



NEURAL REPAIR AFTER SPINAL CORD INJURY: CELLULAR MECHANISMS AND EMERGING REGENERATIVE THERAPIES

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Abstract

Spinal cord injury (SCI) initiates a biphasic process of primary mechanical damage followed by a secondary injury cascade involving ischemia, excitotoxicity, oxidative stress, and inflammation, which together determine the ultimate extent of neurological deficit. Endogenous repair is severely limited by formation of an astroglial-fibrotic scar, myelin-associated growth inhibitors, and the intrinsically weak regenerative capacity of adult central axons. Nevertheless,



surviving spinal circuits below the level of injury retain a degree of activity-dependent plasticity that can be harnessed through locomotor training, epidural electrical stimulation, and functional electrical stimulation. Biological strategies targeting the glial scar, myelin inhibitors, and cell replacement are under active investigation, while brain-computer interfaces and neuroprosthetic devices offer alternative routes to restoring function. This review summarizes the cellular and molecular basis of spinal cord injury and repair, the influence of injury level and completeness on recovery potential, and current and emerging therapeutic strategies aimed at promoting functional neurological recovery.

Keywords: Spinal cord injury, Axon regeneration, Glial scar, Chondroitin sulfate proteoglycans, Epidural stimulation, Neurorehabilitation, Neuroprosthetics.

Introduction

1. Cellular and Pathophysiological Basis of Spinal Cord Injury

Traumatic spinal cord injury produces an initial mechanical insult, typically from contusion, compression, or laceration, that directly disrupts neurons, axonal tracts, and the local vasculature (Ahuja et al., 2017). This primary injury is followed by a secondary injury cascade unfolding over minutes to weeks, characterized by hemorrhage, edema, vascular disruption and ischemia, glutamate-mediated excitotoxicity, calcium influx, free-radical generation, and lipid peroxidation (Oyinbo, 2011). These processes drive both apoptotic and necrotic cell death of neurons and oligodendrocytes well beyond the boundaries of the original lesion, progressively expanding the area of tissue damage. Within days, a cystic cavity typically forms at the injury epicenter, surrounded by a rim of spared but functionally altered white and gray matter. Clinical severity and recovery potential are assessed using the American Spinal Injury Association (ASIA) Impairment Scale, which classifies injuries by neurological level and completeness based on preserved motor and sensory function (Kirshblum et al., 2011). Because axons within the adult central nervous system possess a markedly reduced intrinsic capacity for long-distance regeneration compared with the peripheral nervous system, functional recovery after SCI depends heavily on the



survival and reorganization of spared tissue rather than on regrowth of severed tracts.

2. Molecular and Glial Mechanisms Limiting Axon Regeneration

Failure of axon regeneration after SCI results from both an inhibitory extracellular environment and limited intrinsic neuronal growth capacity. Within days of injury, reactive astrocytes proliferate and upregulate intermediate filament proteins, forming a glial scar that seals the lesion and limits the spread of inflammation but also presents a substantial physical and chemical barrier to regenerating axons (Silver & Miller, 2004). The extracellular matrix within and around the scar becomes enriched in chondroitin sulfate proteoglycans (CSPGs), which bind receptors on the axonal growth cone and activate RhoA/ROCK signaling, collapsing the cytoskeleton and arresting axon extension (Silver & Miller, 2004). Enzymatic digestion of CSPGs using chondroitinase ABC has been shown to promote axonal sprouting and improve functional recovery in experimental models of SCI, establishing the glial scar matrix as a viable therapeutic target (Bradbury et al., 2002). In parallel, myelin debris persisting after oligodendrocyte death releases growth-inhibitory proteins, including Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte-myelin glycoprotein (OMgp), which signal through the Nogo receptor (NgR1) complex to further restrict axonal outgrowth (GrandPre et al., 2000). Microglia and infiltrating macrophages contribute a context-dependent inflammatory response that can both exacerbate secondary injury and support debris clearance and tissue remodeling. Oligodendrocyte precursor cells proliferate after injury and can differentiate into remyelinating oligodendrocytes, although demyelination of spared axons remains a persistent contributor to conduction failure and functional impairment (Ahuja et al., 2017).

