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Meeting Abstract

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1. Oral Presentations

Transcriptional and Cellular Dynamics of Scar-Free Spinal Cord Healing in Acomys

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Abstract

Our lab has recently shown that Acomys dimidiatus (Muridae family) is a unique mammal capable of repairing the spinal cord after complete transection, with remarkable functional recovery. Our initial analyses revealed that this outcome is associated with a pro-regenerative ECM formed at the lesion site, in which high levels of the β3gnt7 enzyme lead to increased keratan sulfate proteoglycan (KSPG) deposition. While this ECM signature is essential for repair, longitudinal bulk transcriptomics revealed that a critical transcriptional switch occurs earlier. In both Acomys and Mus musculus (non-regenerative species), inflammation and fibrosis are activated early after spinal cord injury (SCI). However, in Acomys, these are then downregulated, and followed by activation of gene networks supporting axon growth and synaptogenesis. By contrast, Mus has sustained activation of inflammation and fibrosis, and repression of neuroregenerative programs. This supports that in Acomys, an initial scar-forming response facilitates wound closure but is subsequently resolved to allow regeneration. To elucidate the cellular populations enabling this switch, we generated a single-nucleus RNAseq/ATACseq atlas of the SCI site of both species. Our data identified specific microglial subpopulations as possible key mediators of spinal cord regeneration in Acomys. Moreover, it showed that microglia is the β3gnt7-expressing cell after lesion. These findings laid the foundation to explore the role of specific microglia subpopulations in the regenerative ability of Acomys, including the ongoing generation of Acomys-like Mus models over-expressing β3gnt7 in microglia. These experiments will pave the way for developing microglia-targeted and KSPG-based therapies to promote spinal cord repair in patients.

Keywords

spinal cord injury; regeneration; proteoglycans

DYRK2 Activity Promotes Spontaneous Axon Regeneration After a Complete Spinal Cord Injury

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Abstract

Mature neurons are unable to regenerate their axons following traumatic spinal cord injury in mammals. In contrast, descending neurons of the lamprey brainstem spontaneously regenerate after a complete spinal cord injury. Work from our group showed that GABA signaling through GABAB receptors promotes axon regeneration in lamprey descending neurons. Moreover, baclofen (a GABAB agonist) administration further promoted axon regeneration after spinal cord injury in lampreys. Now, we present RNAseq and RT-qPCR data showing that the baclofen treatment increases DYRK2 expression in the sea lamprey brainstem after a complete spinal cord injury. Dual specificity tyrosine-phosphorylation-regulated kinases (DYRKs) are a group of conserved eukaryotic kinases phosphorylating tyrosine, serine, and threonine residues. Immunofluorescence experiments confirmed that DYRK2 is expressed in both control and injured descending neurons. Based on these expression data, we decided to test the effects of the selective DYRK2 inhibitor LDN-192960, which reduced axon regeneration of giant individually identifiable descending neurons and the regeneration

of descending neuropeptidergic axons. Morpholino administration, to knockdown DYRK2 protein expression only in descending neurons, confirmed that intrinsic DYRK2 activity promotes spontaneous axon regeneration in lampreys. Interestingly, DYRK2 pharmacological and genetic inhibition also decreased axon regeneration in a larval zebrafish model of spinal cord injury, which reveals an evolutionary conserved role for this kinase in promoting axon regeneration. Use of DYRK1A/1B inhibitors in the zebrafish model revealed a selective role for DYRK2 in promoting axon regeneration. Our study provides a novel therapeutic target to promote axonal repair in nonregenerating organisms.

Keywords

DYRK2; axon regeneration; fishes

Swimming Toward Healing: Zebrafish as a Model for Spinal Cord Repair

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Abstract

Zebrafish have emerged as a powerful model to uncover the cellular and molecular mechanisms that enable full functional recovery after spinal cord injury — a capacity largely absent in mammals. This lecture will explore how zebrafish regenerate their spinal cord with remarkable precision, focusing on the roles of inflammation, glial bridging, neuronal regrowth, and vascular remodeling. Beyond fundamental biology, we will discuss how zebrafish larvae offer a unique, high-throughput platform for *in vivo* drug screening, enabling rapid identification of compounds that modulate regenerative pathways. By bridging mechanistic insights with translational potential, zebrafish are proving to be more than a model — they are an inspiration for designing future therapeutics for spinal cord repair.

Keywords

spinal cord injury; vascular repair; inflammation; zebrafish

The Crosstalk Between the Epigenome and Mitochondria as Central Player in Neural Fate Decisions of the Axotomized Neurons After Spinal Cord Injury

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Abstract

Spinal cord injuries (SCI) is a devastating condition of the CNS for which there are no restorative therapies. Neuronal death at the primary lesion site and in remote regions that are functionally connected to it is one of the major contributors to neurological deficits induced by SCI. In this study we examined the crosstalk between mitochondria and the epigenome, defined as “mitonuclear communication” and its contribution to the remote damage-induced by SCI in the red nucleus (RN) contralateral to the injury site. Using a mouse model of SCI, we performed RNA-seq analysis on RN isolated from control and SCI mice. Downstream pathway analysis revealed that the number of differentially expressed genes (DEGs) in RN was very low and most of them were upregulated, rather than downregulated. To get in-depth insight into the translational response activated by SCI, we performed proteomic analysis on RN isolated from control and SCI mice at 7 and 28 days after injury. Our results showed that the proteome of the RN suffers dramatic changes 7 days after SCI, but this translational response is tampered at 28 days. Integrated pathway analysis, points out to the histone demethylase KDM5A as the putative upstream regulator of the observed phenotype. Consistent with these data, immunofluorescence experiments showed a global increase of its downstream target H3K4me3 specifically in the neuronal compartment 7 days after injury. These data suggest that a functional–bidirectional–crosstalk between KDM5A and the mitochondria might coordinate the initial responses activated in the RN after SCI.

