognitive deficits when a new immune response occurs after 30 days post TBI, like the presence of the injected LPS in experimental mice. The monocyte/macrophage (CD11b+ /CD45high) was elevated which enhanced the neuroinflammation. This was driven by resident microglia specifically in CA3 of the hippocampus that increased the levels of the neuroinflammatory mRNA (IL-1b, CCL2, and TNF alpha). Oppositely, the intensity of astrocytes reactivity was unchanged after the new immune response and the neurogenesis in hippocampus was not affected by this response either [11].

Hyperglycemia enhances neuroinflammation, the cognitive and motor impairments compared to sham rats without DM type 2. It demonstrated the worsening of neuronal degeneration and atrophy. At the molecular level, diabetes mellitus type 2 increases proinflammatory cytokines (IL-1β, TNF-α) and decreases the anti-inflammatory factors (IL-10, TGFβ). These effects are caused by the inhibition of the MEK5/ERK5 pathway. This pathway regulates the expression of apoptosis markers, caspase-3 and the Bax/Bcl-2 ratio, preventing neuronal death and neuroinflammation. Treating hyperglycemia post-TBI should also be taken into consideration [12]. Physical exercise can influence neuroinflammation actively. The degree of the impact depends on the timing of doing physical activities. Therefore, it was examined further at different times in relation to TBI. The memory impairment was enhanced in all exercise conditions, such as pre-TBI, late phase TBI etc., except for time during early TBI.

Additionally, exercise during pre- TBI supports neuronal protection. It prevents the neuronal death and microglial activation in hippocampus. On the opposite side, late TBI preserved the hippocampus volume and reduced loss of mature neurons and neuroinflammation. Next, the mice receive physical exercises at different times. The first combination Pre-TBI and TBI-early revealed improvement in memory without affecting neuronal death or activation of neuroinflammatory cells. The second combination, Pre-TBI and TBI-late, illustrated similar results but it had a weaker impact on neuronal death and inflammation compared to TBI-late version alone [13].

N-docosahexaenoylethanolamine (DHEA)

N-docosahexaenoylethanolamine (DHEA) is a possible treatment that can help in the recovery of cognitive deficits after a mild TBI. It was administered at 10 mg/kg/day for 7 days. DHEA is neuroprotective in decreasing pro-inflammatory molecules like cytokines (IL1β, IL6), reactive oxygen species, nitric oxide, nitrites, and CD86. Synchronously, it elevates the anti-inflammatory CD206 and the antioxidant enzyme superoxide dismutase. It helps inhibit the pro-inflammatory microglia and alleviate cognitive impairments like anxiety and long-term memory deficits. These indicate the high efficacy of the use of DHEA against neuroinflammation [14].

MCC950

The inhibition of the NLRP3 inflammasome plays a crucial role in BBB stability and decreasing rupture, and degree of neurological damage post-TBI. This prevents the activation of the proinflammatory caspase-1. A pre-treatment with MCC950 revealed a decline in BBB integrity and enhanced the neurological impairments. It elevates the neuroinflammatory response of astrocytes and microglial cells in expressing cytokines. On the other hand, providing 3mg/kg of MCC950 1-hour post-TBI depletes the expression of the cytokines and improves the BBB integrity and the neurological deficits as well. This drug has parodical roles depending on the administration time, either pre- or post-TBI. The expression of the proinflammatory cytokine IL1β remained unaffected in both experiments showing the independence of NLRP3 inhibition on its production [15].

Glucose-Dependent Insulinotropic Polypeptide (GIP)

Glucose-Dependent Insulinotropic Polypeptide (GIP) reveals a high efficacy against cognitive and motor impairments like recognition memory, balance and motor coordination over 4 weeks. These effects are achieved by a high dose of GIP. GFAP, APP and BMX (nonreceptor protein involved in chronic neuroinflammation) levels were reduced from the first day post-TBI and sustained throughout the entire study period. A decrease in GFAP, biomarker for acute and chronic astrogliosis, indicates an ameliorated anti-inflammatory response. Depletion of APP level protects the neurons, as its elevation is a biomarker for neuronal injury and degeneration. The accumulation of Aß post-TBI is diminished. Therefore, the risk of developing Alzheimer´s disease is also low. The results of this study demonstrate the neuroprotective and anti-inflammatory activity of GIP [16].

Intranasal delivery of IL-4

Intranasal delivery of IL-4 within 6 hours post-TBI promotes hippocampus-dependent cognitive functions and spatial and non-spatial memory. IL-4 leads to the maintenance of long-term potentiation and a reduction in CA3 neuronal loss in the hippocampus. It reinstates cognitive functions to a near-full extent in TBI mice. Furthermore, it enhances the production of anti-inflammatory cytokines (IL-10 and TGF-β) and polarizes the microglia toward an anti-inflammatory phenotype due to the activation of arginase 1 and PPARγ [17].

