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REVIEW ARTICLE **OPEN ACCESS**

The Role of Immune Response in Traumatic Brain Injury: Mechanisms and Therapeutic Targets

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ABSTRACT

Traumatic brain injury (TBI) affects individuals across different ages and genders, ranging from mild concussions to severe cases. The immune system plays a crucial role in TBI development and recovery. Inflammation and neuroinflammation are key factors in how TBI impacts individuals. Both the body's natural defence system (innate immunity) and its learned response (acquired immunity) are important in the later stages of TBI when damage can worsen. Scientists anticipate that new treatments targeting the immune system could improve recovery from TBI in the future. However, in some cases, the immune response to severe TBI may worsen initial damage, leading to poorer outcomes. Despite these challenges, recent research has led to promising treatments that target the immune system to aid in healing brain injuries. This review examines current knowledge about how the immune system affects CNS injuries, explores emerging treatments, and highlights remaining questions. Understanding the immune system's role in TBI could pave the way for better treatments and outcomes for patients in the future.

Keywords: *Traumatic Brain Injury, Neuroinflammation, Immunomodulation, Immune response, Immune secretory products, B-Cell, T-Cell.*

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INTRODUCTION

Traumatic brain injury (TBI) is a major health concern worldwide, causing disability and death across age groups. Every year, millions of new cases are reported, with regions like the United States, Canada, and Europe bearing a heavy burden. In India alone, millions are affected by TBI, often due to road incidents, falls, and violence, with alcohol further complicating matters [1]. TBI occurs when the head suffers a physical impact, leading to damage to brain tissue. This primary injury can result in various lesions such as hemorrhages and contusions. However, it's the secondary damage that worsens over time and significantly impacts neurological function [2]. Secondary injury involves pathways like glutamate-induced excitotoxicity, free radical damage, and neural inflammation. Among these, the role of the immune system has gained attention. Immune cells like neutrophils, microglia, and astrocytes rush to the injury site, followed by peripheral immune cells like monocytes and lymphocytes [3, 4]. While the immune response is vital for tissue repair, it can also worsen inflammation, exacerbating secondary injury. Understanding how the immune system contributes to TBI can offer insights for developing better treatments. In summary, TBI is a significant health issue globally, with millions affected each year. Secondary injury, driven by pathways like inflammation, worsens neurological function over time. The immune system plays a crucial role in this process, and studying it could lead to improved TBI therapies.

