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Review

Is neuroinflammation in the injured spinal cord different than in the brain? Examining intrinsic differences between the brain and spinal cord

B. Zhang, J.C. Gensel *

University of Kentucky, Spinal Cord and Brain Injury Research Center, Department of Physiology, Lexington, KY 40536, USA

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ABSTRACT

The field of neuroimmunology is rapidly advancing. There is a growing appreciation for heterogeneity, both in inflammatory composition and region-specific inflammatory responses. This understanding underscores the importance of developing targeted immunomodulatory therapies for treating neurological disorders. Concerning neurotrauma, there is a dearth of publications directly comparing inflammatory responses in the brain and spinal cord after injury. The question therefore remains as to whether inflammatory cells responding to spinal cord vs. brain injury adopt similar functions and are therefore amenable to common therapies. In this review, we address this question while revisiting and modernizing the conclusions from publications that have directly compared inflammation across brain and spinal cord injuries. By examining molecular differences, anatomical variations, and inflammatory cell phenotypes between the injured brain and spinal cord, we provide insight into how neuroinflammation relates to neurotrauma and into fundamental differences between the brain and spinal cord.

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* Corresponding author at: Spinal Cord and Brain Injury Research Center, Kentucky Injury Prevention and Research Center, B463 Biomedical and Biological Sciences Research Building (BBSRB), University of Kentucky, 741 S. Limestone Street, Lexington, KY 40536-0509, USA.
E-mail address: gensel.1@uky.edu (J.C. Gensel).

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Introduction

When tasked with answering the question: "does neuroinflammation differ between the injured spinal cord and injured brain", one is immediately limited by the small number of studies that have directly compared inflammation after traumatic spinal cord and brain injury (SCI and TBI respectively). In fact, to the best of our knowledge there are only two papers that have done so (Batchelor et al., 2008; Schnell et al., 1999a). The general conclusions from those papers are that the magnitude of the inflammatory response is greater in the injured spinal cord than the brain.

Although the magnitude of the inflammatory response to SCI and TBI may be different, a number of questions with important implications for therapeutic development remain. For instance, are the inflammatory responses different enough that customized therapies for spinal cord or brain injury could not be used interchangeably? What cellular or mechanistic differences contribute to these different inflammatory responses and do they inform us about therapeutic efficacies between the two types of injuries? Although the magnitude of the inflammatory response may differ between the two injury types, does the composition of inflammatory cells and mediators vary? Could the inflammatory response play a more beneficial role in one type of injury than the other? Do inflammatory cells adopt the same functions in the injured brain and spinal cord?

Throughout the course of this review, we will attempt to answer these questions. First, we will revisit the findings of Schnell et al. (1999a) and Batchelor et al. (2008) and discuss them in the current and evolving field of neuroinflammation. Next we will compare and contrast anatomical and molecular components of the brain and spinal cord that influence trauma-induced inflammation. Lastly, we will discuss the potential functions of inflammatory cells in the injured brain and spinal cord with regard to cross-injury therapeutic efficacy and application. Through this examination we hope to provide insight into neuroinflammation as it relates to neurotrauma and gain insight into fundamental differences between the brain and spinal cord.

What we know from direct comparisons between SCI and TBI

When comparing and contrasting inflammatory responses to SCI and TBI, methodological differences in injury severity, injury type, animal strains and species, and analytical techniques potentially confound any differences evident across different studies. For instance with regard to SCI, the neutrophil response is protracted in mice compared to rats (Dusart and Schwab, 1994; Kigerl et al., 2006; Means and Anderson, 1983; Taoka et al., 1997); different strains of mice and rats have different inflammatory responses (Kigerl et al., 2006; Popovich et al., 1997); and in mice, macrophages peak at 7 days post compression SCI vs. 7–14 days post contusion SCI (Kigerl et al., 2006; Thawer et al., 2013). In two separate studies, these confounds were removed by using standardized mechanical, transection-type injuries in both the brain and spinal cord; one in mice (Schnell et al., 1999a) and one in rats (Batchelor et al., 2008). In both studies, identical lesions (with regard to size/depth) were made in the brain and spinal cord. Schnell et al. (1999a) used iridectomy scissors to produce parasagittal lesions in the cerebral cortex or the dorsal spinal cord. Batchelor et al. (2008) used a curved blade to injure either the brain gray matter (cortex) or white matter (corpus callosum) and a Scouten wire knife to injure the spinal cord gray matter (dorsal horn) or white matter (dorsal funiculus). In both studies efforts were made to compare injured spinal cord gray or white matter to similarly injured tissue types in the brain. To count the numbers and density of activated inflammatory cells both groups used standard immunohistological techniques.

