

# Immunomodulatory Strategies for Spinal Cord Injury

**Jonghyuck Park\***

Pharmaceutical Sciences, College of Pharmacy and Spinal Cord and Brain Injury Research Center, University of Kentucky, USA

\*Corresponding author: Jonghyuck Park, Pharmaceutical Sciences, College of Pharmacy, Spinal Cord and Brain Injury Research Center, University of Kentucky 789 S. Limestone, Lexington, KY 40506, USA



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## ABSTRACT

Neuroinflammation is a key secondary event after spinal cord injury (SCI) and can increase barriers to regeneration, leading to various neurological disorders. Infiltrated hematogenous innate immune cells into the injured site are considered the main effector cells of the inflammatory responses after SCI. Glucocorticoids were the standard of care for spinal cord trauma for years due to their anti-inflammatory properties yet were also associated with unwanted side effects. While the administration of glucocorticoids is controversial, immunomodulatory strategies that limit inflammatory responses provide the potential therapeutic approaches to promote functional regeneration following SCI. Herein, we will discuss emerging therapeutic strategies to modulate inflammatory responses to enhance nerve recovery after spinal cord trauma.

**Keywords:** Spinal Cord Injury; Nerve Regeneration; Immunomodulation; Gene Therapy; Nanomedicine; Stem Cell

**Abbreviations:** HGF: Hepatocyte Growth Factor; MSC: Mesenchymal Stem Cells; ESC: Embryonic Stem Cells; MARCO: Macrophage Receptor with Collagenous Structure; PCL: Polycaprolactone; AAV: Adeno-Associated Virus SCI: Spinal Cord Injury

## Introduction

Traumatic Spinal Cord Injury (SCI) results in an initial primary injury, followed by secondary events including ischemia, anoxia, and excitotoxicity for the first minutes, hours, and days after injury [1-4]. As a key secondary event, inflammation is initiated in part by the rapid influx of circulating immune cells such as neutrophils, inflammatory monocytes, and macrophages [5-7]. These cells begin to release various inhibitory factors which contribute to an inhibitory microenvironment and damage adjacent intact tissue, thereby inducing permanent loss of locomotor and somatosensory functions below the level of injured spinal cord [8-10]. Although inflammatory response induces additional secondary damages, it is necessary to trigger wound healing and tissue regeneration after injury [5,11]. Additionally, there can be unwanted results such as systemic infection or disease when depleting immune

cell populations. Therefore, systemic suppression of immune responses is unlikely to provide long-term therapeutic effects for SCI treatment. This review will focus on therapeutic strategies that reprogram the pro-inflammatory microenvironment towards a pro-regenerative milieu to limit inflammation-mediated secondary injury and promote functional regeneration after SCI.

## Gene Therapy

Various gene therapy-based approaches have been introduced in the last twenty years and continue to be utilized as a powerful therapeutic approach to alter or correct defective genes for the treatment of multiple diseases [12,13]. While direct delivery of biologics is effective for short-term dosage, gene therapy provides the long-term sustained expression of the gene of interest. Vectors for gene therapy can be broadly classified as

non-viral and viral vectors [14]. Non-viral vectors are cost-effective and less immunogenic, however, their ability to transfect cells is limited particularly *in vivo* [14]. Viral vectors can overcome these limitations by incorporating their genetic information into the host cell's genome, inducing greater transduction efficacy and long-term expression of target genes. Choosing an appropriate vector will be the most important factor to achieve immunomodulatory therapy for SCI. The timing of onset of delivered transgene expression can be critical. The transgene expression by herpes simplex virus (HSV) or adenovirus occurs within 24 hours after delivery, which is faster than other viral vectors [15]. The transgene expression by lentivirus (LV) exhibits within 48 hours after administration and peaks the expression level of transgene after 3 days [6,16,17]. Vector size also can be an important factor since retrovirus can carry a maximum of 10 kb of single-stranded RNA and adeno-associated virus (AAV) can contain less than 5 kb of single-stranded DNA. Adenovirus and HSV can contain relatively higher transgene capacities. Viral vectors can be immunogenic compared to non-viral vectors which can result in unwanted side effects. While adenovirus can cause significant inflammatory responses, LV and AAV are considered less immunogenic and exhibit a transient immune response after administration [18].

