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Review

# Immune modulatory therapies for spinal cord injury – Past, present and future

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ABSTRACT

Historically, the immune response after spinal cord injury was considered largely detrimental owing to the release of neurotoxic factors. While there is validity to this view, there is much greater heterogeneity of immune cells than was previously realized. Associated with this heterogeneity of immune cell subtypes, there is diversity of functions of immune cells that is still poorly understood after spinal cord injury. Modulating the immune system requires improved understanding of the major players: those immune cell subtypes that are more detrimental than beneficial and those that are important in repair. In this review we will discuss the early findings that supported the use of various anti-inflammatory medications as well as the evolving concept that not all immune subtypes are detrimental and some might even be beneficial. In the last section we will highlight the need to characterize better the role of immune cell subsets in the hopes of developing potential therapeutic targets for the future.



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## Introduction

Trauma to the spinal cord elicits a robust and highly coordinated inflammatory response that includes the rapid activation of microglia and their release of pro-inflammatory mediators such as nitric oxide (NO) and cytokines (i.e., IL-1β, TNF-α, IL-6). The latter, together with neuronal release of pro-inflammatory factors along with endothelial expression of leukocyte chemoattractants and adhesion molecules, drive extravasation of circulating myeloid cells (i.e., neutrophils and monocytes) and lymphocytes into the spinal cord. Other glial compartments such as astrocytes also contribute to the inflammatory response and may regulate myeloid recruitment (Pineau et al., 2010). Similar to the stereotypical response of most organs to injury, spinal cord injury (SCI) elicits a rapid increase in circulating neutrophils followed by monocytes that predict and precede their recruitment to the injured spinal cord (Stirling and Yong, 2008). In contrast to the effects on innate immune cells, SCI also induces several hematological abnormalities including reduced hemoglobin concentration, thrombocytopenia, and lymphopenia (Furlan et al., 2006; Lucin et al., 2009; Stirling and Yong, 2008), which may render SCI patients susceptible to secondary complications such as infection (see also Zhang et al., 2014–in this issue for a detailed review of neurogenic regulation of immune function in periphery after SCI). Interestingly, methylprednisolone, a potent immunosuppressive agent and the only current standard of care for human SCI, exacerbates SCI-induced lymphopenia and causes a pronounced reduction in both neutrophils and macrophages (Bartholdi and Schwab, 1995; Kubeck et al., 2006; Oudega et al., 1999). As discussed in more detail below, the use of methylprednisone remains highly controversial due to its lack of efficacy and safety concerns. Given the known complications of post-injury infection and morbidity following SCI (Meisel et al., 2005), and prior lessons learned from traumatic brain injury (Edwards et al., 2005) and stroke (Qizilbash et al., 2002), continuing to treat SCI patients with globally immunosuppressive agents may seem counterintuitive.

Traditionally, immune responses in the CNS — as opposed to other organ systems — were considered detrimental to wound healing and recovery, with a widely accepted dogma that neuroinflammation and adaptive immunity in the course of CNS disease or trauma are largely undesirable (Allan and Rothwell, 2003). In support of this notion, numerous studies using agents that target neuroinflammatory mediators in general or cellular effectors (microglia/macrophages, lymphocytes or neutrophils) have reported improved neurological outcome following SCI {for review see (David et al., 2012; Hawthorne and Popovich, 2011; Taoka and Okajima, 2000)}. Some of these therapies have entered into clinical trials in CNS trauma and stroke but have consistently shown lack of effect or in some cases adverse effects {for review see (del Zoppo, 2010; Harlan and Winn, 2002; Rigg and Zafonte, 2006)}. Although, there is no doubt that some aspects of neuroinflammation are detrimental after SCI, others have challenged this dogma and provided evidence that microglia/macrophages and other myeloid cell types can be beneficial (Hauben et al., 2000a, 2000b; Kigerl et al., 2009; Prewitt et al., 1997; Rabchevsky and Streit, 1997; Rapalino et al., 1998; Shechter et al., 2009; Stirling et al., 2009). Collectively, these studies highlight the complexity of neuroimmunity following SCI, and they provide evidence of beneficial aspects of neuroinflammation for optimizing CNS repair.

The purpose of this review is to provide a comprehensive appraisal of immune modulatory therapies in the context of SCI and appraise what has been learned from basic science and clinical studies to date. Although there is little doubt that some aspects of the immune response to SCI are detrimental, recent work clearly supports a beneficial role for subsets of macrophages in CNS debris clearance, axonal regeneration, and remyelination. In addition, recent work targeting Gr-1 positive leukocyte subsets indicates an important role for subsets of these cells in repair. Lastly we look to the future and the necessity to understand how different subsets of immune cells influence neurological recovery following SCI. Live imaging studies combined with the availability of subset specific modulators will be necessary to determine the heterogeneity and potential of these diverse immune cells in repair processes as these dynamic processes are occurring. It is hoped that the information gathered from these studies will unravel these complexities and tailor immune therapies to counter negative aspects of neuroimmunity while simultaneously augmenting repair.

## Immune suppressive and modulatory therapies — the past

### *Steroids*

The use of methylprednisolone (MP) for SCI began in the mid 1960s (reviewed by Hall and Springer, 2004). MP is a synthetic glucocorticoid that is used in many conditions due to its anti-inflammatory properties. It acts by binding to and activating glucocorticoid receptors, which are at the head of a number of different anti-inflammatory pathways {review by (Coutinho and Chapman, 2011; Rhen and Cidlowski, 2005)}. Glucocorticoids also physically interact with the important inflammation-inducing transcription factor NF-κB, blocking its transcriptional activity (reviewed by De Bosscheret al., 2003; McKay and Cidlowski, 1999). Despite these anti-inflammatory properties, MP also has antioxidant properties (Braughler and Hall, 1982; Hall and Braughler, 1981), which is important as there is a dramatic increase in damaging reactive oxygen species (ROS) (Bao and Liu, 2004; Liu et al., 1998) and reactive nitrogen species (RNS) after SCI (Scott et al., 1999; Sullivan et al., 2007; Xiong et al., 2007; Xu et al., 2001). Indeed, it was these anti-oxidant properties that were the initial proposed mechanism of MP, while only later was the anti-inflammatory properties of MP recognized (Hsu and Dimitrijevic, 1990). Early findings that MP was neuroprotective in animal models and the general use of MP in the clinic led to the NASCIS I clinical trial which included a high and low dosage of MP, but did not contain a placebo arm due to the belief that MP was beneficial and omitting its use would be unethical; it was found in this trial that there was no significant difference between the high and the low dose (Bracken et al., 1984; Bracken et al., 1985). The second MP trial, NASCIS II, tested a much higher dosing of MP and found modest improvements in motor function at 6 months (Bracken and Holford, 1993; Bracken et al., 1990) and one year after injury (Bracken and Holford, 1993; Bracken et al., 1992) compared to a placebo group. In the NASCIS III trial, all patients were given an initial bolus of 30 mg/kg MP before being randomized into 3 groups: 24 h of MP, 48 h of MP or 48 h of tirilazad, a non-