Utilizing pharmacotherapy and mesenchymal stem cell therapy to reduce inflammation following traumatic brain injury

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Abstract

The pathologic process of chronic phase traumatic brain injury is associated with spreading inflammation, cell death, and neural dysfunction. It is thought that sequestration of inflammatory mediators can facilitate recovery and promote an environment that fosters cellular regeneration. Studies have targeted post-traumatic brain injury inflammation with the use of pharmacotherapy and cell therapy. These therapeutic options are aimed at reducing the edematous and neurodegenerative inflammation that have been associated with compromising the integrity of the blood-brain barrier. Although studies have yielded positive results from anti-inflammatory pharmacotherapy and cell therapy individually, emerging research has begun to target inflammation using combination therapy. The joint use of anti-inflammatory drugs alongside stem cell transplantation may provide better clinical outcomes for traumatic brain injury patients. Despite the promising results in this field of research, it is important to note that most of the studies mentioned in this review have completed their studies using animal models. Translation of this research into a clinical setting will require additional laboratory experiments and larger preclinical trials.

Key Words: stem cells; drugs; neuroinflammation; trauma; neuroprotection; regeneration

Traumatic Brain Injury and Inflammation

Traumatic brain injury (TBI) is characterized by intracranial damage resulting from an external force and can be the product of physical insults such as puncture, blunt impact, or blast (Maas et al., 2008). TBI affects 1.7 million people annually, presenting a significant economic burden, and is particularly prevalent in military casualties, where an increase in explosive warfare has led to a parallel rise in TBI occurrence (Okie, 2005; Acosta et al., 2015b). TBI can be classified as mild, moderate, or severe (Lozano et al., 2015). Determining the severity of TBI is commonly accomplished in humans with the Glasgow Coma Scale (GCS), a simple questionnaire used to evaluate the patient’s degree of consciousness in conjunction with medical imaging techniques (Lozano et al., 2015). Associated symptoms such as headache, dizziness, fatigue, or nausea may be short-lived in the case of mild TBI, while in more severe instances cognitive symptoms may progress chronically to resemble neurodegenerative diseases such as Alzheimer’s disease (AD) and Parkinson’s disease (PD) (Lozano et al., 2015). Epidemiological data also suggest that sufferers of TBI are at an increased risk for developing AD and PD later in life through poorly understood mechanisms (Lozano et al., 2015).

The pathology of TBI is divided into two phases, acute and chronic. The acute phase consists of the immediate damage produced from the insult, and the chronic phase may extend for years and is defined by spreading inflammation, cell death, and neural dysfunction that is triggered by the primary injury (Werner and Engelhard, 2007; Acosta et al., 2015b). The expanded distribution of pro-inflammatory molecules, reactive species, and other damaging byproducts from the primary injury site causes a progressive wave of cell damage, forming a region of dead and endangered cells called the penumbra (Zhao et al., 2005; Acosta et al., 2015b). This region poses the greatest threat of chronic symptom development, but also points to a significant opportunity for cell rescue (Zhao et al., 2005; Acosta et al., 2015b). Once considered to be an acute injury only, our understanding of TBI as possessing this chronic aspect has revealed the opportunity of a greater time frame for therapeutic intervention (Acosta et al., 2015b).

The chronic phase of TBI is marked by a multitude of complex metabolic, immune, and cellular responses which are seen primarily in tissue adjacent to the injury site, but can also spread to distal regions of the brain (Kumar and Loane, 2012; Lozano et al., 2015). While these responses...
are seen universally in TBI, researchers have shown that the specific pathology and intricacies of the injury response are heterogeneous, and vary depending on the nature and location of the TBI (Pabon et al., 2016). The immediate damage that occurs during a TBI includes necrosis, excitotoxicity, and mutilation of local neurons, microglial activation, and vascular cells - none of which present a significant opportunity for intervention (Kumar and Loane, 2012). Instead, recent research has focused on the multiple aspects of chronic TBI as a means of reducing the secondary cell death that ensues after the initial acute phase (Lozano et al., 2015). In particular, the neuroinflammatory aspect of TBI physiopathology has been explored as a target for preventing secondary cell death and symptom progression (Lozano et al., 2015). Inflammation plays a dual role in the brain after a TBI; in the acute phase, inflammation has been shown to be neuroprotective, while aberrant inflammation throughout the chronic phase is a key factor in perpetuating cell death (Lozano et al., 2015). Sequestration of the chronic inflammation has been proven to be neuroprotective (Lozano et al., 2015). The transition from protective inflammation to degenerative inflammation - as well as the large number of competing pro-inflammatory molecules (i.e., tumor necrosis factor (TNF-α) and interleukin (IL-1β)) and anti-inflammatory molecules (i.e., IL-10 and TGF-β) - make for a complex pathology (Lozano et al., 2015).