3. Influence of Injury Level and Completeness on Recovery Potential

The clinical presentation and recovery potential of SCI vary substantially according to the anatomical level and completeness of the lesion. Cervical injuries affect both upper and lower limb function and may compromise respiratory musculature when high cervical segments are involved, whereas



thoracic and lumbar injuries more selectively affect trunk and lower-limb function while sparing upper-extremity independence. Motor-complete injuries, defined by the absence of any voluntary motor function below the neurological level, were historically considered to have negligible potential for further recovery. However, studies using epidural electrical stimulation of the lumbosacral spinal cord have demonstrated that some individuals with chronic, clinically motor-complete SCI retain previously undetected spared descending connections capable of being reactivated to support voluntary movement, standing, and stepping (Harkema et al., 2011; Angeli et al., 2018). This finding indicates that clinical completeness assessed by standard examination does not necessarily reflect true anatomical discontinuity of all descending pathways. Incomplete injuries, in which some motor or sensory function is preserved below the level of injury, generally carry a substantially better prognosis, as spared white-matter pathways can be recruited and strengthened through activity-dependent plasticity of spinal interneuronal circuits located caudal to the lesion (van den Brand et al., 2012).

4. Therapeutic Strategies to Promote Recovery

Acute management of SCI focuses on limiting secondary injury and preserving spared tissue. Early surgical decompression of the injured spinal cord has been associated with improved neurological outcomes compared with delayed decompression in cervical SCI (Fehlings et al., 2012), while pharmacological neuroprotection with high-dose methylprednisolone, once widely used following the NASCIS trials, has become controversial due to an unfavorable risk-benefit profile and is no longer routinely recommended in most current guidelines. Rehabilitative strategies aim to harness activity-dependent plasticity of spared spinal circuits. Task-specific locomotor training, including body-weight-supported treadmill training, promotes recovery of stepping patterns by reinforcing use-dependent reorganization of spinal interneuronal networks. Epidural and transcutaneous electrical spinal cord stimulation can increase the excitability of lumbosacral circuits sufficiently to enable voluntary movement, standing, and, in some cases, assisted overground walking when combined with intensive training (Courtine et al., 2009; Angeli et al., 2018). Functional electrical



stimulation (FES) can directly activate paralyzed musculature to support standing, stepping, or upper-limb function, and can be integrated with robotic exoskeletons to increase training dose and consistency. Neuroprosthetic systems based on implanted brain-computer interfaces have enabled individuals with tetraplegia to control robotic arms for reaching and grasping tasks, offering an alternative pathway to functional independence that bypasses the injured spinal pathway entirely (Ajiboye et al., 2017). Biological approaches remain largely investigational: chondroitinase ABC and anti-Nogo-A strategies aim to reduce inhibition of axonal growth, while neural stem cell and mesenchymal stem cell transplantation have been evaluated in early-phase clinical trials, with proposed mechanisms including trophic support, modulation of the local inflammatory environment, and, more speculatively, remyelination or circuit reconstruction (Curtis et al., 2018).

5. Prognostication, Personalization, and Future Directions

Substantial heterogeneity in recovery after SCI, driven by variability in lesion level, completeness, age, and comorbidities, complicates individual prognostication and trial design. Standardized outcome measures, including the ASIA Impairment Scale and quantitative motor and sensory scoring, provide a common framework for classifying injury severity and tracking recovery over time (Kirshblum et al., 2011). Advanced neuroimaging, including diffusion tensor imaging of residual white-matter tracts, and neurophysiological measures such as motor and somatosensory evoked potentials, are increasingly used to characterize the extent of spared tissue and may improve prediction of responsiveness to activity-based therapies. Combining these measures with electrical stimulation parameters, training intensity, and clinical data through machine-learning approaches may eventually allow rehabilitation strategies to be matched to an individual's specific pattern of spared spinal circuitry. Key challenges for the field include the limited ability of animal models to fully capture the heterogeneity and chronicity of human SCI, the difficulty of directly measuring regenerative and plastic processes in living human tissue, and the need for combinatorial strategies that simultaneously address the inhibitory extracellular environment, insufficient intrinsic axon growth capacity, and the



training required to convert new or reactivated connections into functionally useful behavior.