Keywords

axonal degeneration; mito-nuclear communication; epigenetics

Urethral Serotonin: A Hidden Participant in Neurogenic Detrusor Overactivity After Spinal Cord Injury. An Experimental Study in Female Mice

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Abstract

Spinal Cord Injury (SCI) disrupts neuronal control of micturition, leading to urinary impairment. While the bladder was seen as the central organ in SCI-urinary incontinence, emerging evidence suggests that urethral afferents, modulated by peripheral serotonin (5-HT), influence bladder contractility. How SCI affects this pathway is unclear. Female C57BL/6 mice (WT and tryptophan hydroxylase 1-deficient mice -tph1-/) were submitted to T8/T9 complete spinal cord transection. One or 4 weeks after spinal injury, cystometries showed that WT animals had developed bladder dysfunction, while in tph1-/-, urinary impairment was less severe. At 4w SCI, tph1-/- mice showed decreased frequency of bladder contractions ($p < 0.05$ vs WT 4w SCI), as well as decreased basal ($p < 0.001$ vs WT 4w SCI) and peak pressures ($p < 0.05$ vs WT 4w SCI). In WT mice, bladder overactivity correlated with increased 5-HT+ urethral cells ($p < 0.01$ vs WT INT). Both genotypes had developed an atrophy of the internal urethral sphincter (IUS) at 4w SCI ($p < 0.05$ vs WT INT; $p < 0.05$ vs tph1-/- INT), while fibrosis of the external urethral sphincter (EUS) was only seen in tph1-/- mice ($p < 0.05$ vs tph1-/- INT). Expression of sensory and cholinergic markers was increased in WT but not tph1-/ mice (CGRP: $p < 0.01$ vs WT INT; VAChT: $p < 0.01$ vs WT INT). Experiments in SCI WT mice treated with 5-HT2 and 5-HT3 receptor antagonists resulted in worsened bladder function. Overall, this study builds on prior work on urethral involvement in SCI-urinary dysfunction and demonstrates that urethral 5-HT may have a protective role in bladder function after spinal trauma.

Keywords

spinal cord injury; urinary dysfunction; urethra

Replumbing the Central Nervous System – Macrophages as Potential Modulators of the Vascular Response After Spinal Cord Injury in Adult Zebrafish

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Abstract

A spinal cord injury (SCI) is a devastating condition that, in humans and non-regenerative mammals, causes permanent sensory and motor impairments. Among the initial injury consequences, the vascular damage at the centre of the injury, together with the Blood Spinal Cord Barrier disruption in peri-lesion regions, are not efficiently repaired. Over time, they actively contribute to the progression of the condition through a sustained immune accumulation and continued presence of neurotoxic and inhibitory compounds. In contrast, zebrafish regain their motor and sensory capacity after injury through the recovery of lost cellular populations and repair of the spinal architecture. Despite this, little was known about their spinal vascular structure or its behavior after injury. In our work, we described the homeostatic vascular structure of the adult zebrafish spinal cord and its response to injury. The vascular network is immediately disrupted after injury but quickly displays an early proliferative angiogenic response and a strong revascularization of the injury site. This process is driven by accumulating mpeg1.1 + macrophages/microglia, as their ablation with clodronate liposomes hinders revascularization after SCI. Transcriptome analysis of mpeg1.1 + cells at 3 days post-injury revealed 29 secreted/extracellular players that have been reported in the literature to directly or indirectly modulate angiogenesis. From these, 5 out of 13 genes tested were transcriptionally downregulated after clodronate liposome treatment, representing angiogenic players that might mediate the vascular response after SCI in the adult zebrafish. Future work will assess their role in spinal revascularization and their potential application in non-regenerative models.

Keywords

zebrafish; vascular response; microglia/macrophages

CargoSCItes - Cargocytes as a Novel Delivery Platform for Therapeutic Proteins After Spinal Cord Injury

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Abstract

The secondary injury phase poses the greatest obstacle for neural regeneration after SCI. We pursue a novel therapeutic approach utilizing telomerase-immortalized, enucleated

adipose-derived stem cells (ASC/TERT), termed Cargocytes, loaded with glial cell line-derived neurotrophic factor (GDNF) and Interleukin 10 (IL-10) capable of addressing the complex pathophysiology of this phase. Through the enucleation process all genomic DNA is removed enabling genetic enhancement of the cells without compromising safety. During their life span of approximately three days Cargocytes translate cytoplasmatic mRNA into protein allowing targeted loading and prolonged protein secretion, thereby combining the advantages of cell-free delivery systems and stem cell therapies. By simultaneously delivering multiple therapeutic factors, we aim to modulate the immune reaction and promote tissue regeneration at the site of injury. Enucleation is performed via density gradient ultracentrifugation with Cytochalasin B. Transfection of in-house synthesized mRNAs supplemented N1-methylpseudouridine elicits significant overexpression and secretion of functional GDNF and IL-10 from Cargocytes. Cargocytes are active *in vivo* for at least 72 hours and home to the site of injury after intrathecal injection in a rodent model of moderate spinal cord contusion. Our data prove the feasibility of Cargocytes as delivery vehicles for therapeutically active growth factors in the acute phase of SCI. Our next goal is to show efficacy of Cargocytes in a preclinical SC contusion model in rats.

Keywords

cargocytes; growth factors; acute phase

Stimulation of Corticospinal Neurons by Optogenetic cAMP Inductions Promotes Motor Recovery After Spinal Cord Injury via Raphespinal Tract Modulation

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Abstract

After spinal cord injury (SCI), cAMP levels significantly drop in the spinal cord, the sensorimotor cortex, and the brainstem, contrary to what occurs in regenerating peripheral neurons after a nerve injury. To address SCI recovery, we delivered the bacterial photoactivatable adenylate cyclase (bPAC) overexpression for on-demand cAMP inductions in corticospinal neurons. Daily optogenetic corticospinal neuron stimulation in rats suffering a thoracic dorsal hemisection, increased P-CREB and c-Fos in the motor cortex, increased passive membrane excitability and restored the firing threshold and action potential delay to the healthy levels. bPAC stimulation in SCI animals promoted an early and sustained locomotor recovery compared to non-treated rats without affecting nociception. bPAC treatment increased the numbers of retrogradely labeled neurons from the lumbar segment in the motor cortex and the raphe-reticular formation, but not in the red nuclei, demonstrating greater preservation/regeneration of the corticospinal and raphe/reticulospinal tracts through the injury site. Accordingly, higher density of 5-hydroxytryptamine positive descending serotoninergic axons were found caudal to the injury in bPAC-stimulated rats, significantly correlating with enhanced functional performance. Serotonergic descending pathway implication in motor recovery was further evidenced by selective depletion of the serotonergic neurons (via 5,7-dihydroxytryptamine injections) resulting in the abrogation of bPAC-mediated functional recovery. Overall, our findings underscore the efficacy of bPAC-stimulated cAMP induction in corticospinal neurons in recovering function after SCI, which allowed us to describe a cortical rerouting pathway via the serotonergic descending tract.