## Nanoparticles

Nanomedicine employing polymeric nanoparticle (NP) has received significant attention due to its inherent therapeutic potential to modulate immune responses to cure inflammatory responses-mediated disorders including SCI [19-22]. Previous study utilizing poly(lactide-coglycolide) (PLG)-based NPs with a negative surface charge indicated that intravenously administered NPs distracted circulating immune cells such as neutrophils and inflammatory monocytes prior to extravasation into the injured spinal cord, thereby reducing the pathological system indirectly after SCI [22]. NPs with highly negative zeta potential are taken up by targeted circulating immune cells through the scavenger receptors such as macrophage receptor with collagenous structure (MARCO) and reprogram them to affect their migration to the spleen [23]. Furthermore, some NP-positive cells accumulate at the injury, enabling upregulation of the expression of pro-regenerative factors that directly promote a more permissive environment after SCI [24,25]. Additionally, locally delivered poly (2-hydroxyethyl methacrylate) (PHEMA) and polycaprolactone (PCL) based NPs have been shown to modulate immune responses by attenuating the activation of pro-inflammatory macrophages and microglia specifically after SCI [26]. Other NPs including polystyrene [27], poly (lactic acid) [28], iron oxide [29], and gold [30] have also been employed to reprogram immune cells to modulate inflammatory responses after injury.

## Stem Cell Therapy

Stem cells can proliferate and differentiate into any cell type present in the body. Considering their therapeutic potential and abilities of self-renewal and differentiation, stem cells are widely used following SCI [31,32]. In a preclinical study, the transplantation of mouse embryonic stem cells (ESC) into a rat spinal cord after SCI, demonstrated differentiation of transplanted stem cells into astrocytes, oligodendrocytes and neurons improving hindlimb weight support and coordination [33]. In a clinical study, bone-marrow derived mesenchymal stem cell transplanted patients showed improvement in American Spinal Injury Association Impairment Scale (AIS) grade from A to B in SCI patients [34]. Adult stem cells are more susceptible to immune rejection compared to ESC since they express major histocompatibility complex (MHC)-II and CD86 [35]. However, adult stem cells can reprogram the inflammatory environment by releasing multiple anti-inflammatory cytokines [36]. The neural stem cells (NSC) in the spinal cord have the ability to reprogram the immune cells after SCI [37]. They promote macrophage polarization towards a more pro-regenerative phenotype enhancing the expression of anti-inflammatory factors to improve nerve regeneration. NSC release multiple factors after an injury such as TGF- $\beta$ , prostaglandin E, and nitric oxide that increase the number of regulatory T cells enhancing the expression of pro-regenerative factors. In addition, NSC can directly contact T cells and increase regulatory T cell populations, thereby enhancing the expression of anti-inflammatory factors while limiting the expression of pro-inflammatory factors [37]. Mesenchymal stem cells (MSC) can also modulate the inflammatory responses after SCI. MSC secrete interleukin 1 receptor antagonist (IL1-RA) that can induce the polarization of macrophages into pro-regenerative phenotype [38]. In addition, MSC-mediated over-expression of IL-6 and hepatocyte growth factor (HGF) can influence monocytes and induce the secretion of the high level of pro-regenerative factors including IL-10 in the injured site for immunomodulation [39]. Moreover, delivered MSC into the injured spinal cord limited the infiltration of the circulating inflammatory subset of immune cells to the injured site and promoted the phenotypical changes of macrophages and microglia into a more anti-inflammatory phenotype. MSC also restored the broken blood spinal cord barrier to prevent additional damage, thereby enhancing functional recovery after SCI [39].

## Conclusion and Future Directions

Immunotherapeutic approaches for the treatment of SCI have the capacity to indirectly and/or directly enhance functional recovery. Although many preclinical studies have demonstrated therapeutic effects of immunomodulatory factors on SCI, the introduction

of these strategies in the clinic faces various limitations for SCI victims. Further investigations will be required to assess how each of the immunomodulatory factors can be employed synergistically to reprogram the immune system to promote functional recovery after SCI while limiting life-threatening side effects.

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