

● PERSPECTIVE

## Drug- and cell-based therapies for targeting neuroinflammation in traumatic brain injury

**TBI pathology:** Traumatic brain injury (TBI) is caused by an external force to the head, resulting in trauma to the brain. Approximately 1.7 million Americans suffer from TBI every year. Out of the 1.7 million suffering from TBI, an estimated 52,000 injuries result in death, leaving a mass amount of people with symptoms that could last a few days, a few years, or their entire life (Faul et al., 2010). TBI can be classified as mild, moderate and severe. Depending on the classification and the extent of the injury, TBI can cause both physical symptoms and cognitive disorders (Lozano et al., 2015). The most common physical symptoms include headaches, dizziness, nausea, fatigue, sleep disruption, hearing problems and visual disturbances. Cognitive disorders include attention deficit, memory and executive functioning problems. Brain damage occurs following TBI as a result of direct neural cell loss. Within minutes following the initial injury, secondary cell death occurs, exacerbating the damage and worsening the symptoms (Campolo et al., 2013). Neuroinflammation is one of many factors that can lead to neurodegeneration and cause secondary cell death, indicating that TBI presents with equally debilitating symptoms as a chronic disease in addition to the widely accepted pathological manifestations acutely after injury (DelaPeña et al., 2014).

**TBI-induced secondary death mechanisms and neuroinflammation:** The immune system has a critical role in the pathogenesis of neurological disorders, including TBI and neurodegenerative diseases, mitigating the neural environment *via* cytokines with opposing roles, ones which aid cellular repair and others that drive molecular damage. While the mode of injury in TBI is predominantly ascribed to the acute stage, it is now being recognized that there is a massive chronic neuroinflammation that propagates the secondary cell death over a prolonged period of time after the initial insult (Frugier et al., 2010; Acosta et al., 2013). Chronic neuroinflammation initiates an upsurge of pro-inflammatory cytokines that drive neuronal cell death, increase reactive oxygen species and reduce neurogenesis (Acosta et al., 2014). Patients with a history of TBI require long-term care, and unfortunately a treatment does not yet exist that can ameliorate the long-standing effects of neuroinflammation.

Whereas the primary insult in TBI occurs at the moment of impact as mechanical cell destruction (Frugier et al., 2010), the secondary injury commences thereafter and may persist for months and even years *via* chemical and molecular cell death-propagating processes that impede host brain repair and lead to progressive cell death reminiscent of neurodegeneration with co-morbid symptoms. Following the acute injury, activity of pro-inflammatory cytokines interleukin (IL)-1 and IL-6 rise, followed by increases in tumor necrosis factor (TNF), IL-6, IL-8, IL-10, transforming growth factor beta (TGF- $\beta$ ) in the ensuing weeks after injury (Frugier et al., 2010). One of the best studied cytokines and the one released in the greatest amounts involved in TBI is IL-6, an important inducer of the acute phase reaction. Immediately following impact in TBI, cerebrospinal fluid (CSF) levels of IL-6 have already doubled (Frugier et al., 2010).

A diffuse axonal injury coincides with vigorous cytokine re-

sponse following injury, independent of the macroscopic injury pattern as evidenced in a study of human patients (Frugier et al., 2010). In tandem, inflammation in chronic TBI upregulates active microglia both proximally and distally to the location of injury, a study of chronic TBI by Acosta et al. (2013) demonstrated multiple sites of increased neuroinflammation in sites adjacent to and remote to the injury origin. In addition, there is a decrease in cell proliferation in areas of the subventricular zone (SVZ) and subgranular zone (SGZ), sites of endogenous stem cell growth (Acosta, 2013).

**Current drug treatments for TBI:** Currently there are limited treatment options for TBI, leaving most patients relying on rehabilitation therapy. Damage resulting from the initial injury is almost impossible to treat; therefore for this practical reason, the logical target for treatment intervention to afford clinically relevant benefits is to sequester the secondary cell death. Due to the delay in damage derived from secondary cell death, it allows a wide therapeutic window (Lozano et al., 2015). Among the secondary wave of biochemical cascades, targeting neuroinflammation appeals to this extended time for treatment initiation (Lozano et al., 2015). There have been a variety of drugs that have been reported to reduce inflammation in the central nervous system, including melatonin, minocycline and statins.

Melatonin, derived from the pineal gland, has been shown to provide neuroprotection for brain and spinal cord trauma. Melatonin is a lipophilic enzyme, meaning it does not need a specific binding site or a receptor on the cell brain causing the drug to be more flexible than others (Campolo et al., 2013). Melatonin exerts anti-neuroinflammatory effects through its capability to inhibit microglial activation and lower proinflammatory cytokine secretion (Lozano et al., 2015).

Minocycline, a tetracycline antibiotic, also possesses anti-inflammatory properties and has been shown as an effective neuroprotective agent in many animal models of neurological disorders. This drug has the ability to cross the blood-brain barrier, decrease damaged tissues, and reduce inflammation (Lozano et al., 2015). Minocycline suppresses proinflammatory cytokine and chemokine secretion, and inhibits activation of detrimental microglial cells thereby limiting the progression of secondary cell death (Lozano et al., 2015).