Keywords

spinal cord injury; cAMP; optogenetics; serotonergic tract

Genetic Engineering of the CD81 Large Extracellular Loop for Targeted Delivery of Extracellular Vesicles for Spinal Cord Injury Repair

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Abstract

Spinal cord injury (SCI) is a devastating condition. Its consequences relate with the acute and chronic inflammatory response and the establishment of an environment that limits regenerative processes. Systemic administrations of extracellular vesicles (EVs), namely from mesenchymal stem cells, have been shown to promote locomotor recovery in rodent models of SCI. However, most of the systemically administered EVs do not reach the injury site. Here, we aimed at genetic engineering CD81 (highly expressed on EVs), for target delivery of EVs towards the SCI site. To achieve this, we used a previously established yeast library displaying the large extracellular loop (LEL) of CD81, randomized in specific solvent exposed amino acids. By consecutive rounds of MACS and FACS sorting, we selected versions of the CD81 LEL with binding ability to relevant proteins found specifically at the SCI site, both acutely (myelin associated glycoprotein, MAG) and chronically (neurocan). These versions were able to be expressed and maintained their binding ability when expressed in full length CD81 on HEK-293 cells. Furthermore, EVs from these cells also bound to MAG (but not neurocan). Finally, we performed HEK-293 lentiviral transduction of the binding-CD81s with mCherry and nanoLuc tags. Next, we will assess the homing ability of their EVs towards the SCI site in a mouse compression SCI model, comparing with wild type CD81 transduced cells. By directing the EVs to the specific growth inhibiting environment of SCI, we hope to maximize the potential of EV therapies for SCI.

Keywords

extracellular vesicle; spinal cord injury; CD81

CD9 as a Driver of Neurophatic Pain Through Adaptive Immunity After Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) triggers a multifaceted immune response that influences motor recovery. However, underneath the big iceberg of SCI pathophysiology and motor impairment, there is an uncounted of secondary conditions, such as persistent inflammation and chronic pain. Our lab has identified for the first time CD9 as a new vascular injury-induced player. CD9 is a tetraspanin protein, known to regulate cell adhesion and growth. In addition, it influences the immune response by promoting the transendothelial migration of leukocytes into the tissue. After SCI CD9 expression is upregulated in mouse endothelial cells and pericytes during the acute phase of the lesion - 3–7 days post-injury (dpi), with a pronounce presence on the caudal side of the injury. During injury progression, this overexpression is sustained as well in immune cells, peaking at 7 dpi, an important time period for the infiltration of lymphocytes and the shift from innate into adaptive immunity. In the absence of CD9 (CD9 KO), locomotion is impaired when compared with wild-type mice, but there is a protection to thermal cold hypersensitivity (allodynia) at 7 dpi. This phenotype is associated with changes in the intraspinal cytokine profile, where CD9 KO mice presented lower levels of IL-6, IL-5 and CD40, know to active B cells, but higher levels of IL-2, TNF-α and VCAM, when compared with WT animals, once again supporting the shift into adaptive immunity. Given that adaptive immunity, particularly B cells, can play a pivotal role in neuropathic pain development, we hypothesise that CD9 might have an important role in B cells activation, thereby modulating allodynia and neuropathic pain, secondary conditions commonly understudied in SCI.

Keywords

pericytes; immune cells; CD9; allodynia; adaptive immunity; pain

DHA Priming Reprograms the Metabolism of Human Adipose Mesenchymal Stromal Cells and Improves the Therapeutic Performance of Its Secretome in Translational Studies of Spinal Cord Injury

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Abstract

Herein, we studied the effects of a newly developed priming approach using the omega-3 fatty-acid docosahexaenoic acid (DHA) on several aspects of adipose stem-cell biology and on the neuroregulatory profile of their secretome for regenerative applications in spinal cord injury (SCI). By

using dose-escalation studies coupled with metabolic viability and temporally resolved evaluation of cellular morphology, the optimal DHA priming protocol was determined to be 40 µM for 72 h. Transcriptomic experiments and metabolic profiling revealed over-represented pathways that unify metabolic sensing and higher biosynthetic capacity with DHA priming. This transcriptional response was correlated with increased glycolytic output and mitochondrial activity which culminated in an increased concentration of proteins and extracellular vesicles in the secretome. Unbiased LC/MS proteomics revealed a link between the transcriptional landscape and the proteome of the hASCs secretome, with up-regulated proteins being functionally associated with anti-oxidant and neurotrophic responses. Functionally, the DHA-primed secretome protected spinal cord cells and modulated astrogliosis and microglial cell reactivity by reducing their proliferation after a hyperosmotic stress injury *in vitro*. In a clinically relevant model of thoracic compression SCI, DHA-primed secretome reduced astrocyte and microglial reactivity in the grey matter and degenerating corticospinal tracts of the spinal cord. These effects correlated with similar motor recovery when compared to standard secretome and a differential performance on the amelioration of SCI-induced behavioral deficits in sensory and spasticity domains. Overall, this work proposes a novel priming strategy that promotes significant improvements in the therapeutic potential of ASC secretome when applied for spinal cord injury.