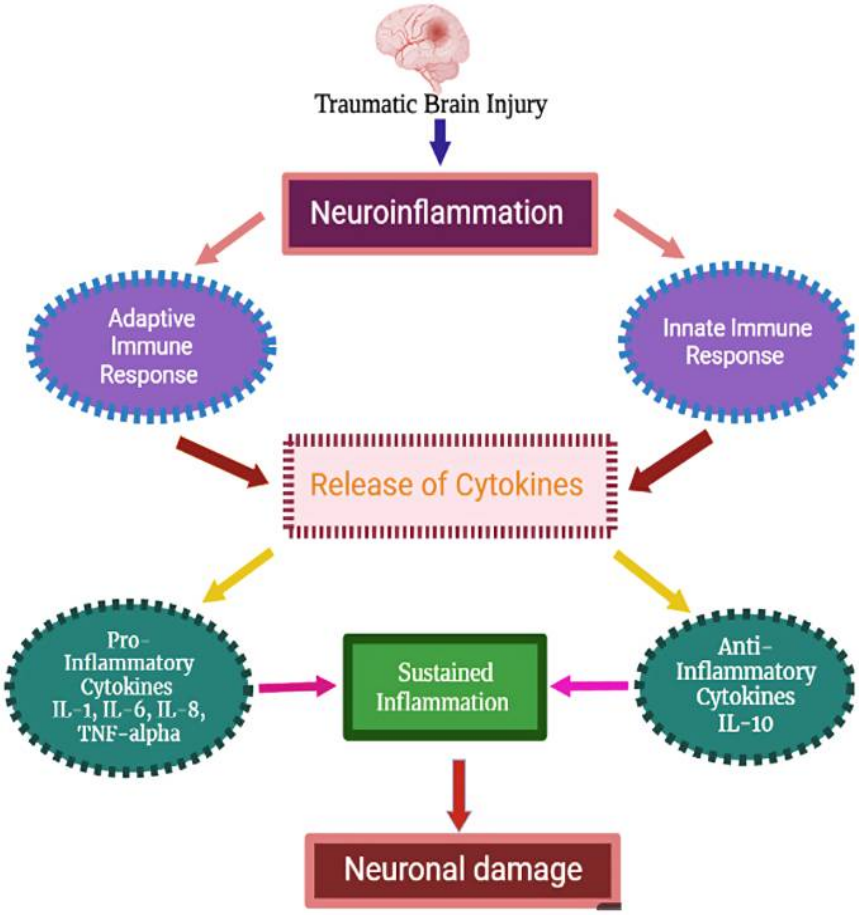

Fig 1. TBI-related pathophysiological alterations that result in short- and long-term neurovascular injury as well as immune activation.

ROLE OF IMMUNE SYSTEM ON TBI

Recent studies have revealed that the immune system plays a vital role in brain development and function. While traditionally believed to be separate, it's now understood that the brain interacts dynamically with the immune system [5]. Following a traumatic brain injury, there's a complex interaction between different types of immune cells, leading to an inflammatory response in the brain involving both innate and acquired immune cells. After a traumatic brain injury (TBI), the protective barrier in the brain, called the blood-brain barrier (BBB), gets weakened. This happens because of swelling and inflammation caused by the injury [6]. This allows immune cells to reach the injured area. First, the brain's own defence team, the microglia, get activated. Then, other immune cells like neutrophils join them. Later on, more immune cells, including lymphocytes and macrophages, come to help [7].

Innate Immunity:

The innate immune system, a network of cells and signaling agents, acts as the body's first line of defense against foreign threats and damage. In the case of traumatic brain injury (TBI), glial cells like microglia and astrocytes initiate immunological processes in response to the initial damage, releasing molecules associated with injury. This triggers inflammation in the brain, activating immune cells like mononuclear phagocytes, which further stimulate local glia. These immune responses contribute to the continuation of brain damage, with over 100 inflammation-related genes significantly elevated after TBI [8].

Neutrophils:

Neutrophils, the most abundant circulating white blood cells, are vital components of the innate immune system. They defend against infections through processes like phagocytosis and the release of neutrophil extracellular traps. Following TBI, inflammatory signals attract neutrophils to the injury site, where they release molecules that can harm the blood-brain barrier (BBB). Neutrophil infiltration and activation contribute to tissue destruction, inflammation, and potentially neurodegenerative disorders associated with TBI [9].

Blood-Borne Macrophages and Microglia:
Microglia, specialized macrophages in the central nervous system (CNS), and blood-borne macrophages play key roles in immune responses to brain injury. These cells emit pro-inflammatory and anti-inflammatory signals, regulating the local inflammatory response. They are involved in neural circuit development, neurotransmission modulation, and brain homeostasis maintenance [10].

Astrocytes:
Astrocytes, another type of glial cell, have essential functions in brain health, including structural support, BBB maintenance, and neurotransmitter regulation. Following TBI, astrocytes become activated, releasing various molecules that trigger neuroinflammation. Reactive astrocytes may contribute to cytotoxic edema and exacerbate brain damage. Targeting astrocytes with specific drugs could mitigate excessive inflammation and edema formation, potentially improving TBI outcomes [11].

