Review Article

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Neuroinflammation in traumatic brain injury: A chronic response to an acute injury

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Abstract:

Every year, approximately 1.4 million US citizens visit emergency rooms for traumatic brain injuries. Formerly known as an acute injury, chronic neurodegenerative symptoms such as compromised motor skills, decreased cognitive abilities, and emotional and behavioral changes have caused the scientific community to consider chronic aspects of the disorder. The injury causing impact prompts multiple cell death processes, starting with neuronal necrosis, and progressing to various secondary cell death mechanisms. Secondary cell death mechanisms, including excitotoxicity, oxidative stress, mitochondrial dysfunction, blood–brain barrier disruption, and inflammation accompany chronic traumatic brain injury (TBI) and often contribute to long-term disabilities. One hallmark of both acute and chronic TBI is neuroinflammation. In acute stages, neuroinflammation is beneficial and stimulates an anti-inflammatory response to the damage. Conversely, in chronic TBI, excessive inflammation stimulates the aforementioned secondary cell death. Converting inflammatory cells from pro-inflammatory to anti-inflammatory may expand the therapeutic window for treating TBI, as inflammation plays a role in all stages of the injury. By expanding current research on the role of inflammation in TBI, treatment options and clinical outcomes for afflicted individuals may improve. This paper is a review article. Referred literature in this paper has been listed in the references section. The data sets supporting the conclusions of this article are available online by searching various databases, including PubMed. Some original points in this article come from the laboratory practice in our research center and the authors' experiences.

Keywords:

Central nervous system disorders, neuroinflammation, neuroprotection, regenerative medicine, secondary cell death, stem cell therapy, traumatic brain injury

Introduction

A traumatic brain injury (TBI) is an injury caused by excessive force to the head that may cause external brain injury, brain dysfunction, or death.[1-4] Every TBI is different, so duration of the damage may be either temporary or permanent.[2-4]

Clinically, the Glasgow coma scale classifies the severity of TBI based on patient consciousness, motor skills, verbal abilities, and eye reflexes (the scale classifies scores of 3–8 as severe TBI, 9–13 as mild TBI, and 14–15 as moderate TBI, also known as a concussion).[1,3,5-8] The severity of TBI cases may also be classified based on technological imaging machines and patients' existing health conditions.[9-12] While animal and human TBI pathologies are different, both display neuroinflammation postinjury.[5,9-12]

Recent evidence suggests that TBI is not just an acute injury, as it shares chronic symptoms with diseases such as Parkinson's and Alzheimer's.[13-18] The neuroinflammation associated with both chronic and acute TBI symptoms may be a central component of the injury, presenting

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researchers with a potential target when creating new treatments.[2-6]

In the United States, 30% of all injury-related deaths are from TBI.[3,4] Annually, these injuries kill about 50,000 people, cause 1.4 million people to seek medical services, cause 235,000 hospitalizations, and leave 85,000 surviving individuals disabled.[19-21] The widespread nature of TBI – it is estimated that 3.2–5.3 million people suffer from it has cost the US about $37.8 billion dollars ($4.5 billion for hospital and long-term treatments, $20.6 billion from disability or work complications, and $12.7 billion from untimely deaths).[22] Socially speaking, TBI profoundly affects friends and families of afflicted individuals.

Because of the large amount of people vulnerable to TBI,[23,24] more research is needed to come up with an effective treatment. The following study looks into neuroinflammation as a target for new treatments because of its occurrence in both acute and chronic stages of the injury.

Clinical Manifestations of Traumatic Brain Injury

Approximately 30%–80% of TBI victims suffer from symptoms following the initial injury.[25] These symptoms often go away within the following hours or days, but occasionally individuals will be faced with post-TBI symptoms for years or the rest of their lives.[26] Factors such as increased severity of the injury, being female, older age, low socioeconomic status, and mental disorders all contribute to the intensity and duration of post-TBI symptoms.[25,27]

The study focuses on mild TBI symptoms, due to the high prevalence of them, but TBI may also injure axons, bruise the brain, or even cause comas.