Keywords

docosahexaenoic acid; mesenchymal stem cells; spinal cord injury

2. Posters

Modeling Spinal Cord Injury in a Dish With Hyperosmotic Stress: The Effects of Mesenchymal Stromal Cell Secretome Treatment

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Abstract

Innovations in spinal cord injury (SCI) models are crucial for developing effective therapies. This study introduces a novel *in vitro* SCI model using cultures of primary mixed spinal cord cells from rat pups, featuring key spinal cord cell types. This model offers distinct advantages in terms of feasibility, reproducibility, and cost-effectiveness, requiring only basic cell culture equipment. Following hyperosmotic stress via sorbitol treatment, the model recapitulated SCI pathophysiological hallmarks, with a 65% reduction in cell viability and gradual cell death over 48 hours, making it ideal for evaluating neuroprotective agents. Notably, the human adipose tissue stem cells (hASCs) secretome provided significant protection: it preserved metabolic viability, reduced β-APP expression in surviving neurons and modulated the shift of astrocytic morphotype. A transcriptomic profile of the effect of the hASCs secretome treatment showed significant functional enrichments related to cell proliferation and cycle progression pathways. In addition to supporting the use of the hASCs secretome as a therapy for SCI, this study is the first to use sorbitol as a hyperosmolar stressor to recapitulate key aspects of SCI pathophysiology. Thereby, this model can be used as promising platform for evaluating therapeutic agents targeting neuroprotection and neuroregeneration, offering outputs related to cell death, neuronal stress and protection as well as induction of glial reactivity.

Keywords

spinal cord injury; osmotic shock; sorbitol; stem cells; MSCs; secretome; *in vitro* model

Macrophage-Derived Secretome as a Potential Therapy for Spinal Cord Injury

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Abstract

The inflammatory response after spinal cord injury (SCI) is an important contributor to secondary damage. Infiltrating macrophages can acquire a spectrum of activation states, however, the microenvironment at the SCI site favors macrophage polarization into a pro-inflammatory phe-

notype, which is one of the reasons why macrophage transplantation has failed. In this study, we investigated the therapeutic potential of the macrophage secretome for SCI recovery. We demonstrated that different macrophage phenotypes have a distinct effect on neuronal growth and survival, namely, the alternative activation with IL-10 and TGF-β1 ($M_{(IL\text{-}10+TGF\text{-}\beta1)}$) promotes significant axonal regeneration. Systemic injection of $M_{(IL\text{-}10+TGF\text{-}\beta1)}$ secretome promotes significant functional recovery after compressive SCI and leads to higher survival of spinal cord neurons. Additionally, the $M_{(IL\text{-}10+TGF\text{-}\beta1)}$ secretome supported the recovery of bladder function and decreased microglial activation, astrogliosis and fibrotic scar in the spinal cord. Animals treated with M2c secretome express higher levels of CCR2 in circulating inflammatory monocytes and we observed a reduction of CD16/32 in macrophages that infiltrate the spinal cord. Moreover, we observed an increase of CD54 in infiltrative lymphocytes and myeloid cells, and as well as in microglia after treatment. Proteomic analysis of the $M_{(IL\text{-}10+TGF\text{-}\beta1)}$-derived secretome identified clusters of proteins involved in axon extension, dendritic spine maintenance, cell polarity establishment, and regulation of astrocytic activation.

Keywords

macrophage secretome; neuroregeneration; functional recovery

Integrin Mediated Gene Therapy for Sensory and Bladder Function Restoration After Thoracic Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) leads to the formation of a complex scar characterized by the upregulation of inhibitory extracellular matrix (ECM) molecules such as laminins, tenascin-C, and osteopontin. Adult mammalian sensory axons exhibit limited regenerative capacity, partly due to insufficient expression of adhesion molecules necessary for interaction with these ECM components. Integrin α9, expressed only during early stages of central nervous system (CNS) development, pairs with endogenous β1 to form the $\alpha9\beta1$ receptor. This receptor is activated by kindlin-1, enabling adhesion and axon growth through the inhibitory environment. The aim of our project was to promote sensory axon regeneration across dorsal column tract lesions by expressing activated integrin α9 in sensory neurons using an AAV1 viral vector. Animals showed significant improvement in behavioral tests assessing sensory function (Von Frey test, tape removal test, and the Hargreaves test for thermal sensation) compared to controls. These positive behavioral outcomes were further confirmed by c-Fos staining following electrical nerve stimulation. Axons positive for integrin α9 and kindlin-1 successfully regenerated beyond the lesion site and reached the medulla oblongata. The current phase of the project focuses on applying activated integrin α9 gene therapy to restore bladder function. The experimental design involves incomplete Th8 spinal cord transection combined with L6 and S1 dorsal root ganglion (DRG) injections. Animals will undergo behavioral testing over 12 weeks, including voiding spot assays, the Von Frey test, and an adapted tape removal test to assess perineal sensation. Bladder condition will be monitored through ultrasound imaging. Regeneration of axons will be confirmed with immunohistochemical staining.

Keywords

SCI; sensory regeneration; gene therapy; bladder function restoration

Early Genetic Drivers of Nerve Regeneration: Insights from Peripheral and Central Injury Models

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Abstract

Spinal cord injury (SCI) remains a devastating condition with no effective treatment options, primarily due to the limited regenerative capacity of neurons in the central nervous system. In contrast, peripheral nerve injury (PNI) can elicit a regenerative response, making it a valuable model for identifying molecular drivers of successful repair. To investigate the early genetic programs that differentiate regenerative from non-regenerative responses, we analysed the transcriptomic profiles of rat motor and sensory neurons 24 h following SCI and PNI. Neurons were collected 24 hours after injury using laser capture microdissection, and RNA sequencing was performed to assess gene expression changes. Differential expression analysis uncovered distinct transcriptional signatures between the two injury paradigms and neuron types. Regenerating neurons (PNI model) shown broader and more dynamic gene regulation. Over 100 genes were found to be specifically regulated in the regenerative setting, pointing to their potential roles as early regeneration-associated genes (RAGs).

These candidates include genes involved in neural development, signaling, and axon growth, along with several novel genes not previously associated with regeneration. One of the strategies used to prioritize genes with therapeutic relevance, involved a functional screen of a subset of genes using a differentiating sensory neuron cell line. Various genes were demonstrated to be essential for promoting neurite outgrowth. Our findings start to underscore key molecular differences in the injury response between peripheral and central neurons, and start highlighting promising genetic targets for enhancing regeneration in SCI. Ongoing studies are focused not only on validating these and other candidates, but also in studying the pathways these genes are involved in.