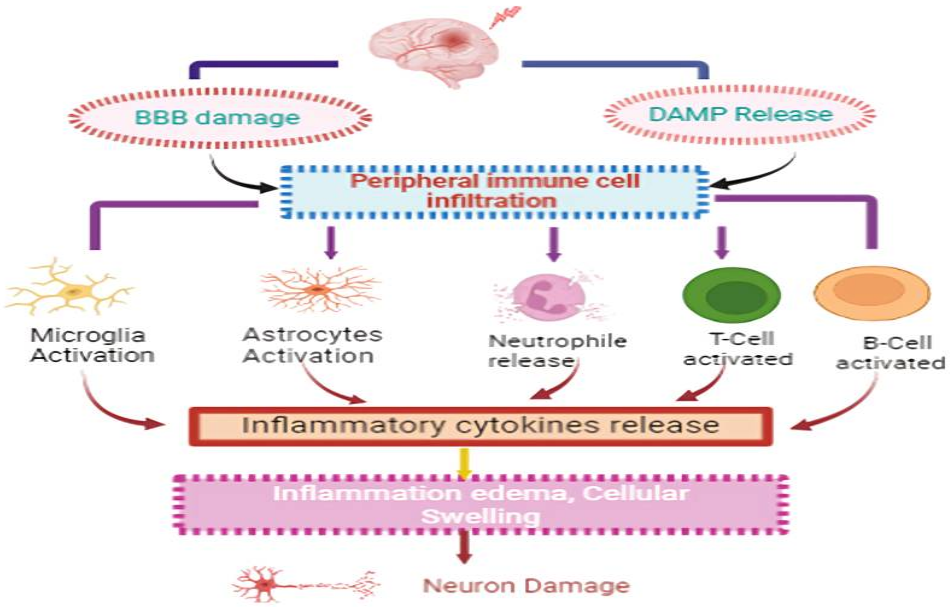

Fig 2.
Interlink pathway between Traumatic brain injury and inflammation

Mast cell
Mast cells, derived from the myeloid cell lineage, are an integral part of the innate immune system. mast cells play a key role in causing inflammation and further injury [12,13]. Upon activation by trauma-related signals, mast cells release inflammatory substances like histamine, enzymes, and signaling molecules. These substances contribute to disrupting the blood-brain barrier, swelling, and bringing in immune cells to the injury site [14]. Furthermore, mast cell-derived substances can directly cause nerve cell death, making the initial injury worse [15]. Notably, mast cells are located in the brain's outer covering and other regions, allowing them to respond quickly to TBI (16). As a result, controlling mast cell activity or preventing their activation has emerged as a potential treatment strategy to reduce the harmful effects of inflammation and improve outcomes in TBI patients [17].

Adaptive Immunity
T cells and B cells are the main immune cells that form the adaptive immune system [18]. Adaptive immunity implies the cascading activation and proliferation of T or B cells that target particular antigens, as well as a memory of prior antigen exposure that enables a targeted, intense, and quick response to subsequent antigen treatments [19]. T lymphocytes i.e CD4+ and CD8+ T cells are activated and reactivated by detecting antigens displayed in major immunogenetic markers and have cytotoxic, regulatory activities. In addition to producing immunoglobulins, B lymphocytes also interact with T cells and innate immune cells in a reciprocal fashion. Adaptive immunity plays a role in atopy and autoimmune disorders [20].

B cells
The main participants in humoral immunity are B Cells. Precursors are transformed into B-lymphocytes in the bone marrow, and these cells subsequently travel throughout the body before settling in the spleen and

lymph nodes. These cells differentiate into plasma cells after being stimulated by a pathogen, and their primary function is to produce antibodies. Demonstration of B cell participation after TBI has not been analyzed as much as more immune-related topics. IFN-g and TNF-a production as well as inflammatory T cell infiltration can both be restricted by B cells [21]. Cells expressing the B cell marker OX33 have only been found 4-6 days after experimental injury [22]. Levels of CCL20, a chemokine linked to B cell chemotaxis, are high four hours after injury and remain high for three days following CCI [23]. However, following a weight loss injury, it was found that mice lacking the Rag1 gene, which prevents the development of mature B and T cells, were not significantly separate from wild type controls in terms of neuronal function or histopathological damage, as shown by the size of lesions, TUNEL staining, and staining for the neuronal marker NeuN [24].

Several clinical investigations have been undertaken to ascertain the impact of TBI on B cell populations. A particular study delved into B cell (CD5+/CD19+) populations in the peripheral blood of 20 patients acknowledged with severe TBI, yet it unearthed no significant variance compared to healthy controls [25].

