# Complete Spinal Cord Injury

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Complete spinal cord injury (SCI) leads to permanent motor, sensitive and sensory deficits. In humans, there is currently no therapy to promote recovery and the only available treatments include surgical intervention to prevent further damage and symptomatic relief of pain and infections in the acute and chronic phases, respectively. Basically, the spinal cord is classically viewed as a nonregenerative tissue with limited plasticity. Thereby the establishment of the “glial” scar which appears within the SCI is mainly described as a hermetic barrier for axon regeneration. However, recent discoveries have shed new light on the intrinsic functional plasticity and endogenous recovery potential of the spinal cord.

Keywords: spinal cord injury ; plasticity ; stem cells ; transplantation ; repair ; rehabilitation ; glial scar

## 1. Introduction

In order to study SCI, several lesion paradigms and different animal species have been proposed, used and described. In fact, experimental SCI models can be classified, firstly, according to their severity, such as mild or severe, secondly, according to the type of injury: contusion or transection and, thirdly, according to anatomical considerations, such as complete or incomplete. These classifications are of primary importance since the type of injury will influence the secondary event cascades. Indeed, several studies have described that axonal regrowth can occur after SCI in the case of incomplete injury such as hemisection [1]. Maier et al., in 2008, have shown in an elegant study that after a unilateral corticospinal tract (CST) injury, constraint-induced movement therapy enhances axonal regrowth. Using anterograde tracing, this study demonstrated that CST fibers can cross the midline and grow toward the contralateral denervated gray matter, inducing functional recovery [2].

The peripheral nervous system (PNS) is well known for its intrinsic regrowth capabilities. In fact, peripheral nerve (PN) injury induces degeneration of the distal part of the PN, called Wallerian degeneration, dedifferentiation of the Schwann cells present in the distal stump and axonal regrowth from the axonal growth cone present in the proximal stump of the injured nerve [3]. Researchers took advantage of these properties and propose to use them as therapy. Peripheral nerve graft (PNG) bridging model-based studies have shown elegantly that axons can regrow in an injury context. In effect, in 2002, Gauthier et al. used, for the first time, this paradigm in a cervical hemisection model [4]. They described that a peripheral nerve can be used as a graft to bridge the two stumps of a lesioned spinal cord, the spared axons which are present above the lesion grow into the graft and restore the breathing function by the denervated hemidiaphragm [4][5]. Interestingly, Alilain et al., using the same model in 2011, have shown that restored breathing function is abolished after transection of the PNG, underlining the main importance of the axonal regrowth in breathing recovery [5].

Another experimental model based on the link between the PNS and the central nervous system is the conditioning lesion paradigm. This model was described several decades ago [6], in this model a crush lesion of a PN (conditioning lesion) before SCI induces axonal regrowth into the lesioned spinal cord. This effect can also be found after the administration of chemical demyelinating agents into the PN [7]. Even if the precise cellular and molecular mechanisms which enhance axonal regrowth are not well known, this model reflects the plasticity which can take place in the injured spinal cord.

Interestingly, recently, a new conditioning model has been described. Indeed, intermittent hypoxia preconditioning has been described as a model which enhances axonal plasticity of the injured spinal cord [8].

## 2. Plasticity of the Injured Spinal Cord

The spinal cord, and in particular the injured spinal cord, possesses an underestimated and underexploited plasticity. The increasing knowledge regarding the microenvironment after SCI could in the near future bring new potential therapies. Several limitations still need to be overcome. Indeed, most of the studies which try to evaluate axonal regrowth after SCI and/or treatment are often blind about the nature, the origin and the targets of the regrowing fibers. Moreover, to date, after SCI, no treatment can induce axonal regrowth of selective fibers. Thus, several studies have reported that axonal

regrowth can be correlated to allodynia or neuropathic pain [9]. In order to know and understand not only the targets of the regrowing fibers it will be important also to stress the functionality and, in particular, the relevance of these fibers during locomotion. This question could be addressed with gain and loss of function approaches using optogenetic or chemogenetic tools [10][11].

Another very important question which needs to be investigated is the precise role played by the different populations and subpopulations of cells in the establishment of the inhibitory microenvironment at the lesion site. Indeed, the main events and the overall implicated cells are known, however, the precise role played by astrocytes, ependymal cells, microglia, macrophages, pericytes, e.g., subpopulations, are not clearly known. Moreover, the lesioned spinal cord microenvironment evolves over time after SCI, it could be very important to investigate the evolution of the different cellular populations at acute and chronic phases which could be achieved by spatial mapping using single cell/single nucleus sequencing experiments [12].

An associated question is also the role of the cells implicated in the lesion scar during aging. In fact, SCI nowadays in occidental countries, concerns not only teenagers and young adults but also the elderly [13]. Few studies have inquired about the effects of SCI during aging. What is already known is that the spinal cord stem cell potential decreases over time [14]. The investigation about the other cell types is of primary importance to propose personalized treatment according to the age of the injured patient.