Keywords

spinal cord injury; peripheral nerve injury; gene therapy; neuro-regeneration; regeneration-associated genes

Synthesis and Pharmacodynamic Profiling of a Novel Regenerative Drug Delivery Platform

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Abstract

Spinal cord injury (SCI) is a debilitating neurological disorder, characterised by irreversible functional loss, largely due to the failure of axonal regeneration and the inhibitory environment created by the glial scar. Current treatments are limited and do not effectively promote neural regeneration or functional recovery. This study aimed to develop an implantable controlled drug-release biomaterial to enhance targeted axonal regeneration and modulate the injury microenvironment, including glial scar formation, at the site of injury. Two natural polymers were selected for material matrix due their biocompatibility, biodegradability, and non-toxicity. Zinc oxide nanoparticles were included to leverage their anti-inflammatory and antioxidant effects, while a pro-regenerative drug was nanoencapsulated and embedded into the biomaterial to promote axonal growth and functional recovery. Comprehensive characterization of the biomaterials demonstrated adequate mechanical strength and biocompatibility, and *in vitro* assays confirmed biocompatibility. Although zinc oxide nanoparticles exhibited selective cytotoxicity, drug encapsulated nanoparticles showed promising effects in injury models, enhancing neurite outgrowth, reducing lesion size, and upregulating pro-regenerative protein expression. These findings highlight their potential utility within the drug delivery system. Overall, this work presents a novel drug delivery platform that synergistically combines biomaterial properties and pharmacological agents to enhance regenerative outcomes after SCI. The approach holds promise for advancing therapeutic strategies aimed at restoring function in this challenging neurological disorder.

Keywords

regeneration; drug delivery; biomaterial

Enhanced Quality of Life for Spinal Cord Injured Patients Treated With MOWOOT Device to Manage and Regularize Their Bowel Movements. A Case Series

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Abstract

Intermittent Colonic Exoperistalsis (ICE), delivered via the MOWOOT medical device, is a non-invasive, non-drug therapy for constipation. Spinal cord injury (SCI) patients require strict bowel management. This case series evaluates outcomes from 10 SCI patients treated in three German centers using ICE either long-term or during a transition phase until discharge under laxatives, enemas, or suppositories (LES), and controlled diet. Quantitative and qualitative data was extracted and compared pre- and post-treatment. All patients had paraplegia or tetraplegia with severe constipation, requiring high doses of laxatives, and reporting frequent incontinence episodes and long evacuation times, all impacting their quality of life. Five used MOWOOT long-term (1.16 to 3.75 years), and five during a transition phase (1.5 to 2.2 months). Long-term users increased bowel movements/week (BM/w) from 3.53 (2.58) to 4.78 (2.57) and reduced LES combined intakes/day from 6.18 (2.80) to 1.03 (0.42) ($p = 0.0095$). Transition users improved BM/w from 2.63 (1.24) to 7.00 (0.00) and reduced LES/d from 5.30 (2.28) to 2.90 (2.56). Overall, BM/w increased by 2.29 from to 3.23 (2.13) to 5.73 (2.17) ($p = 0.0465$), while reducing LES/d by 3.77 from 5.74 (2.45) to 1.97 (1.99) ($p = 0.0026$). Evacuation time (reported in 3 patients) dropped by 65 minutes. All patients reported fewer incontinence episodes and improved quality of life ("Days when I am continent"; "No fear that something will go wrong"; "No comparison to before"). ICE therapy with MOWOOT significantly improved bowel regularity and reduced reliance on laxatives in SCI patients. Both short- and long-term use enhanced quality of life, offering a valuable nonpharmacological option for bowel management.

Keywords

constipation; intermittent colonic exoperistalsis; spinal cord injury

Exploring TRPV4 as a Molecular Mechanism Driving Inflammatory Cells' Infiltration Into the Spinal Cord After Injury

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Abstract

Spinal cord injury (SCI) ignites excessive inflammation through pro-inflammatory microglia and infiltrative peripheral inflammatory cells. While regulated inflammation supports recovery, excessive response worsens damage. Our lab has previously demonstrated that the spleen, via sympathetic signals, promotes infiltration of myeloid cells into the spinal cord after SCI. However, the recruitment mechanism remains unclear. RNAseq data indicate that SCI-associated sympathetic signals up-regulate genes in splenic myeloid cells enriched for ion channel pathways, with Transient Receptor Potential Cation Channel Subfamily V member 4 (TRPV4) showing the highest expression. This project aims to assess the TRPV4's role in immune cell infiltration following SCI. First, we assessed whether norepinephrine (NE) induces TRPV4 expression on splenocytes. For that, total splenocytes were stimulated *in vitro* with increasing NE concentrations, and TRPV4 expression analysed by flow cytometry. In parallel, TRPV4 expression and immune cell infiltration were evaluated *in vivo*, by analysing the spleen and the spinal cord at 3, 6 and 24 h post-injury using flow cytometry. NE stimulation increased TRPV4 expression on pro-inflammatory monocytes and neutrophils at 9 h poststimulation with 10-9 M NE, whereas a lower concentration (10–12 M) selectively increased TRPV4 expression on neutrophils. *In vivo*, SCI animals exhibited an expected higher number of infiltrating myeloid cells - specifically pro-inflammatory monocytes, LY6Glow and $Ly6G^{+}$ neutrophils - at the lesion site at 6 and 24 h post-injury compared to laminectomy (LAM) controls. Pharmacological modulation of TRPV4 altered this response, specifically, TRPV4 antagonism significantly reduced myeloid infiltration Together, these results suggest that TRPV4 contributes to early mobilization and recruitment of myeloid cells towards the lesion site after SCI.