T cells

The primary adaptive immune system mediators are T cells, lymphocytes with thymus-derived origins that can function cytotoxically, usefully, or in a regulatory capacity. T cells are important components of the peripheral immune system and comprise a variety of subcategories, including CD3+, CD4+, and CD8+ [26] . Over 75% of CD4+ T cells were present in the cerebral tissue as opposed to the meningeal membranes [27]. CD4+ T cells are categorized into four subcategories, which include Th1, Th2, Treg, and Th17 cells. Both CD4+ and CD8+ T cells possess the capability to transit into the CNS, leading to inflammation and neural degeneration, and performing binary roles of damage and restoration [28]. CD4+ T cells identify antigens presented by major histocompatibility complex (MHC) class II molecules [29] CD8+ T cells identify antigens exhibited by MHC class I molecules [30].

Interleukin-2 (IL-2) and the pro-inflammatory cytokines, TNF and interferon (IFN) are released by activated CD8+ T cells. Through these combined effector capabilities, CD8+ T cells are essential for the regulation of neoplastic cells and intracellular pathogens [31].

According to TBI models, CD4+ T lymphocytes will first expand before declining [32]. However, CD8+ T cells exhibit the opposite trend. Following TBI, infiltrating CD8+ T lymphocytes were located near IL-15-expressing astrocytes in the lesions, which released granzyme B, stimulating caspase-3 and cleaving poly-ADP-ribose polymerase, finally leading to the induction of neuronal death. In addition to producing TNF and IFN, CD8+ T lymphocytes also induce astrocytes to release pro-inflammatory cytokines [33]. T cell recruitment and trafficking are targeted by neuroprotective CNS therapy [34].

Table 1: Exploring T-Helper Cell Functions and Cytokine Roles in Traumatic Brain Injury

T cell type	Cytokines	Role	Function in TBI	Reference
Th 1	IL-2	Pro inflammatory	Immunomodulation of IL-2-controlled response in TBI patients. Interrupt with the cognitive abilities of TBI patients.	[35]
Th 1	INF- γ	Pro inflammatory		
Th 1	IL-12	Pro inflammatory		
Th 2	IL-4	Anti- inflammatory	Inhibit activated macrophages and suppresses secretion of potent pro-inflammatory mediators including IL-1, TNF and ROS/RNS.	[36]
Th 2	IL-5	Pro inflammatory	Neuroregenerative and Neuroshielding Effects in Animal Models and Patients with TBI.	
Th 2	IL-6	Anti-inflammatory		
Th 9	IL-9	Pro inflammatory	Promotes the survival of Tregs and enhance their suppressive function	[37]
Th 17	IL-17 A	Pro inflammatory	Promotes recruitment of neutrophils, activation of innate immune cell, enhance B cell function. Stimulate the synthesis and mobilization of pro-inflammatory cytokines post-TBI.	[38]
Th 17	IL-17 F	Pro inflammatory		
Th 22	IL-22	Anti- inflammatory	Regulates autoantibody production but the exact mechanism of pathogenesis is unknown.	[39]
Treg	TGF- β	Anti- inflammatory	Immune suppression Maintenance of mucosal homeostasis	[40]