Statins have also been demonstrated neuroprotective properties. This class of drugs is typically used to lower cholesterol, but renders inactivation of cell death-associated microglia and astrocytes. With this deactivation, statins are able to dampen the expression of proinflammatory cytokines and improve the inflammatory response in the damaged tissues (Lozano et al., 2015).

**Stem cell therapy for TBI-mediated neuroinflammation:** Neuroinflammation has been observed in TBI patients up to 17 years after the initial impact (Giunta et al., 2012). As discussed previously, this inflammatory response involves immune cells, microglia, cytokines, chemotactic cytokines, and other cells that exacerbate the evolution of cell death temporally and spatially (Lozano et al., 2015). In addition to drugs, stem cell therapy offers a novel option in reducing the aberrant inflammation. While stem cells have been originally explored as a key component of regenerative medicine for brain disorders, including TBI, *via* their ability to replace dead or dying cells and to stimulate endogenous repair mechanism, accumulating evidence implicates robust anti-inflammatory effects of stem cells (Lozano et al., 2015). Mesenchymal stem cells (MSCs) in particular have been widely studied *in vitro* and *in*



*vivo* for the treatment of TBI. Co-culture of MSCs with purified immune cells causes an increase in production of the anti-inflammatory interleukins IL-4 and IL-10, while decreasing the amount of TNF- $\alpha$  and interferon gamma (IFN- $\gamma$ ) (Walker et al., 2009). The upregulation of IL-4 along with the decrease in IFN- $\gamma$  promotes a shift in the helper T cell subsets, from cytotoxic Th1 cells to Th2 cells (Walker et al., 2009). Additionally, a decrement in TNF- $\alpha$  with an elevated IL-10 could lessen the maturation of dendritic cells, while increasing the number of regulatory T cells that promote an anti-inflammatory or tolerant response (Walker et al., 2009). Studies in TBI experimental models have shown that stem cell therapy suppresses inflammation through their secretion of TNF- $\alpha$ -stimulated gene/protein 6 (TSG-6). This secretion interferes with the signaling pathway involved in the activation of toll-like receptors and nuclear factor- $\kappa$ B (NF- $\kappa$ B), the latter known to be involved in the synthesis of pro-inflammatory cytokines (Lozano et al., 2015). Thus, the NF- $\kappa$ B pathway is inhibited along with further pro-inflammatory cascades that follow (Lozano, 2015). Other benefits of MSCs in dampening the inflammatory response include the inactivation of hyaluronan, modulating pro-inflammatory cytokines to producing anti-inflammatory cytokines, and limiting the influx of devastating chemokines into the brain (Lozano et al., 2015).

Among many other stem cells, human umbilical cord blood cells (HUCBCs) also have the potential to treat TBI as evidenced through extensive studies in which inflammation is attenuated. HUCBCs suppress lymphocyte, granulocyte, and monocyte infiltration (Arien-Zakay et al., 2011). Suppression of astrocytic and microglial activation in the parenchyma is also accomplished by transplanted HUCBCs, coincident with an increase in the production of IL-10 and the decrease in IFN- $\gamma$  (Arien-Zakay et al., 2011).

A combination therapy involving stem cells and drugs for arresting inflammation in TBI should also be considered. Stem cells afford neuroprotection, however, they cannot survive in a hostile environment by themselves (Lozano et al., 2015). Adjunctive treatment with growth factors that will improve the environment and further enhance the regeneration of damaged tissue can be achieved by using granulocyte-colony stimulating factor (G-CSF) (Lozano et al., 2015). G-CSF enhances endogenous stem cells and promotes stemness maintenance, affords an anti-inflammatory effect, reduces brain edema, and improves the control of glutamate levels (Lozano et al., 2015). Accordingly, a combination therapy, as opposed to stand-alone treatment, may prove as an optimal regimen to combat neuroinflammation, as well as the other multi-pronged cell death mechanisms in TBI in order to produce a robust and longer-lasting sequestration of progressive neurodegeneration.

#### **Future directions of research on neuroinflammation for TBI:**

Drugs and cell based-therapies are being investigated as potential treatments for TBI. The recognition of acute and chronic phases of TBI is paramount to truly capturing the pathological manifestations of the disease. Among the many secondary cell death processes associated with TBI, neuroinflammation offers a wider therapeutic window. Immune cells, astrocytes, cytokines and chemokines are all necessary for brain repair. However those are the same cells that cause secondary cell death and further damage to TBI when they reach excessive levels. Drugs, such as melatonin, minocycline and statins, may render anti-inflammatory responses in TBI. Stem cell therapy has also emerged as a promising therapeutic intervention for TBI, and recently stem cells been implicated as vehicles of anti-inflam-

matory factors. Further investigations are necessary to find the optimal regimens for drugs, stem cells, or a combination thereof in order to sequester the TBI-mediated secondary cell death mechanisms, especially inflammation. Discovering, understanding and transitioning secondary cell death factors from being detrimental to serving as an anti-inflammatory brain repair mechanisms likely to provide a therapeutic benefit for TBI.

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