Physically, between 25% and 90% of patients with mild-TBI claim to suffer from headaches postinjury and several other patients experience nausea, dizziness, sleep disruptions, and visual and auditory complications.[25,26] In addition, damage to the frontal or temporal lobe may cause TBI patients to experience seizures, which may prove to be an obstacle to treatment and diagnosis due to confusion with epilepsy.[25]

Regarding cognitive symptoms, TBI patients may suffer from attention deficit, memory impairment, and overall executive function deficit.[26] These symptoms are likely caused by injuries to the frontal lobe, subcortical systems, white matter tracts, and axons; these structures and systems are partially responsible for information processing, stamina, and mental speed.[28,29]

Patients of mild TBI may also experience several behavioral (or personality) changes following the injury. These changes include mood shifts, irritability, aggression, lack of motivation, selfishness, depression, anxiety, and posttraumatic stress disorder.[25,26,28,30,31] TBI patients are also at an increased risk of developing several neurodegenerative disorders (such as Parkinson's disease and Alzheimer's disease).[15-17,32,33]

Finally, many patients present with epilepsy-like symptoms such as partial seizures that affect cognition, emotional processes, and inflammatory responses.[25]

Secondary Cell Death and Neuroinflammation

Following TBI, several detrimental processes begin to affect the injured brain. Mechanical injury damage to neurons, axons, glia, and blood vessels initiates the primary injury.[34] The degree of primary injury varies in each case of TBI and usually causes direct neural cell loss and necrotic cell death.[35]

Primary injury next triggers various biochemical cascades that usually cause secondary cell death and prolonged neurodegeneration. These cascades occur seconds to minutes after the initial insult and can last anywhere from days to years following injury.[35,36] The secondary cellular injuries primarily affect the site of injury and neighboring tissues but have the potential to spread throughout the brain.[3] Secondary cell death processes consist of excitotoxicity, oxidative stress, mitochondrial impairment, damaging of the blood–brain barrier (BBB), and inflammation.[2,5,14,31,37-42] The aforementioned processes often interact to further increase progressive neurodegeneration.[37]

Excitotoxicity, a secondary cell death mechanism that may follow TBI, is characterized by the secretion of intracellular glutamate (a neurotransmitter) into extracellular spaces by injured nerve cells.[43] The increased glutamate in the synaptic space overstimulates amino-3-hydroxy-5-methylisoxazole-4-propionic acid and N-methyl-d-aspartate subtype glutamate receptors, which in turn allows a flood of sodium and calcium ions into the cell.[43,44] The increased calcium ions then activate protein phosphatases, phospholipases, and endonucleases to fragment DNA and other membranes and structures of the cell, eventually causing cell death by necrosis and apoptosis.[45] In addition, the excess glutamate causes the creation of additional nitric oxide, free radicals, and prodeath transcription factors.[46]

Oxidative stress is another secondary cell death mechanism attributed with abnormal levels of two free radicals, reactive oxygen species (ROS), and reactive

nitrogen species (RON).[47] Free radicals are extremely reactive, causing their level to stay low and be regulated by enzymes and antioxidants.[48] The increase in ROS and dysfunction of antioxidants following TBI[49] causes an increase in ROS and RON levels, a dangerous occurrence that disrupts normal cell function due to the radicals' oxidative abilities.[50] Furthermore, ROS cause lipoperoxidation of cell membranes. Lipoperoxidation damages various organelles and cellular structures causes mutations by fragmenting DNA and intrudes neutrophils to further increase production of ROS.[48,49] The above processes all contribute to widespread neuronal cell death in TBI inflicted brains.