The neurodegenerative inflammation and edema seen after TBI is linked to the dysfunction of the blood-brain barrier (BBB) that occurs after the insult (Shlosberg et al., 2010; Neuwelt et al., 2011). The protective effects of the BBB are contingent on the presence of uninterrupted, selective endothelial cells which moderate the entrance of blood-borne particles (Neuwelt et al., 2011). Additionally, the health of these endothelial cells and the fidelity of the BBB is intimately connected to the health of supportive astrocytes. The mechanical force from the TBI compromises this fidelity, allowing a host of exogenous proteins such as albumin, fibrinogen, and thrombin, as well as peripheral immune cells, to enter the brain parenchyma (Shlosberg et al., 2010; Neuwelt et al., 2011; Lozano et al., 2015). These invading substances trigger the activation of microglia within the injured brain region, causing an immune response that persists for as long as the BBB remains compromised (Shlosberg et al., 2010; Neuwelt et al., 2011). Initially, the microglial activation is a protective response, but the activation can become excessive and self-perpetuating over time (Lozano et al., 2015). Additionally, the invading peripheral cells have been shown to release pro-inflammatory mediators such as cytokines, chemokines, prostaglandins, and free radicals, serving to progressively exacerbate the inflammatory process as well as increasing the permeability of the BBB (Lozano et al., 2015). This elevated permeability to large molecules and cells shifts the osmotic pressure within the brain, causing edema and an increase in intracranial pressure (Neuwelt et al., 2011; Lozano et al., 2015). Damage to the BBB is a continuing issue, as increased levels of molecules which damage tight junctions such as matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF) occur post-TBI and impede the recovery of the BBB (Guo et al., 1989; Lozano et al., 2015).

The immune response is further complicated by differentiation of environment-sensitive microglia into multiple phenotypes (Lozano et al., 2015). Depending on the microenvironment that the microglia is exposed to, the cell may assume an M1, pro-inflammatory, phenotype or an M2, anti-inflammatory phenotype that attenuates the pro-inflammatory M1 microglia (Lozano et al., 2015). Possible therapeutic techniques aim to minimize harmful chronic inflammation, while not preventing acute-phase neuroprotective inflammation, by developing means of downregulating pro-inflammatory molecules, upregulating anti-inflammatory molecules, and aiding in BBB repair (Lozano et al., 2015).

The only defense against the primary injury caused by a TBI is prevention with the use of safety equipment such as helmets and seatbelts (Hirschenfänger et al., 1968; Lozano et al., 2015). The window of opportunity for potential therapies lies within the period of secondary cell death which may last for days, months, or years (Ida et al., 1987). Of the different secondary death mechanisms, neuro-inflammation provides the greatest potential for intervention due to its delayed onset. Glutamate excitotoxicity for example has a much narrower range for intervention as it is an immediate response and may normalize within 120 hours after insult (Matsumoto et al., 1986). Based on the length of time required for enough inflammatory cells to migrate and induce secondary cell death, the onset of damaging neuroinflammation is a slower process (Offit et al., 1986). Neuroinflammation may also persist as a chronic consequence of TBI and this secondary effect is closely linked to many neurodegenerative diseases such as dementia pugilistica (DP), AD, PD and other pathologies (Colman and Gross, 1971).