Keywords

spinal cord injury; immune system; spleen; sympathetic signals; TRPV4

Unraveling the Role of Pericytic IDOL in Lipid Dysfunction After Spinal Cord Injury

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Abstract

Besides motor and sensory deficits, spinal cord injury (SCI) induces severe metabolic dysregulation, contributing to systemic complications including insulin resistance, dyslipidemia and cardiovascular diseases. Disruption of cholesterol homeostasis appears to be a major driver of this dysfunction, as shown by elevated low-density lipoprotein (LDL) cholesterol in patients. After SCI, pericyte dysfunction contributes to blood-spinal cord barrier (BSCB) breakdown, neuroinflammation and fibrosis, all of which exacerbate metabolic disturbances. However, the role of vascular-associated pericytes in SCI-induced metabolic dysfunction remains poorly understood. Our lab has identified the Inducible Degrader of the LDL Receptor (IDOL/MYLIP), a key cholesterol metabolism regulator, as a new injury-induced vascular player. Our data demonstrated that IDOL expression is pericyte-specific at 7 days post-injury, with notable enrichment in the caudal region of the lesion. IDOL promotes degradation of the LDL receptor, thereby reducing cholesterol uptake, which may contribute to both vascular dysfunction and systemic metabolic impairment. Nevertheless, the role of IDOL in pericytes and SCI remains unexplored. We hypothesize that SCI-induced IDOL overexpression in pericytes leads to metabolic dysfunction, positioning pericytes as key metabolic regulators in the neurovascular response to injury. Preliminary data show a dysregulation of the cholesterol homeostasis pathway, notably marked by reduced LDL receptor levels after SCI. In ongoing studies, we are investigating the therapeutic potential of targeting IDOL using antisense oligonucleotide (ASOs) and dissecting the molecular signature of IDOL+ pericytes in the context of injury.

Keywords

pericytes; IDOL; cholesterol; BSCB

iPSC-Derived Mesenchymal Stem Cells and Their Secretome: Effects on Neurovascular and Cellular Responses

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Abstract

Spinal cord injury (SCI) is a devastating condition that disrupts the communication between brain and body. Its complex interconnected mechanisms demand a combinatorial therapeutic approach for a higher chance of success, with a strong window of opportunity in the acute phase. Mesenchymal stem cells (MSCs) and their secretome have independently shown beneficial effects in SCI, due to their immunomodulatory, angiogenic and neuroregenerative/protective activity. Furthermore, MSCs derived from induced pluripotent stem cells (iMSCs) present a similar secretory profile with a rejuvenated phenotype, while being obtained from a less invasive, more clinically translatable source. However, functional validation of iMSCs and their interaction with neural cells remains limited. This project aims to understand how iMSCs and their secretome modulate neural cells. Using a vascular morphogenesis assay and an *in vitro* hyperosmotic stress model of SCI, the effect of secretome on spinal cord cells viability, morphology and phenotype was evaluated. Additionally, the combination of iMSCs and their secretome was studied in an acute SCI mouse model. Given the critical role of vascular function in tissue regeneration and homeostasis, a focused analysis on the neurovascular unit was performed. Immunofluorescence staining was employed to evaluate glial and immune responses, barrier phenotype, vessel maturation, cell proliferation and neurovascular integrity. Although iMSCs treatment produced overall positive effects, further studies are required to achieve full functional recovery and elucidate underlying mechanisms behind the treatment positive effects. This work provides a comprehensive characterization of iMSCs effects across different paradigms, while highlighting cytoarchitectural alterations following SCI.

Keywords

mesenchymal stem cells; secretome; neurovascular unit

Compound Library Screening for Neural Repair: Finding New Drugs for Old Problems

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Abstract

Traumatic central nervous system (CNS) injuries lead to severe and irreversible physical, cognitive, and psychological impairments. Despite ongoing research, no effective therapeutic strategies have been developed to address the complex pathophysiological and inhibitory microenvironments that restrain neuroplasticity and tissue repair. In this study, we aimed to explore novel therapeutic approaches by screening a recently synthesized compound library for its neural repair capabilities. This library was screened in cortex and spinal cord cell cultures derived from rats, employing the MTS assay to identify compound-induced metabolic alterations. This initial screening led to the identification of seven promising compounds (ST1059, ST1055, ST673, ST656, ST149, ST666, and ST18). Further characterization revealed that three of these compounds promoted enhanced oligodendrocyte branching, suggesting possible potentiation of remyelination. Additionally, three compounds were able to induce significant increases in microglia area which can indicate possible immune activation. Molecular analysis of our cultures did not reveal significant changes in the mRNA expression levels of genes associated with oligodendrocyte maturation, though there was a trend towards increased expression of oligodendrocyte progenitor markers. Analysis of the Rho/ROCK signaling pathway, known to play an important role in CNS injury and repair, did not show alterations in RhoA mRNA expression, however, one compound significantly upregulated ROCK1 mRNA expression. In summary, this study identified three compounds that promote oligodendrocyte branching, which may enhance myelination and provide structural and functional support to neurons. These findings suggest that these compounds may possess neuroregenerative properties, however more studies are needed to understand their real therapeutic value.

Keywords

drug screening; molecular therapy; neurotrauma; spinal cord injury; traumatic brain injury

Postganglionic Neurons Remodelling in the Spleen After SCI as a Target for Immunomodulation

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Abstract

Despite spinal cord injuries frequently manifesting complications in immune system activity, the underlying mechanisms remain poorly understood. Autonomic circuits that culminate in the innervation of lymphoid organs play a pivotal role in immune response regulation. Spinal cord injuries directly impact the central component of these circuits, leading to disrupted neuronal communication between the peripheral nervous system (specifically postganglionic neurons) and lymphoid organs. In this study, our objective is to elucidate the indirect effects of spinal cord injuries on the peripheral segment of the autonomic circuit to the spleen, with a particular focus on postganglionic neurons. To explore potential neuroplasticity modulation in these neurons, we performed a comprehensive histological investigation of the celiac ganglia, housing the cell bodies of peripheral autonomic neurons, along with the fibers innervating the spleen. Additionally, we quantified the expression levels of genes associated with axonal growth and repulsion. In parallel, we are currently optimizing viral-tracing approaches to establish a chemogenetic model for selective manipulation of spleen-innervating neurons, which will enable causal testing of their role in neuroimmune interactions. Our findings indicate that within a few hours after spinal cord injury, discernible alterations in the plasticity of postganglionic neurons innervating the spleen occur, along with changes in the expression of molecules involved in spleen plasticity modulation. Despite being preliminary, this observation of altered molecule expression associated with axonal growth/repulsion in the spleen and its link to rapid modulation of postganglionic neuron plasticity underscores the potential of these neurons as a viable therapeutic target for immunomodulation following spinal cord injuries.

