Tissue Eng Regen Med (2024) 21(3):367–368
https://doi.org/10.1007/s13770-024-00639-z

Online ISSN 2212-5469

EDITORIAL

Modulation of Inflammatory Responses to Enhance Nerve Recovery after Spinal Cord Injury

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Accepted: 15 March 2024 / Published online: 26 March 2024

Abstract Inflammation can occur at the wound site, and immune cells are necessary to trigger wound healing and tissue regeneration after injury. It is partly initiated by the rapid migration of immune cells such as neutrophils, inflammatory monocytes, and macrophages after spinal cord injury (SCI). Secondary inflammation can increase the wound area; thus, the function of tissues below the injury levels. Monocytes can differentiate into macrophages, and the macrophage phenotype can change from a pro-inflammatory phenotype to an anti-inflammatory phenotype. Therefore, various studies on immunomodulation have been performed to suppress secondary inflammation upon nerve damage. This editorial commentary focuses on various therapeutic methods that modulate inflammation and promote functional regeneration after SCI.

Keywords Immunomodulation · Spinal cord injury · α-gal nanoparticles

Mesenchymal stem cells (MSCs), neuronal stem cells, and Schwann cells may release anti-inflammatory cytokines and activate endogenous M2 macrophages and microglia [1]. Cheng et al. showed that neural stem cell (NSC) transplantation remarkably reduces the migration of neutrophils and iNOS + /Mac-2 + cells to an injured area, and TNF-α, IL-1β, IL-6, and IL-12 levels decrease in spinal cord injury (SCI) [2]. Other researchers reported that MSC transplantation reduces cavitation size and TNF-α and IL-1β expression and further restores motor function [3]. Therefore, stem cells can promote recovery from spinal cord damage through immunomodulation and nerve cell protection.

Cytokine or molecule delivery is an important method that can synergistically affect the therapeutic efficacy of these stem cells in alleviating SCI. Erens et al. studied spinal regeneration by injecting recombinant arginase-1 (rArg-1) into the abdominal cavity [4]. They showed a decrease in T-cell infiltration and suppression of Th1 and Th17 cells. Furthermore, rArg-1 treatment reduces the amount of NO production and the number of apoptotic neurons and neuron–macrophage/microglial contacts at the site of SCI [4]. Park et al. investigated the localized expression of the anti-inflammatory cytokines IL-10 and IL-4 via lentiviral transduction in polylatic-glycolide (PLG) microspheres. They observed that the induced IL-10 and IL-4 expression decreases the expression of pro-inflammatory genes and increases pro-regenerative genes at the wound site. Therefore, the number of oligodendrocyte-myelinated axons increases, and motor function at the SCI site improves [5].

Studies have been performed to enhance the therapeutic effect on SCI through inflammation suppression or immunomodulation involving various cytokines and small molecules. Among these small molecules, α-gal (Galα1-3Galβ1-4GlcNAc-R) nanoparticles are used for tissue healing. Wigglesworth et al. showed that topically applied

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α-gal nanoparticles in anti-Gal-producing mice induce the recruitment and activation of macrophages, thereby releasing various cytokines, such as VEGF, FGF-1, FGF-2, PDGF-A, PDGF-B, CSF-1, and CSF-2 [6]. Kaymakcalan et al. also showed that the topical treatment of α-gal nanoparticles on the full-thickness skin wounds of diabetic mice increases M2 phage recruitment; as a result, the rates of epithelialization, vascularization, and granulation tissue deposition are accelerated [7]. Based on these results, studies have used α-gal nanoparticles in wound healing such as skin regeneration and have demonstrated their effectiveness in clinical healing [8, 9]

Few studies have used α-gal nanoparticles on the central nervous system, which is sensitive to inflammatory reactions. Recent cell and animal experiments involve α-gal nanoparticles for nerve regeneration. For instance, Gopalakrishnan et al. reported that α-gal nanoparticles induce the in vitro activation of microglia toward a pro-healing state [10]; they also conducted animal studies on immunomodulation following SCI and observed an improvement in functional outcomes [11]. These two papers to be published in this April issue of *Tissue Eng Regen Med* present the results of a study on the efficacy of α-gal nanoparticles in central nerve regeneration. These studies are possibly the first in vitro and in vivo experiments on the regeneration of the SCI in the central nervous system, and they will be published through this journal.

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