Finally, it is important to put into a clinical perspective all these recent discoveries and knowledge which have been mainly reported in rodents. Indeed, there are several differences between humans and rodents regarding SCI. First, in humans, SCIs are mainly due to falls or traffic accidents, meaning that injuries are mainly contusive or compressive [13]. Moreover, in humans, between half to two thirds of the SCIs are incomplete and more than half of them happen at cervical level [1]. In the preclinical model, SCIs are rarely performed at cervical level due to possible respiratory complications, most of the experimental SCIs are performed at thoracic level and mostly by transection [15]. Another difference is also the location and the relative importance of the different anatomical tracts [16]. Indeed, the descending neuronal tracts are not positioned in the same parts of the spinal cord and the CST is more developed in humans than in rodents [16]. These differences between humans and rodents are particularly important. In effect, as discussed above, the intrinsic regrowth capacities of CST are limited, however, on the other hand, the rerouting of the axonal tracts or even axonal regrowth has been described after incomplete SCI. Thereby, modulating the descending and ascending tracts after incomplete SCI in humans could lead to functional recovery. Epidural electrical stimulation (EES) has been already investigated in humans in order to initiate locomotion in injured patients [17]. This treatment has shown promising results. However, this technique is invasive and it has been reported that EES can lose its effect over time, due to the encapsulation of the electrodes by fibrous tissue [18].

The comparison of the cellular events and the establishment of the spinal scar, which takes place after SCI, should also be compared between humans and rodents. As described above, in mice the spinal scar is composed of a fibrotic component and presents no cystic cavity even several months after SCI. Whereas in rats, the first weeks after SCI the spinal scar is composed of a fibrotic component in the transection model and also in contusive SCI. However, several months after SCI the fibrotic component of the scar decreases and the spinal cord presents cystic cavities in both penetrating and contusive injuries [19]. These differences are of primary importance because they illustrate the heterogeneity of the cells which compose the scars between species. The knowledge regarding the cellular heterogeneity of the lesioned spine is not well characterized in humans. For example, the reactivity of ependymal cells after SCI in humans is still under debate. Indeed, Garcia-Ovejero et al. have demonstrated using MRI, immunohistology and gene expression profiling, that the central canal is virtually absent and is mainly constituted by perivascular pseudorosettes in humans [20]. Whereas, in contrast, Ghazale et al. have demonstrated, also using immunohistology and gene expression profiling, that the central canal region in humans expresses stem cell markers [21]. Further investigations will be needed to clarify the precise structure of the central canal and the precise role which can be played by ependymal cells after SCI in humans. These questions regarding the stem cell potential of the ependymal cells in humans might be broadened to the different cells which compose the scar after SCI. We can hope that the human atlas project will unveil even partially the cellular heterogeneity of the spinal cord in physiological and in injury contexts and will provide new insights for future research [22][23].