Keywords

postganglionic neurons; neuroplasticity; spleen

Bioenergetic Responses of Remote Neurons to Axonal Injury: Implications for Survival and Recovery After Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) disrupts axonal integrity, triggering remote degeneration that significantly impairs functional recovery. In our study, we investigated the bioenergetic adaptations of neurons in the red nucleus (RN)—a brain region distant yet functionally connected to the injury site—and their influence on long-term outcomes post-SCI. Axonal damage induces profound alterations in neuronal energy metabolism in remote regions, including mitochondrial dysfunction and reduced ATP synthesis. These bioenergetic impairments compromise critical cellular functions such as ion homeostasis, axonal transport, and synaptic activity, which are essential for neuronal survival and regenerative potential. To investigate the mitochondrial adaptations triggered by SCI, we performed biochemical analyses of RN isolated from control and injured mice at 7- and 28 days post-injury. At 7 days post-SCI, RN neurons displayed a marked upregulation of mitochondrial biogenesis, evidenced by increased expression of PGC-1α protein. This was accompanied by enhanced activity of key electron transport chain (ETC) components—most notably Complex I and Complex IV—as well as a significant increase in overall mitochondrial mass. However, by 28 days post-injury, these mitochondrial enhancements were substantially attenuated, indicating a transient bioenergetic response to axonal damage. These findings reveal that neurons in remote regions initially mount a strong mitochondrial and metabolic response after SCI, which fades over time. These metabolic shifts underscore the dynamic mitochondrial adaptations occurring in remote axotomized neuronal populations following SCI and highlight a critical window in which mitochondrial biogenesis and function can be therapeutically enhanced to support neuronal survival and promote long-term functional recovery.

Keywords

mitochondria; remote degeneration; metabolic rewiring; axonal damage.

Lipid Priming of ASCs Secretome for Spinal Cord Injury: An Investigation of its Modulatory Roles in Microglial Pruning and Phagocytosis

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Abstract

Microglia regulate synaptic plasticity by pruning weak synapses and reinforcing appropriate ones. While essential for recovery, dysregulated activity—either excessive pruning or impaired debris clearance—can drive maladaptive plasticity. Adipose tissue-derived mesenchymal stem cells (ASCs) are valued in regenerative medicine for their secretome (SEC). To enhance neuroregulatory potential for spinal cord injury (SCI) repair, priming strategies have been developed. Our lab has shown that targeting the FFAR4 receptor in ASC primary cilia with the omega-3 fatty acid docosahexaenoic acid (DHA) yields a protein-rich secretome (ω-SEC) with protective effects in SCI models. Animals treated with ω-SEC displayed fewer activated microglia—similar to healthy controls—and reduced spasticity compared to unprimed SEC. Building on that, our goal is to investigate maladaptive plasticity after SCI in relation to microglial function, exploring DHA-primed secretome as a treatment to mitigate pathological outcomes. *In vitro* testing in mixed SCI cultures demonstrated that ω-SEC restored microglial interaction with myelin debris, while injured controls showed reduced microglial presence and debris clearance—suggesting restored microglial structural-functional coupling. *In vivo*, histological analysis revealed that perisomatic microglial process size in motor neurons positively correlated with the size of GABAergic inputs. The ω-SEC group exhibited significantly greater GABAergic input area and a trend toward larger microglial contact areas compared to the NBA-treated group, potentially counteracting spasticity by enhancing inhibitory tone. These preliminary results support ω-SEC as a potential modulator of microglia to promote adaptive plasticity after SCI and highlight the need for further investigation into their role in synaptic balance and recovery.

Keywords

spinal cord injury; microglia; plasticity

Correlates of Spinal Cord Injury-Induced Immune Dysfunction: From Preclinical Models to Human Studies

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Abstract

Traumatic spinal cord injury (SCI) is a devastating condition with complex pathophysiology. Beyond motor and sensory deficits, SCI triggers systemic immune changes ranging from subtle immune cell activation shifts to harmful pro-inflammatory responses, autoimmunity, and immunosuppression. This dysregulation increases infection risk, damages peripheral organs, and worsens secondary injury, impairing patient outcomes. While research mainly focuses on spinal inflammation, evidence indicates broader peripheral immune involvement. Our preliminary data show SCI induces progressive morphological and secretory changes in sympathetic nerve endings innervating lymphoid organs, causing immune alterations dependent on sympathetic signaling and injury severity. Within 24 hours post-injury, norepinephrine (NE) levels rise in the spleen, with concentration-dependent effects: high NE induces splenocyte apoptosis, while lower levels typical of acute SCI enhance neutrophil activation, mobilization, and trained immunity in monocytes. These shifts align with early myeloid skewing, increased inflammation, and reduced neutrophil spinal infiltration when sympathetic signaling is disrupted. Further studies are needed to clarify the timing and dynamics of innate and adaptive immune responses. This project aims to comprehensively characterize SCI-induced immune dysfunction in mouse models by analyzing lymphoid organs, immune cell populations, cytokine profiles, and function to understand post-injury responses with translational potential. Additionally, we will investigate molecular, metabolic, and epigenetic changes to identify biomarkers and develop a predictive immune dysfunction signature relevant to patients, which will be clinically validated. Ultimately, this research aims to bridge preclinical findings with patient care by creating a treatment stratification system that improves diagnosis and enables earlier interventions. These predictive markers could pave the way for innovative diagnostic and monitoring tools to assess immunodeficiency and infection susceptibility, guide treatment decisions, and refine patient management strategies to improve outcomes.