A third secondary cell death process observed in some TBI cases is mitochondrial dysfunction.[51] Post-TBI, the ROS regulators become damaged, allowing for an increased production of ROS from the electron transport chain.[52,53] The excess ROS cause lipid-peroxidation mediated oxidation damage to mitochondrial membranes, disrupting normal mitochondrial function.[54] Another function of mitochondria, working as a calcium buffer to maintain homeostasis, becomes impaired due to excitotoxicity.[36,55] Excess calcium ions cause the calcium-dependent mitochondrial permeability transition pore to stay opened, altering the mitochondrial membrane potential.[55] This altered membrane potential halts the production of ATP and causes the destruction of the mitochondria. Faulty mitochondria then release several toxins and apoptotic factors into the cell, eventually resulting in cell death.[56]

The breakdown of the BBB is another powerful secondary cell death process following TBI.[43,51,57] The BBB, made of endothelial cells that interact with glia and astrocytes, is a selective barrier to the brain that prevents the entry of bloodborne pathogens and immune cells.[58] Disruption of the BBB occurs when the primary injury weakens cell junctions through the upregulation of protein matrix metallopeptidase 9 (MMP-9), which digests tight junctions to allow the entry of peripheral immune cells and circulating factors.[59,60] These factors and cells alter the interactions between endothelial and glial cells in the brain, increasing the permeability of the BBB.[58] These immune cells also increase osmotic pressure, which causes edema and intracranial pressure.[61] BBB dysfunction contributes to neural cell death, cognitive impairments, and is an obstacle for treatment.[59]

Finally, the major cause of secondary cell death following TBI is neuroinflammation.[2-4,14,18,31,41] Neuroinflammation follows the initial impact and may persist up to 17 years post-TBI.[62] Neuroinflammation increases neural cell death by interfering with endogenous repair mechanisms and acts through immune cells, microglia, cytokines, chemokines, and other inflammatory molecules.[63] Initially, an inflammatory response is activated to repair damaged cells and protect the brain from invading pathogens.[37] Following the activation of the inflammatory response, inflammatory cells, neutrophils, monocytes, and lymphocytes cross the BBB and release prostaglandins, pro-inflammatory cytokines, and other inflammation regulators.[64,65] These regulators further recruit microglia and immune cells to the brain by increasing the expression of chemokines and cell adhesion molecules.[64,65]

Microglia cells, which are systemic macrophages, initially benefit the brain post-TBI by separating healthy and injured tissues to limit the spread of damage.[66] Microglial activation, however, becomes excessive and causes the release and upregulation of several pro-inflammatory cytokines, increased production of neurotoxic molecules and free radicals, and increased expression of major histocompatibility complex class II (MHCII+).[4,35,37] The pro-inflammatory cytokines released tumor necrosis factor alpha (TNF)-α, interleukin (IL-1) β, IL-6, IL-12, and interferon δ) increase the inflammatory response by weakening the BBB.[4,37,58,60] The production of unnecessary neurotoxic molecules and free radicals initiates additional cell death mechanisms.[4,35] Finally, the overexpression of MHCII+ contributes to neurodegeneration. Glial cells also contribute to an increased inflammatory response, as they express and produce chemokines that upregulate adhesion molecules.[67] This upregulation eases leukocyte migration across the BBB, causing a further intensified immune response.[67]

While microglia often promotes inflammation, they occasionally decrease inflammatory responses.[4,66] Whether or not microglia promotes or decrease inflammation depends on their phenotype (which is determined by their microenvironment).[4,66] Microglia with M1 phenotypes occur in the presence of lipopolysaccharide and interferon γ and stimulate the production of pro-inflammatory cytokines while discouraging production of anti-inflammatory cytokines (i.e., IL-10).[68] In contrast, microglia develops the M2 phenotype when in contact with cytokines IL-4 or IL-13.[68] M2 microglia decreases inflammation by reducing the production of pro-inflammatory cytokines and promoting the production of anti-inflammatory molecules (IL-10, transforming growth factor 1 β, suppressor of cytokine signaling).[4,66]