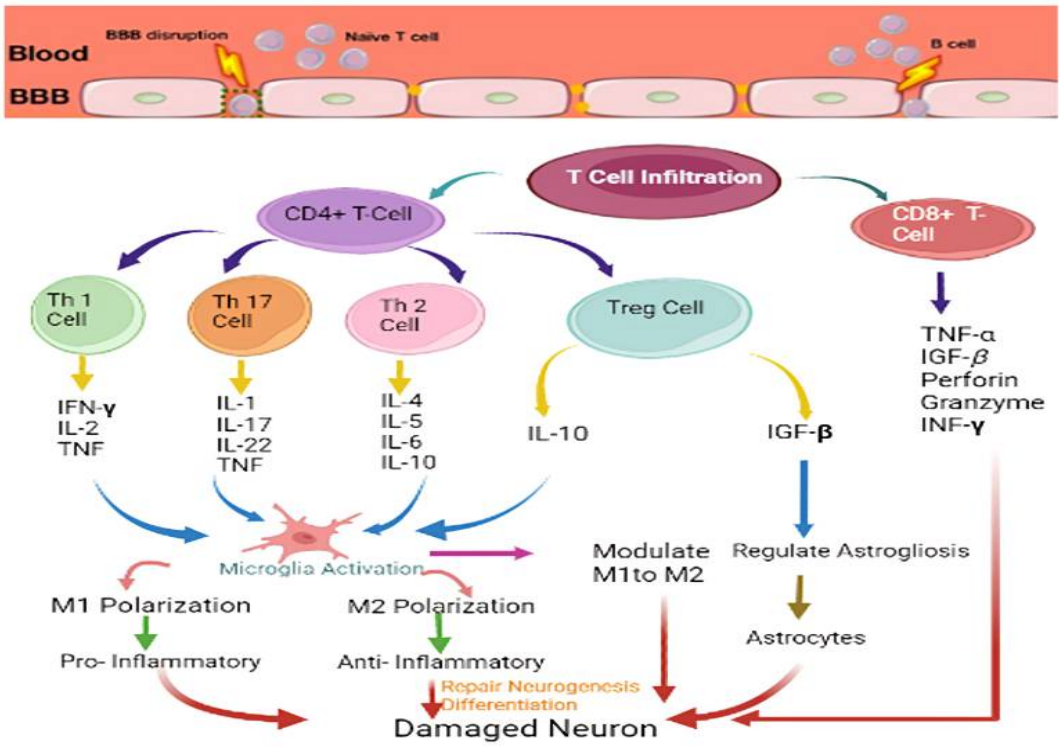

Fig: 3 T cell subsets of various types, including CD4+ and CD8+ T cells, infiltrate the damaged brain. When CD4+ cells develop, they become Th1, Th2, Th17, or Tregs, which have pro- or anti-inflammatory properties. Th1 cells secrete proinflammatory cytokines like IFN-γ, TNF-α, and IL-2 to induce M1 polarization. Th2 cells generate anti-inflammatory cytokines like IL-4, IL-10, and IL-13 to facilitate M2 polarization. Moreover, Th17 cells activate microglia by release proinflammatory cytokines IL-1, IL-6, IL-17, IL-22, TNF. Treg cells engage with microglia, driving microglial response polarization from the M1 phenotype to the M2 phenotype through IL-10. Additionally, they stabilize as the cytokine IGF-β. CD8+ T lymphocytes induce neuronal death through the release of granzyme and perforin

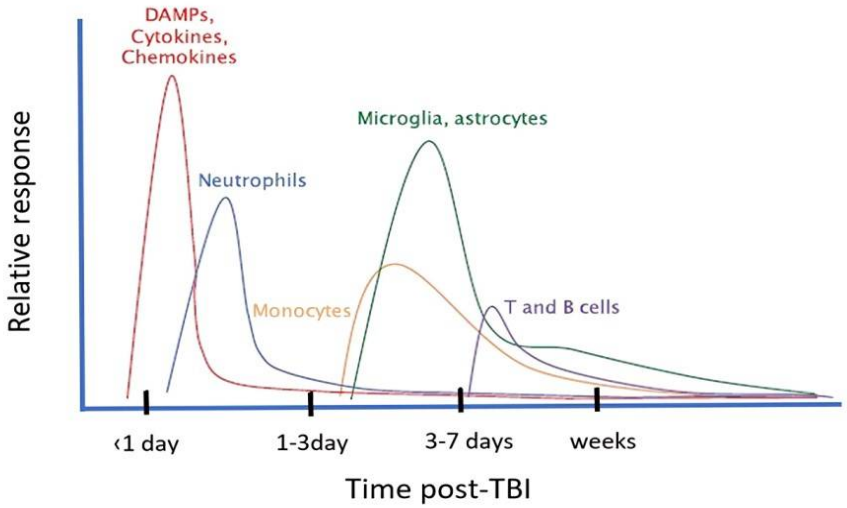

Fig 4: Sequential progression of the immune response in TBI [41]

Immunotherapeutic Strategies

For the purpose of eliminating microglia, pharmacological strategies, such as inhibitors of the colony stimulating factor-1 receptor (CSF1R), have been developed. Microglia requires CSF1R for survival, and blocking this receptor with CSF1R inhibitors causes a significant reduction in microglial cells. In

intracerebral hemorrhage models, microglial depletion using CSF1R inhibitors has been shown to reduce inflammation, promote brain recovery, and prevent blood-brain barrier disruption, thereby reducing leukocyte infiltration. However, in a mouse model of TBI, microglial depletion increased the core area of injury. It was discovered that microglia are necessary for converting astrocytes to their protective state by inhibiting the astrocyte P2Y1 receptor. [42]