**Anti-inflammation Pharmacotherapy**

While targeting neuroinflammation is a reasonable approach to sequestering secondary cell death in TBI, it should be noted that neuroinflammation also has beneficial effects. Previous studies have shown that high doses of anti-inflammatory drugs administered after TBI led to worse outcomes due to the loss of neuroprotective effects in addition to the existing harmful effects (Ziebell and Morgan-Kossmann, 2010).

Several stand-alone anti-inflammatory drugs have been tested for efficacy in TBI treatment. Minocycline is a tetracycline derivative known to have both neuroprotective and
anti-inflammatory properties (Kumar and Loane, 2012). Minocycline is a prime candidate for clinical trials due to its ability to cross the BBB in addition to its safety for human use as declared by the US Food and Drug Administration (Saatman et al., 2008). This drug minimizes the release of proinflammatory cytokines and chemokines, in conjunction with other mediators of inflammation, decreases nitric oxide by directly inhibiting the overactivation and proliferation of microglia cells (Homsy et al., 2009; Kovesdi et al., 2012). Reducing and inactivating microglial cells is key as it attributes to the decline in cytokines IL-1β, IL-6, and matrix metallopeptidase 9 (MMP-9), all of which facilitate the proinflammatory response (Homsy et al., 2009; Ziebell and Morgenstern-Kossmann, 2010; Guo et al., 2011). The use of minocycline in animal models has illustrated a significant reduction in inflammation and tissue damage, thereby improving outcomes (Homsy et al., 2009; Kovesdi et al., 2012). However, results of other studies contradict this, suggesting there is no beneficial effects of minocycline on TBI. These opposing outcomes are a predicted result of deviations in dosage and administration intervals, calling for further investigation (Homsy et al., 2009; Kelso et al., 2011).

Melatonin is a hormone produced in the pineal gland and is currently being explored as a stand-alone drug due to its neuroprotective characteristics (Lozano et al., 2015). It is an enzyme that easily passes through cell membranes due to its lipophilic properties. The mechanism of action for its anti-inflammatory effects are by way of inhibiting microglial activation and reducing pro-inflammatory cytokine secretion, such as IL-1β and TNF-α (Wang et al., 2013; Ding et al., 2014a). The effects of melatonin as a TBI therapeutic drug vary, similar to the results of minocycline administration. Lower brain edema and reduced cortical neural degeneration was displayed in successful trials, implying improvement of cognitive deficits (Ding et al., 2014b). However, there was no significant cognitive enhancements in experimental models, the likely cause being attributed to dosage (Kelso et al., 2011). While melatonin is a prospective therapy to sequester secondary damage caused by inflammation, additional studies are necessary to address the long-term feasibility, safety, and efficacy of melatonin in multiple models of TBI (Hirschenfang et al., 1968; Lozano et al., 2015).

Statins are a well-known group of drugs used to treat high cholesterol that have additionally shown neuroprotective and anti-inflammatory effects in a mouse model of subarachnoid hemorrhage (Uekawa et al., 2014). The proposed mode of action is through interaction with microglia and astrocytes. Statins inhibits the signaling pathways of toll-like receptor 4, nuclear factor κB (NF-κB) activation, and some small G-proteins, all of which contribute to the reduction of microglia activation (Loane and Faden, 2010; Wang et al., 2014). By additionally inhibiting epidermal growth factor receptors that play a part in astrogliosis, statins also decrease astrocyte activation (Wu et al., 2010). Without microglia and astrocytes contributing their proinflammatory effects, there is a reduction in the expression of proinflammatory cytokines IL-1β and TNF-α, as well as intracellular and intercellular adhesion molecules, and consequently an overall sequestration of the neuroinflammatory process (Loane and Faden, 2010; Wu et al., 2010; Uekawa et al., 2014). In TBI models accompanied by statin administration, results have displayed an increase in neuronal survival, growth, and differentiation and a lessening of functional impairment (Loane and Faden, 2010). Minor improvements in amnesia and disorientation (as assessed by the Galveston Orientation Amnesia Test) were achieved after rosuvastatin was given over a 10 day period to TBI patients within a clinical trial (Tapia-Perez et al., 2008). Statins are an already well established class of drugs that are tolerated by patients, with occasional mild side effects that are distinct and can be monitored without difficulty. Statins show promise in preclinical for other neurological deficits such as stroke, intracerebral hemorrhage, but more extensive laboratory studies in TBI models are needed to improve clinical outcomes (Hirschenfang et al., 1968; Lozano et al., 2015).