Conclusion

Recovery after spinal cord injury depends on a complex interaction between the extent of primary and secondary tissue damage, the inhibitory glial and molecular environment that restricts axon regeneration, and the capacity of spared spinal circuits to undergo activity-dependent reorganization. Epidural stimulation studies have shown that even clinically motor-complete injuries may retain functionally significant spared connections, challenging traditional assumptions about the limits of recovery. Rehabilitation strategies that combine intensive, task-specific training with electrical stimulation, robotics, and neuroprosthetic devices are expanding the range of achievable functional outcomes, while biological therapies targeting the glial scar, myelin inhibitors, and cell replacement continue to be refined in early clinical investigation. As with other forms of central nervous system injury, the central challenge is not merely to promote plasticity or regeneration, but to direct these processes, through precisely timed and individualized rehabilitation, toward functionally meaningful and durable neurological recovery.

References

1. Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M. R. N., Druschel, C., Curt, A., & Fehlings, M. G. (2017). Traumatic spinal cord injury. *Nature Reviews Disease Primers*, 3, 17018.
2. Ajiboye, A. B., Willett, F. R., Young, D. R., Memberg, W. D., Murphy, B. A., Miller, J. P., et al. (2017). Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia. *The Lancet*, 389(10081), 1821–1830.
3. Angeli, C. A., Boakye, M., Morton, R. A., Vogt, J., Benton, K., Chen, Y., et al. (2018). Recovery of over-ground walking after chronic motor complete spinal cord injury. *New England Journal of Medicine*, 379(13), 1244–1250.



4. Bradbury, E. J., Moon, L. D., Popat, R. J., King, V. R., Bennett, G. S., Patel, P. N., et al. (2002). Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature*, 416(6881), 636–640.
5. Courtine, G., Gerasimenko, Y., van den Brand, R., Yew, A., Musienko, P., Zhong, H., et al. (2009). Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nature Neuroscience*, 12(10), 1333–1342.
6. Curtis, E., Martin, J. R., Gabel, B., Sidhu, N., Rzesiewicz, T. K., Mandeville, R., et al. (2018). A first-in-human, phase I study of neural stem cell transplantation for chronic spinal cord injury. *Cell Stem Cell*, 22(6), 941–950.
7. Fehlings, M. G., Vaccaro, A., Wilson, J. R., Singh, A., Cadotte, D. W., Harrop, J. S., et al. (2012). Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *PLoS ONE*, 7(2), e32037.
8. GrandPre, T., Nakamura, F., Vartanian, T., & Strittmatter, S. M. (2000). Identification of the Nogo inhibitor of axon regeneration as a Reticulon protein. *Nature*, 403(6768), 439–444.
9. Harkema, S., Gerasimenko, Y., Hodes, J., Burdick, J., Angeli, C., Chen, Y., et al. (2011). Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *The Lancet*, 377(9781), 1938–1947.
10. Kirshblum, S. C., Burns, S. P., Biering-Sorensen, F., Donovan, W., Graves, D. E., Jha, A., et al. (2011). International standards for neurological classification of spinal cord injury (revised 2011). *Journal of Spinal Cord Medicine*, 34(6), 535–546.
11. Oyinbo, C. A. (2011). Secondary injury mechanisms in traumatic spinal cord injury: a nugget of this multiply cascade. *Acta Neurobiologiae Experimentalis*, 71(2), 281–299.
12. Silver, J., & Miller, J. H. (2004). Regeneration beyond the glial scar. *Nature Reviews Neuroscience*, 5(2), 146–156.
13. van den Brand, R., Heutschi, J., Barraud, Q., DiGiovanna, J., Bartholdi, K., Huerlimann, M., et al. (2012). Restoring voluntary control of locomotion after paralyzing spinal cord injury. *Science*, 336(6085), 1182–1185.