Keywords

spinal cord injury; immune dysfunction; predictive signature

Toward Integrated Rehabilitation in Lebanon: Exploring the Relationship Between Spinal Cord Injury (SCI) Complications and Quality of Life in Lebanese Individuals With SCI

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Abstract

Spinal cord injury (SCI) often leads to secondary complications such as pressure ulcers, urinary tract infections, and spasticity, which negatively affect quality of life (QoL). In Lebanon, there are no prior studies examining the prevalence or impact of these complications. Moreover, the country lacks a national framework for rehabilitation (HI, 2023). This study, part of the International Spinal Cord Injury (InSCI) survey in Lebanon, aims to fill this gap by assessing the burden of secondary complications and their association with health-related quality of life (HRQoL). Between January and June 2025, 50 Lebanese individuals with SCI were recruited from rehabilitation centers across Lebanon. Participants (mean age = 42.6 $\pm$ 14.9 years; 66.7% male) completed Arabic versions of the Secondary Complications Scale (SCS), the Self-Reported Spinal Cord Independence Measure (SCIM-SR), and the SF-36. Pearson correlations examined the relationship between secondary complications and HRQoL. Participants reported a moderate burden of complications (mean SCS = 18.9 $\pm$ 10.8). Higher SCS scores were significantly associated with lower scores in general health (r = –0.642, $p < 0.001$), emotional well-being (r = –0.509, $p = 0.004$), fatigue (r = –0.483, $p = 0.007$), pain (r = –0.436, $p = 0.016$), social functioning (r = –0.405, $p = 0.026$), and emotional role limitations (r = –0.486, $p = 0.006$). Findings confirm a high burden of secondary complications and their detrimental effect on QoL in Lebanese individuals with SCI. A comprehensive, stakeholder-driven SCI rehabilitation framework is now under development to address this national gap in Lebanon.

Keywords

spinal cord injury; secondary complications; quality of life; Lebanon

Enucleated ASCs: A Novel Delivery System for Prolonged Expression of Therapeutic Antibody/Receptors After Spinal Cord Injury

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Abstract

Traumatic spinal cord injury (SCI), often caused by falls or motor vehicle accidents, leads to irreversible sensory and/or motor impairment due to neuronal loss, demyelination, and chronic inflammation. The secondary stage of SCI involves inflammation-induced tissue degeneration, leukocyte infiltration due to increased vascular permeability, and glial scar formation at the injury site, ultimately hindering regeneration and causing permanent damage. Adipose-derived stem cells (ASCs) are promising cell-based therapy due to their immunomodulatory properties and ease of harvesting. In this study, we generated enucleated ASCs as a therapeutic delivery vehicle. Enucleated cells have 72 hours lifespan, are non-proliferative but maintain functional organelles, providing the beneficial properties of a cell and cargo-loading abilities without permanent engraftment in the host. Enucleated ASCs will be loaded with mRNA of neuro-regenerative (anti-NogoA antibody) and anti-inflammatory proteins (human soluble interleukin-1 receptor antagonist/tumor necrosis factor- α receptor 1). To date, expression of therapeutic antibodies using ASCs remains rare, highlighting the innovative nature and potential of this approach. We evaluated the survival of enucleated ASCs up to 96 hours. Moreover, transfection with mRNA of the therapeutic antibody/receptors showed expression over the course of 72 hours. The levels of proteins were compared to intact ASCs to assess the efficacy of their protein secretion. Following a moderate contusion injury at T11, rats will receive a single intrathecal injection of loaded enucleated ASCs. Motor and sensory function tests will be assessed over twelve weeks. Histological analyses of the spinal cord will be performed to assess inflammatory infiltration, and axonal regeneration.

Keywords

spinal cord injury; adipose-derived stem cells; therapeutic antibody; IL-1b; Nogo-A; TNFα

The Impact of Biological Sex on Peripheral and Local Immune Profiles After Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) is a devastating neurological condition that disrupts motor, sensory and autonomic functions, and often causes profound immune dysfunction. Following SCI, a sustained inflammatory response at the lesion site worsens tissue damage, while systemic immune alterations increase infection susceptibility or trigger harmful inflammation in unaffected organs, contributing to long-term complications. Although evidence highlights sexual dimorphism in immune and nervous system function, preclinical SCI research has historically relied on female-only rodent models, limiting translational relevance, as ~80% of human SCI cases occur in males. We investigated how biological sex influences immune responses and recovery following SCI, focusing on myeloid dynamics during acute and chronic phases. Using flow cytometry and behavioral assessments in male and female mice, we identified notable sex differences in immune progression. Males exhibited delayed myeloid cell infiltration into the injured spinal cord, whereas females displayed a more complex acute response, combining the pro-inflammatory activation profile observed in males with a reparative profile. This reparative signature disappeared chronically, leading to convergence of immune profiles. Despite these differences, which translated into slower postoperative recovery in males, no significant sex differences appeared in later motor and sensory outcomes. These findings underscore the importance of including both sexes in SCI research to capture variability in immune responses and recovery. Understanding sex-specific immune mechanisms is essential for developing more effective, personalized therapies to improve SCI outcomes.

Keywords

sex-differences; immune response; spinal cord injury

Levetiracetam Treatment Promotes Functional Recovery Following Cervical or Thoracic Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) leads to severe impairments in motor, sensory, and autonomic functions. Acute SCI is characterized by excessive glutamate release, which contributes to excitotoxicity and progressive neuronal loss. Mitigating glutamate-mediated damage holds promise as a neuroprotective strategy. This study assessed the therapeutic potential of levetiracetam (LEV)—an FDA-approved antiepileptic agent targeting synaptic vesicle protein 2A (SV2A)—to confer neuroprotection in acute SCI. We administered LEV in two well-established rodent models of SCI (cervical and thoracic). Functional recovery was evaluated through both gross and fine motor assessments. Histopathological analysis quantified lesion cavity volume and survival of neurons and oligodendrocytes. Molecular studies focused on astrocytic function and glutamate clearance. LEV treatment significantly enhanced motor performance in both SCI models. Histological evaluation revealed a marked reduction in lesion cavity size and increased survival of neurons and oligodendrocytes in LEV-treated animals. Molecular findings indicate that LEV stabilizes astrocytic function, resulting in improved extracellular glutamate uptake and diminished excitotoxic stress. This study demonstrates that LEV provides robust neuroprotection in models of acute SCI, promoting structural preservation and functional improvement. The findings underscore LEV's potential as a viable early intervention strategy in traumatic SCI. Further translational research is warranted to confirm these benefits in preclinical and clinical settings.

Keywords

levetiracetam; functional recovery; neuroprotection

Statement:

From a total of **34** accepted abstracts, **5** authors **chose to opt out of publication**; therefore, their abstracts are **not included** in these proceedings.

All submitted abstracts were reviewed by the Scientific Committee, which evaluated their scientific quality, clarity, and relevance to the scope of the meeting. Only abstracts that met the established criteria were accepted for presentation and inclusion in these proceedings.