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LETTER

Neuroinflammatory responses to traumatic brain injury

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Dear editor

We read with great interest the recent study by Lozano et al[1] published in the *Neuropsychiatric Disease and Treatment*. The recovery after traumatic brain injury (TBI) is related to severity of the initial injury (primary injury) and the presence of secondary injury.[2] Evidences suggest that inflammation, oxidative stress, excitotoxicity, apoptosis, and neuroendocrine responses play an important role in the development of secondary brain injury.[3] Therefore, an important part in the management of patients with TBI is trying to minimize the occurrence of deleterious secondary lesions. Lozano et al's[1] paper focused on the role of neuroinflammation in brain injury.

Although some studies have described experimental drugs which may eventually have neuroprotective effects in patients with TBI,[2–4] there is currently no approved pharmacological treatment for neuroinflammatory effects of the acute phase of the injury. The dissociation between experimental data with positive results and consecutive clinical trials with negative results leads to a dilemma for the treatment of patients with TBI. And, we agree with Lozano et al[1] that further clarification of the neuroinflammatory mechanisms could be the basis for addressing the gap between bench and clinical results to provide better treatment and reduce death and sequelae of TBI.

A strong point of the paper[1] is the detailed description of signaling pathways of biochemical cascades of secondary injury in TBI, highlighting the metabolic and cellular processes. The discussion about cell death mechanisms is comprehensive and in simple language, which makes it accessible for clinical teams. The description of acute excitatory mechanisms, oxidative stress, and mitochondrial dysfunction is broad and interesting. Another prominent aspect in the review is the section "Neuroinflammation-based therapies", which allows an analysis of the current status and perspectives for treatment of post-traumatic neuroinflammation. Our group has a particular interest in the role of MMPs, zinc-dependent peptides capable to break down most of the extracellular matrix components such as COL, ELN, and FN, in the mechanisms of enhancement of brain injury. As discussed by Lozano et al many processes in secondary injury depends on the integrity of the blood–brain barrier,[5] an anatomical structure formed by tight junctions, basement membrane, podocyte and glial cells that prevents the passive transport of hydrophilic molecules larger than 500 Da between brain structures and blood.[5,6] Experimental studies have shown that MMP-9 levels increase after TBI, breaking down basal lamina components and disrupting the blood–brain barrier.[7] In animal studies, Wang et al[8] demonstrated increased levels of MMP-9 after TBI which persisted for up to 1 week and such an increase also occurred

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in the contralateral hemisphere, suggesting that after trauma, changes in cerebral state are not restricted to the injured area. Suehiro et al[7] found high levels of MMP-9 in TBI patients in the acute phase correlated with high levels of IL-6. They suggested that MMP-9 might play a role in the damage of TBI and be associated with inflammatory events post-TBI. Moreover, during normal development and physiological conditioning of the cell, activated metalloproteinases are required to break down extracellular matrix molecules to allow cell migration.[6] In this context, metalloproteinases may also play a role in allowing the interaction of different types of cells during brain injury or repair.

Inflammatory process, as reported by the authors, is a double-edged sword, good toward neuroregeneration and bad toward enhancing brain damage. The comprehension of the mechanisms that rule this subtle switch to one side or the other should be the goal of this group and others working in this challenging domain.

Disclosure

The authors have no conflicts of interest to disclose.

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Author's reply

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Dear editor

We appreciate Paiva et al's commentary on our recent article[1] highlighting the concept that neuroinflammation after traumatic brain injury (TBI) can be a double-edged sword, conferring both protective and exacerbating effects after the insult. Indeed, we and others have recognized this key feature of inflammation.[2,3] Following the primary insult, an inflammatory response is triggered in order to repair the damaged cells and defend the injury site from pathogens.[4] This inflammatory response is partly modulated by the immune system. Dead cells from the necrotic tissue and dying cells from the surrounding area release signals that activate an immune response, with the stressed cells attracting immune cells into the brain.[5] During this acute period after the injury, inflammation may be therapeutic, in that the inflammatory cells are trying to clear the dead cells, but thereafter the inflammation transitions from mounting a protective effect into exacerbating the disease progression. The massive brain infiltration of inflammatory cells, via a breach in the injury-compromised blood–brain barrier (BBB), allows the secretion of pro-inflammatory molecules, including MMPs, chemokines, and cytokines,[6] further mobilizing the influx of inflammatory cells into the brain and exacerbating the TBI pathology.

The therapeutic outcome of inflammation-based treatments may be highly dependent on the timing of initiation and the level of sequestration of inflammation. Therapeutic regimens can either aid in the pro-inflammatory response that is beneficial early on, or facilitate the anti-inflammatory effects at the later stage of the disease. Understanding the dynamics of inflammation is key to producing therapeutic efficacy; maintaining a certain level of inflammation is likely to assist in brain repair, but in excessive levels, or complete lack thereof, may exacerbate the existing damage. A safe and effective inflammation-based therapy will require a balance of pro-inflammatory and anti-inflammatory effects in order to cater to the dynamically progressive cell death associated with TBI. Microglial cells may serve as the polarizing factors of the double-edge sword function of inflammation, in that these cells can mount both pro-survival and pro-death actions after injury.[7] The advent of novel inflammation-based biomarkers may monitor the M1's degenerative and the M2's regenerative events associated with the microglia in response to TBI. Microglial cells exert neuroprotection via a receptor-mediated phagocytosis, engulfing and degrading dead cells and microbes in the brain, but the same phagocytotic activity of microglial cells may also contribute to the unwanted exacerbation of cell death.[8] The challenge for developing therapies targeting microglial cell function, and inflammation in general, is to harness the cell activation toward a reparative process that could retard, or even halt the progressive pathological symptoms of TBI and its comorbidity factors.

A prolonged state of inflammation after brain injury may linger for years and predispose patients to develop neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease, as evidenced by the detection of expedited accumulation of Aβ and SNCA in our animal models of chronic TBI.[9,10] Such pathological symptoms of neurodegeneration are also seen in chronic TBI patients. In concert with Paiva et al's assertion, elucidating the inflammatory mechanisms that accompany TBI will aid in our understanding of the evolving pathological condition over time, and we can begin to translate these findings for defining new and existing inflammation-based biomarkers and treatments for TBI.

Equally important, drawing from the observations that the degree and extent of inflammation closely approximates TBI outcomes, Paiva et al referred to the potential of drugs targeting the inflammatory response. We also recently alluded to this need for innovative pharmacotherapy for TBI,[11,12] pointing to GLP-1, a drug approved for diabetes with anti-inflammatory properties that has reached clinical trials. Building upon the major thesis of a Janus-faced inflammation, drugs that may augment the early pro-inflammatory response deserve due consideration similar to that afforded to anti-inflammatory drugs for the late stage of the disease when contemplating TBI pharmacotherapy. Paiva et al also emphasized our focused discussion on the mechanisms of action underlying cell death in TBI and converting these same pathways as targets for developing cell survival therapies for TBI. Here, the authors indicated their keen interest in our review of the BBB as a major element of disease pathology, as well as a therapeutic target for TBI. To this

end, they highlighted their long-standing interest in MMPs, which have been implicated in the barrier's breakdown during TBI progression, possibly acting via inflammatory signaling pathway. A tailored drug regimen for attenuating the inflammatory response at specific stages of the disease, in tandem with BBB repair, may prove an effective combination therapy for TBI.

Altogether, we welcome Paiva et al's appreciation of our viewpoints about the multifaceted characteristics of inflammation, and completely agree with their motivation to solicit additional experiments designed to optimize the potential of inflammation-based therapies for TBI.

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