Endocannabinoid (EC)

Endocannabinoid (EC) degradation inhibition with 2-arachidonoyl glycerol (2-AG) using JZL184, 16 mg/kg was administered 30 minutes post TBI. It inhibits monoacylglycerol lipase. It enhances neuroprotection, maintains BBB stability and significantly the cognitive and motor impairments 24 h post TBI. Additionally, the expression of GFAP was declined which indicates the suppression of astrocytes. However, the levels of the cytokines (IL-1β, IL-6, CCL2, TNF-α) or oxidative stress markers (COX2, NOX2) remained unaffected after the treatment. JZL184 was effective in aiding recovery of impairments and decreasing neuroinflammation post-TBI [18].

Anakinra

Anakinra drug targets secondary neurological injury post-TBI by specifically on blocking the IL-1 receptor. It provides cognitive and neuronal protection. This direct inhibition is more effective against neuroinflammation than blocking IL-1 alpha or beta separately. It depletes the IL-1 and IL-6 levels post-TBI. Anakinra decreases cognitive deficits particularly spatial learning. It enhances the recovery post-TBI. However, the lesion size is not affected by this blockage [19].

MLC901

MLC901 (NeuroAiD IITM) administration (0.8g capsules/day for 6 months) did not show any significant improvement in cognitive functioning like complex attention. On the other hand, it positively affected post-concussion symptoms like the speed of processing information , quality of life, anxiety and depression. These results were sustained after the treatment as revealed in the 9-month follow-up [20].

Target	Therapeutic approach	Potential drugs
NLRP3 Inflammasome	Direct Inhibitors	MCC950
JAK2/STAT3 pathway	JAK2 Inhibition, STAT3 Suppression, NLRP3 Down-regulation	Ruxolitinib
interleukin-1β (IL-1β) inhibitor	Down regulates the pro inflammatory cytokines	IL-1β antibody Canakinumab
Gasdermin D inhibitor	Reduces the expression of proptosis related proteins	JDHXD
Reactive oxygen species	Inhibits TRPM2 channel activation	N-acetyl-l-cysteine
Oxidative stress	Reduces inflammation and oxidative stress markers	resveratrol
Necroptosis	RIPK1 Activation inhibitor	Necrostatin-1
HMGB1 and interleukin IL-1 inhibitors	Anti-inflammatory by reducing the expression of the receptors	Glycyrrhizin

Discussion

TBI triggers a multifaceted injury response involving both immediate mechanical damage and secondary biochemical cascades that unfold over time. Among these, neuroinflammation is now recognized not merely as a secondary effect but as a key pathological driver of long-term dysfunction. Activated microglia and astrocytes orchestrate a potent inflammatory response that can persist chronically, even after the resolution of the initial injury. The sustained presence of pro-inflammatory cytokines, ROS, and activated glial cells contributes to a maladaptive environment, promoting neurodegeneration and impeding recovery.

Importantly, the role of inflammasome, specifically NLRP3—has gained attention in recent years. These cytosolic complexes amplify the inflammatory response and are directly involved in neuronal death through caspase-1 activation and release of IL-1β. Persistent inflammasome activation post-TBI suggests that therapeutic modulation of this pathway could be highly beneficial.

Furthermore, TBI-induced disruption of the BBB allows peripheral immune cell infiltration, which further amplifies neuroinflammatory signaling and primes microglia for chronic reactivity. This persistent inflammatory state shares similarities with the pathogenesis of various neurodegenerative diseases, implying shared mechanistic pathways and therapeutic targets.

While the immune response is essential for debris clearance and initial repair, unchecked inflammation is detrimental. Thus, a key challenge lies in developing therapies that modulate, rather than suppress, the immune system to strike a balance between neuroprotection and immune resolution.

Conclusion

TBI is a complex condition in which neuroinflammation plays a pivotal role in shaping both acute and chronic outcomes. The involvement of glial cells, systemic immune infiltration, and inflammasome activation underscores the multifactorial nature of post-TBI pathology. Understanding these interconnected pathways provides a valuable framework for identifying new therapeutic interventions. Future strategies must aim to target specific components of the inflammatory response, such as microglial activation or inflammasome signaling, without compromising the essential repair functions of the immune system. Tailored, time-sensitive therapies hold promise for mitigating long-term consequences of TBI, improving neurological outcomes, and reducing the risk of subsequent neurodegeneration.

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