Currently, there remain safety and efficacy optimization hurdles about the use of anti-inflammatory pharmacotherapy for the treatment of TBI. The use of these drugs has demonstrated a notable reduction in the inflammatory response; however, it is crucial to further investigate the applicability of these treatment options in a clinical setting. As previously mentioned, concerns regarding dosage and long-term outcomes warrant further investigation of these drugs prior to their clinical use.

### Stem Cell Therapy for Sequestration of Inflammation

An alternative approach to treating TBI is the concept of stem cell therapy. Stem cells are undifferentiated cells that have the potential to regenerate damaged tissue secondary to their ability to proliferate numerous, differentiate into multiple cell lines, and provide restorative resources to surviving cells (Antonacci et al., 2014; Tajiri et al., 2014c; Tajiri et al., 2014a). Preclinical studies have demonstrated the remarkable regenerative ability of stem cells to transform into newly differentiated neurons following TBI (Antonacci et al., 2012; Rodrigues et al., 2012; Liu et al., 2013; Acosta et al., 2014; Tajiri et al., 2014b, c). Following brain injury, stem cell therapy shows notable potential in sequestering neuronal cell death and a prolonged inflammatory response, which results in increased recovery in both cognitive and motor function (Acosta et al., 2014; de la Pena et al., 2014).

The hallmark of stem cells dampening the TBI-induced inflammatory response lies within their mechanism of action. Mesenchymal stem cells (MSCs) possess the ability to
migrate to the site of injury and activate cellular effectors of the inflammatory response such as microglia, T lymphocytes, and neutrophils (Borlongan, 2011; Borlongan et al., 2011; Zhang et al., 2013). Key inflammatory signals, such as TNF-α and IL-1, induce MSCs secrete an anti-inflammatory protein called TNF-α-stimulated gene/protein 6 (TSG-6) (Watanabe et al., 2013; Zhang et al., 2013). The anti-inflammatory role of TSG-6 is carried out by disrupting the inflammatory signaling pathways of both toll-like receptors (TLRs) and NF-κB (Watanabe et al., 2013; Zhang et al., 2013). The inflammatory NF-κB signaling cascade is characterized by the production of proinflammatory cytokines by T cells, such as interferon γ (Russo et al., 2011). Interestingly, TSG-6 is able to modulate the activity of T cells to instead produce anti-inflammatory cytokines, such as IL-4 (Russo et al., 2011).