Astrocytes are also involved in injury sites post-TBI by working with neurotrophic factors to upregulate neurotrophic factors that aide in axonal repair, increase cell proliferation, aid in neuronal survival, and inhibit programmed cell death.[66,69,70] In addition, astrocytes reduce glutamate excitotoxicity by regulating extracellular

glutamate levels.[66] While astrocytes produce beneficial effects post-TBI, excessive amounts of them often create a glial scar.[66,71] A glial scar is a physical and chemical barrier that surrounds the injury site and is created when astrocytes produce an inhibitory cellular matrix.[66,71] While glial scars do protect healthy portions of the brain from the neurotoxins of the injury site, it is damaging because it prevents efficient repair of damaged tissue.[66,71]

Neuroinflammation-based Therapies

Since the primary injury is only treatable through preventative methods, most research focuses on secondary cell death. The delayed onset of neuroinflammation, compared to other secondary cell death processes, makes it a desirable treatment target.[72] Since neuroinflammation does not occur immediately after the injury, there is a greater therapeutic window for the administration of treatments. Future treatments ought to focus on methods to enhance the protective effects of neuroinflammation while simulataneously eliminating detrimental side effects.

One potential drug that may be used to target TBI-related inflammation is minocycline, a safe tetracycline derivative with anti-inflammatory characteristics that can pass through intact BBBs.[73-77] In animal studies, minocycline improved outcomes by decreasing inflammation and tissue damage.[77,78] Minocycline controls inflammation through several mechanisms by acting with other inflammatory regulators to decrease the concentrations of pro-inflammatory cytokines and chemokines. This in turn reduces nitric oxide presence and prevents the over activation of microglia.[77,78] Because microglia promotes the pro-inflammatory cytokines IL-1 β, IL-6, and MMP-9, the reduction of microglial activity reduces inflammation.[78-80] Even though minocycline has numerous anti-inflammatory properties, it has not proven to be very beneficial in TBI cases. Novel studies will need to examine whether the drug does not work in TBI or if the lack of therapeutic effect is due to factors such as dosage and method of administration.[78,81]

Melatonin, a hormone produced from the pineal gland with neuroprotective properties, may also prove useful in treating TBI.[82-92] Melatonin is a lipophilic enzyme, meaning that it can cross cell membranes, that decreases inflammation by inhibiting microglial activation and reducing pro-inflammatory cytokine concentrations (i.e., IL-1 β and TNF-α).[89,90] While some experimental trials have shown melatonin to reduce brain edema and cortical neuron degeneration, no cognitive benefits have been proven.[91] A possible reason for the lack of observed cognitive improvement is incorrect treatment dosages,[81] suggesting that melatonin may be able to repair inflammation-based secondary damage. Before melatonin can be translated into a clinical setting, studies will need to test the hormone's long-term effects and safety in TBI-models.

Statins, cholesterol-lowering drugs, displayed anti-inflammatory, and neuroprotective properties in a mouse model of subarachnoid hemorrhage.[93] Statins decrease microglia and astrocyte activation: microglia by inhibiting the signaling pathways of toll-like receptor 4, nuclear factor kB (NF-kB), and G-proteins and astrocytes through the inhibition of epidermal growth factor receptors.[38,94,95] The reduced amount of microglia and astrocytes leads to a reduction of pro-inflammatory cytokines IL-1 β and TNF-α and intracellular adhesion molecules.[38,93,95] Statins have shown therapeutic effects in both animal and human TBI models. Preclinical studies have cited improved neuronal survival, growth, and differentiation[38] while clinical studies using rosuvastin over 10 days reported slight improvements in disorientation and amnesia.[96] While statins are relatively safe and predictable, more preclinical studies using the drug in TBI cases are needed to enhance clinical outcomes.

Another potential treatment option for TBI cases are stem cells, unspecialized cells with regenerative properties.[2,3,97] Stem cells have lots of potential in TBI because of their high degree of proliferation, ability to provide trophic support to surviving host cells, regulation of inflammation, and their potential to differentiate into and replace specific cells (such as neurons).[2,3,98-102] Stem cell therapy has been shown to improve cognitive and motor abilities, decrease inflammation and cell death, and promote regeneration.[3,103] Stem cells are either derived from adults, embryos, and fetuses. Adult stem cells are less likely to form tumors, easier to control, and raise less moral questions; embryo and fetal stem cells show higher degrees of plasticity, release more trophic factors, and show higher degrees of proliferation.[2,3,71]