Regardless of species, the type of tissue damaged (gray vs. white matter), or the exact method of injury, SCI resulted in greater macrophage, microglia, and astrocyte activation and greater accumulation of neutrophils, T cells, and B cells compared to TBI (Fig. 1) (Batchelor et al., 2008; Schnell et al., 1999a). Collectively, a greater inflammatory response was detected after SCI vs. TBI regardless of the time point examined (Fig. 1).

SCI activated and recruited more microglia and macrophages in and around the injury site compared to TBI (Batchelor et al., 2008; Schnell et al., 1999a). SCI resulted in widespread microglia activation and dense macrophage accumulation in the injury site. In contrast, TBI caused focal microglial activation and less dense areas of activated macrophages. The magnitude of the microglia/macrophage response ranged from 2 to 15× more activated cells in the spinal cord relative to the brain depending upon the proximity of the analysis to the lesion site (Batchelor et al., 2008) (Fig. 1).

Significant variation in neutrophil accumulation in different CNS compartments was also observed. Twenty-four hours following incision, the influx of neutrophil in the brain was minimal and restricted to the lesion site. In contrast, significantly more neutrophils accumulated at the lesion center, as well as the surrounding parenchyma, in the injured spinal cord (Schnell et al., 1999a) (Fig. 1). Similarly, non-traumatic microinjection of cytokines TNF-alpha and IL-1beta also resulted in greater neutrophil infiltration in the spinal cord than in the brain (Schnell et al., 1999b).

Cytokines, chemokines, and proteins released from damaged neurons and activated glia influence the magnitude of the inflammatory response to injury. Any observed differences in macrophage activation, for example, could be downstream of tissue-specific astrocyte reactions to injury. Indeed, by 1-day post injury (dpi) Schnell et al. (1999a) detected a stronger astrocyte reaction in the spinal cord vs. the brain (Fig. 1). Activated astrocytes, with "sheath-like" processes, encompassed both the frank injury and the lesion penumbra and covered a large area in the spinal cord. In contrast, astrocytes adopted a stellate phenotype and were detected primarily in the immediate vicinity of the injured brain. Interestingly, ablation of reactive astrocytes after both SCI and TBI results in increased macrophage activation around the lesion site suggesting that astrocytes play a role in restricting neuroinflammation in both types of injuries (Faulkner et al., 2004; Myer et al., 2006).

The adaptive immune response, composed of T cells and B cells, was also greater after SCI vs. TBI. Although the relative numbers of

	SCI			TBI		
	1-2d	4d	7d	1-2d	4d	7d
Neutrophil	++++	-		+	-	
Macrophage/microglia	++	++++	+++	++	++	+
T cell	+++	++	+	+	+	+
B cell	+++	++	+	+	+	+
Astrocyte	+++	+++	++	++	+++	+++
BBB	++++	+++	++	+	+	-

Fig. 1. Differences in the neuroinflammatory responses to spinal cord injury (SCI) vs. traumatic brain injury (TBI). The overall magnitude (indicated by the relative number of +'s; − signifies no response detected) of the inflammatory response is greater after identical injuries to the spinal cord vs. the brain. Schematic is a summary of the the data reported by Schnell et al. (1999a) and Batchelor et al. (2008). *Note that relative +'s illustrate differences between injury and not cell types. For example, the overall magnitude of T cells and neutrophils is not necessarily comparable 1–2 days (1-2d) after TBI although both are depicted with a single +.*