Different neurotherapeutic approaches through Astrocytes manipulation

Astrocytes can now be targeted more precisely and used as therapeutic agents due to advancement in the molecular biology and gene transfer technology. Researchers successfully established lentiviral vectors, which generate superior level of transgene expression in astrocytes while transgene expression is suppressed in neuron, making viral vectors an effective alternative approach. These vectors will make it easier to activate astrocytes specifically while avoiding other cell types. When utilized as experimental tool, lentiviral vectors can carry conditional sequences that regulate the pattern of transgene expression throughtout time. They can also be inserted into constricted structure in adult's animals of diverse species. They also provide a unique strategy for the targeted delivery of therapeutic compound to brain cells while causing the fewest adverse effects.[43]

Additionally new opportunities to study the function of reactive astrocyte have been made possible by the development of powerful imaging tools, particularly for live imaging. Such approach enables quantification of astrocytes activation at the brain structure level or evaluation of changes in activated astrocytes at the individual cell level. In the context of a cell-based treatment approaches, such as the targeted activation of astrocytes, precise monitoring of activated astrocytes is particularly necessary.

A different noninvasive and statistical imaging method is positron emission tomography (PET), which can be used to simultaneously investigate the entire brain as opposed to two-photon micropscopy's investigation of visible structure. The available PET ligands for monitoring neuroinflammation primarily bind to activated microglia but may also partially identify activated astrocytes.

Different neurotherapeutic approaches through T-Cell manipulation

T cell plays both a helpful and a negative role in the immune response and repair process in the CNS after traumatic injury. Recent technological advancement, like mass spectroscopy-based flow cytometry, recent live-cell imaging etc. have conducted researches on T cell one of the most key aspect for the treatment of traumatic CNS injury. A prolonged rise in effector/memory CD8+ T cell (expressing granzyme B) is observed in the damaged brain, according to flow cytometric analyses. Pharmacological suppression of CD8+T cells can accelerate rehabilitation in TBI mice and is a viable strategy for trauma patients to minimize long term impairment [44]. After TBI in mice, a competitive antagonist for MHC Class II-associated invariant peptide lowers peripheral splenic cells and inhibits neuroinflammtion and neurodegeneration. Patient with SCI have previously received a big dose of glucocorticoids to lessen the immunological response of the CNS, even if there isn't enough to indicate that the therapy/medication has a significant impact. Pre-treatment by influencing peripheral T-cell immunological function, pituitary adenylate cyclase-activating polypeptide may be able to prevent TBI. A study employing a mouse model demonstrated that three days of consequent Fingolimod administration was a novel immunotherapeutic treatment. Three days after TBI, it may decrease the permeation of T lymphocytes and NK cells, raise the percentage of treg cell, and increase the level of IL-10. Fingolimod enhances brain function after a TBI by minimize general microglia activation, BBB damage and axonal destruction. Fingolimod therapy can be used to treat secondary TBI since it modulates a number of immune inflammatory reactions and improve neurological impairment. Along with the above therapies, we predict that nutritional supplements, 107 rehabilitative exercises, psychological intervention and other approaches may be able to modulate T cell and immune system, which may enhance participants predictions following CNS trauma injury [45].

CONCLUSIONS

In conclusion, brain injury triggers a complex immune response involving inflammation, which can make the initial injury worse and lead to poorer outcomes in severe cases. However, recent advances have uncovered promising treatments targeting specific immune pathways, such as controlling innate and adaptive immune cells, for healing brain injuries. Important questions remain about the best timing for these treatments, potential side effects, and the need for personalized approaches. Research combining different fields is crucial to understand the interplay between the immune system and other brain injury processes. Ultimately, using the immune system's ability to control injury and promote healing could improve outcomes and quality of life for brain injury patients.

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Abbreviations: TBI: Traumatic Brain Injury**, BBB:** Blood-Brain Barrier**, CNS:** Central Nervous System, **TNF:** Tumour Necrosis Factor**, ROS:** Reactive Oxygen Species

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