Mesenchymal stem cells (MSCs) are particularly attractive for TBI treatments because they travel to the site of injury, regulate inflammation, proliferate, and activate other inflammatory cells.[104-106] MSCs likely control inflammation through TNF-α-stimulated gene/protein 6 (TSG-6). TSG-6, promoted by TNF-α and IL-1, is an anti-inflammatory protein that inhibits the signaling pathway involved with toll-like receptors and NF-kB, inactivates parts of hyaluronan, and modifies T-cell behavior.[104,107,108] Because NF-kB regulates genes involved in inflammation and the synthesis of pro-inflammatory cytokines, inhibiting NF-kB impedes both the NF-kB signaling pathway and the following pro-inflammatory effects.[107] TSG-6's inactivation of hyaluronan and modification of T-cell behavior also decreases inflammation, as hyaluronan is a pro-inflammatory molecule and T-cells go from

producing pro-inflammatory cytokines (interferon γ) to anti-inflammatory cytokines (IL-4).[107,108]

In addition, MSCs strengthen the BBB by reducing the synthesis of several chemokines implicated in increased BBB permeability (CXCL2, CCL2, and RATNES). These chemokines are often produced by neurons and microglia and may contribute to immune and inflammatory responses.[104] CXCL2 contributes to neutrophil infiltration, CCL2 is a chemoattractant that incites immune cell relocation, and RANTES aids in T-cell activation.[104,109] MSCs use transforming growth factor β to downregulate the chemokines, in particular, CCL2. Transforming growth factor β works by activating Smad3, which in turn reduces transcription of CCL2. The reduction of the chemokines serves as an anti-inflammatory method because of a subsequent reduction in the harmful effects of leukocytes, neutrophils, and microglia post-TBI.

A major issue with stem cell transplantations is the stem cells' low survival rate in the injured area.[110] If stem cells are used in conjunction with treatments that can improve the host environment, it is likely that a better therapeutic outcome will occur. One potential second treatment option is granulocyte-colony stimulating factor (G-CSF), a cytokine able to augment the benefits of endogenous stem cells.[3] G-CSF as an unaccompanied treatment slightly decreases inflammation, improves motor dysfunctions, decreases brain edema, and regulates glutamate levels. In addition, treatment consisting of only human umbilical cord blood cells increases neurogenesis and slightly decreases hippocampal cell death. When the two treatments are combined, however, neurogenesis greatly improves, cell death significantly decreases, and therapeutic effects last longer.[3]

The US Food and Drug Administration has approved the usage of G-CSF as a drug due to its ability to enlist endogenous stem cells from the bone marrow into the blood stream for the purpose of promoting neuroprotection.[3] Furthermore, G-CSF is likely able to cross the BBB, bind to the G-CSF receptor on neurons and microglia, and promote therapeutic effects. These effects include a decreased concentration of inflammatory cytokines, increased angiogenesis in the brain, and decreased apoptosis.[3] Furthermore, bone marrow derived stem cells may indirectly affect the central nervous system by secreting trophic growth factors, chemokines, and cytokines that aid in neuroprotection and neuroregeneration.[3]

Future Direction of Anti-inflammation as a Therapy for Traumatic Brain Injury

Regulating neuroinflammation appears to be a strong potential treatment option for dealing with TBI, as it can be both detrimental and beneficial to the recovering brain. Immune cells, astrocytes, cytokines, and chemokines are all important to the brain's recovery, but contribute to secondary death when present in excessive levels. Ideally, a treatment would be able to regulate the activation and deactivation of these cells to provide their needed benefits and avoid their hindrances. Additional studies are warranted to reveal cell death pathways relevant to inflammation, which should reveal insights on potential strategies in sequestering inflammation and its associated neurodegenerative processes. A complete understanding of TBI, inflammation, and disease progression will prove beneficial in improving clinical outcomes for TBI patients.

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Conflicts of interest

There are no conflicts of interest.

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