Once transplanted, stem cells are faced with the struggle of surviving in the hostile environment at the site of injury (Dela Pena et al., 2014). Certain factors, such as granulocyte-colony stimulating factor (G-CSF), can be introduced alongside stem cells to promote the neuroprotection of the transplanted stem cells (Acosta et al., 2014). Combining stem cells with factors such as G-CSF provide a significant improvement in neurogenesis and a reduction in cell death, when compared to being administered alone (Acosta et al., 2014). G-CSF, a cytokine, has the inherent capability to reduce brain edema, enable recovery of motor function, and to improve control of glutamate levels (Acosta et al., 2014). The mechanism of G-CSF utilizes receptor-mediated transport to recruit endogenous stem cells from the bone marrow into the peripheral blood. These mobilized stem cells can then migrate to the site of injury, where they can synthesize and release growth factors, chemokines, and cytokines that aid in the process of brain tissue repair (Acosta et al., 2014). Recent studies demonstrate that transplanted stem cells preferentially migrate to the spleen, rather than the brain (Acosta et al., 2015a). The concept of increased stem cell survival in the spleen over the brain suggests that direct, targeted therapy may not always be the best treatment option (Acosta et al., 2015a). Indeed, studies are investigating the efficacy of systemic delivery of stem cells in TBI and other disease models, such as stroke (Acosta et al., 2015a). Several types of transplantable cells have been tested in the laboratory, with a few reaching clinical trials, for cell therapy in stroke, including fetal cells, NT2N cells, CTX0E3, embryonic stem cells, neural stem/progenitor cells, umbilical cord blood, amnion, adipose, and induced pluripotent stem cells (Hara et al., 2008; Li et al., 2008; Stroemer et al., 2009; Kaneko et al., 2011; Liu et al., 2014; De La Pena et al., 2015). Primarily due to solid safety profile in other disease indications, preclinical studies and on-going clinical trials have given special attention to bone marrow and its cellular derivatives (Borlongan et al., 2011; Steinberg et al., 2016). Direct intracerebral implantation and peripheral transplantation, such as intravenous, intra-arterial, and intranasal, have documented the functional benefits of bone marrow-derived stem cells (Borlongan et al., 2004; Borlongan, 2011; Borlongan et al., 2011; Prasad et al., 2014; Acosta et al., 2015a). Clinical trials have been initiated, and preliminary reports have demonstrated safety, although efficacy warrants additional investigations (Steinberg et al., 2016). This concept highlights the need for investigations of combination therapy (Figure 1 and Table 1), in order to improve the outcomes.

Table 1 Recent studies combining stem cell therapy and drugs

| Studies | Stem cell-drug combination |
|---------|---------------------------|
| Chen et al. (2016) | MSC + hyperbaric oxygen treatment |
| Zhang and Wang (2015) | NSC + hypothermia |
| Smith et al. (2015) | eNSC + progesterone |
| Borlongan and Pena (2015) | HUCB cells + G-CSF |
| Tian et al. (2015) | NSC + iPSC + QKL (Chinese patented medicine) |
| Huang et al. (2015) | NSC + simvastatin |
| Olson et al. (2015) | MSC + propranolol |
| Liu et al. (2015) | MSC + ginsenoside Rg1 |
| Wang et al. (2014) | NSC + olfactory ensheathing cells |
| Kang et al. (2013) | MSC + ziprasidone |
| Date et al. (2013) | MSC + mannitol |
| Delibasi et al. (2013) | MSC + minocycline |
| Pisano et al. (2013) | EPC |

MSC: Mesenchymal stem cells; NSC: neural stem cells; eNSC: embryonic neural stem cells; HUCB: human umbilical cord blood; G-CSF: granulocyte-colony stimulating factor; iPSC: induced pluripotent stem cells; QKL: qing-kai-ling (Chinese patented medicine); EPC: endothelial progenitor cells; EPO: erythropoietin.

**Figure 1** Combination therapies for traumatic brain injury (TBI).

Stand-alone treatments may not be optimal for conferring brain repair. Combination of drugs and stem cell therapy may synergistically enhance the therapeutic outcomes. Indeed, combining drugs, such as granulocyte-colony stimulating factor (G-CSF), erythropoietin (EPO), and statins may improve the functional benefits of stem cells towards brain repair in TBI and other related disorders.
of drugs and stem transplantation in TBI and other related brain disorders.

**Future Directions**

In this review, the outlined studies detailed treatment options for TBI that focus on either stand-alone pharmacotherapy or cell therapy. A single therapeutic approach may not be optimal in reducing inflammation and in initiating the brain repair process after TBI. It is more likely that combination therapy of anti-inflammatory drugs alongside stem cell transplantation will yield enhanced results that can be translated to the clinical setting. In addition, most preclinical studies are Limited by their use of small animal models for TBI, which may not accurately mimic the clinical scenario in humans. Thus, limited clinical trials of stand-alone therapies, alongside more advanced laboratory studies incorporating optimization of safety and efficacy on dosages and long-term functional assessments of combined pharmacotherapy and stem cell transplantation in large animal models, are required to allow these treatment options to become available at the bedside.

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