## References

1. Courtine, G.; Sofroniew, M.V. Spinal cord repair: Advances in biology and technology. Nat. Med. 2019, 25, 898–908.

2. Maier, I.C.; Baumann, K.; Thallmair, M.; Weinmann, O.; Scholl, J.; Schwab, M.E. Constraint-induced movement therapy in the adult rat after unilateral corticospinal tract injury. J. Neurosci. 2008, 28, 9386–9403.
3. Allodi, I.; Udina, E.; Navarro, X. Specificity of peripheral nerve regeneration: Interactions at the axon level. Prog. Neurobiol. 2012, 98, 16–37.
4. Gauthier, P.; Réga, P.; Lammari-Barreault, N.; Polentes, J. Functional reconnections established by central respiratory neurons regenerating axons into a nerve graft bridging the respiratory centers to the cervical spinal cord. J. Neurosci. Res. 2002, 70, 65–81.
5. Alilain, W.J.; Horn, K.P.; Hu, H.; Dick, T.E.; Silver, J. Functional regeneration of respiratory pathways after spinal cord injury. Nature 2011, 475, 196–200.
6. McQuarrie, I.G.; Grafstein, B. Axon outgrowth enhanced by a previous nerve injury. Arch. Neurol. 1973, 29, 53–55.
7. Hollis, E.R., II; Ishiko, N.; Tolentino, K.; Doherty, E.; Rodriguez, M.J.; Calcutt, N.A.; Zou, Y. A novel and robust conditioning lesion induced by ethidium bromide. Exp. Neurol. 2015, 265, 30–39.
8. Gonzalez-Rothi, E.J.; Tadjalli, A.; Allen, L.L.; Ciesla, M.C.; El Chami, M.; Mitchell, G.S. Protocol-Specific Effects of Intermittent Hypoxia Pre-Conditioning on Phrenic Motor Plasticity in Rats with Chronic Cervical Spinal Cord Injury. J. Neurotrauma 2021, 38, 1292–1305.
9. Nakhjavan-Shahraki, B.; Yousefifard, M.; Rahimi-Movaghar, V.; Baikpour, M.; Nasirinezhad, F.; Safari, S.; Yaseri, M.; Jafari, A.M.; Ghelichkhani, P.; Tafakhori, A.; et al. Transplantation of olfactory ensheathing cells on functional recovery and neuropathic pain after spinal cord injury; systematic review and meta-analysis. Sci. Rep. 2018, 8, 325.
10. Usseglio, G.; Gatier, E.; Heuzé, A.; Hérent, C.; Bouvier, J. Control of Orienting Movements and Locomotion by Projection-Defined Subsets of Brainstem V2a Neurons. Curr. Biol. 2020, 30, 4665–4681.e6.
11. Gao, Z.; Yang, Y.; Feng, Z.; Li, X.; Min, C.; Zhu, Z.; Song, H.; Hu, Y.; Wang, Y.; He, X. Chemogenetic stimulation of proprioceptors remodels lumbar interneuron excitability and promotes motor recovery after SCI. Mol. Ther. 2021.
12. Dani, N.; Herbst, R.H.; McCabe, C.; Green, G.S.; Kaiser, K.; Head, J.P.; Cui, J.; Shipley, F.B.; Jang, A.; Dionne, D.; et al. A cellular and spatial map of the choroid plexus across brain ventricles and ages. Cell 2021, 184, 3056–3074.e21.
13. Algahtany, M.; McFaull, S.; Chen, L.; Zhang, S.; Saarela, O.; Alqahtani, F.; Cusimano, M.D. The Changing Etiology and Epidemiology of Traumatic Spinal Injury: A Population-Based Study. World Neurosurg. 2021, 149, e116–e127.
14. Li, X.; Floriddia, E.M.; Toskas, K.; Fernandes, K.J.L.; Guérout, N.; Barnabé-Heider, F. Regenerative Potential of Ependymal Cells for Spinal Cord Injuries over Time. EBioMedicine 2016, 13, 55–65.
15. Watzlawick, R.; Rind, J.; Sena, E.S.; Brommer, B.; Zhang, T.; Kopp, M.A.; Dirnagl, U.; MacLeod, M.R.; Howells, D.W.; Schwab, J.M. Olfactory Ensheathing Cell Transplantation in Experimental Spinal Cord Injury: Effect size and Reporting Bias of 62 Experimental Treatments: A Systematic Review and Meta-Analysis. PLoS Biol. 2016, 14, e1002468.
16. Kjell, J.; Olson, L. Rat models of spinal cord injury: From pathology to potential therapies. Dis. Model. Mech. 2016, 9, 1125–1137.
17. Harkema, S.; Gerasimenko, Y.; Hodes, J.; Burdick, J.; Angeli, C.; Chen, Y.; Ferreira, C.; Willhite, A.; Rejc, E.; Grossman, R.G.; et al. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: A case study. Lancet 2011, 377, 1938–1947.
18. Taccola, G.; Barber, S.; Horner, P.J.; Bazo, H.A.C.; Sayenko, D. Complications of epidural spinal stimulation: Lessons from the past and alternatives for the future. Spinal Cord 2020, 58, 1049–1059.
19. Chedly, J.; Soares, S.; Montembault, A.; von Boxberg, Y.; Veron-Ravaille, M.; Mouffle, C.; Benassy, M.-N.; Taxi, J.; David, L.; Nothias, F. Physical chitosan microhydrogels as scaffolds for spinal cord injury restoration and axon regeneration. Biomaterials 2017, 138, 91–107.
20. Garcia-Ovejero, D.; Arevalo-Martin, A.; Paniagua-Torija, B.; Florensa-Vila, J.; Ferrer, I.; Grassner, L.; Molina-Holgado, E. The ependymal region of the adult human spinal cord differs from other species and shows ependymoma-like features. Brain 2015, 138 Pt 6, 1583–1597.
21. Ghazale, H.; Ripoll, C.; Leventoux, N.; Jacob, L.; Azar, S.; Mamaeva, D.; Glasson, Y.; Calvo, C.-F.; Thomas, J.-L.; Meneceur, S.; et al. RNA Profiling of the Human and Mouse Spinal Cord Stem Cell Niches Reveals an Embryonic-like Regionalization with MSX1+ Roof-Plate-Derived Cells. Stem Cell Rep. 2019, 12, 1159–1177.
22. Rozenblatt-Rosen, O.; Shin, J.W.; Rood, J.E.; Hupalowska, A.; Human Cell Atlas Standards and Technology Working Group; Regev, A.; Heyn, H. Building a high-quality Human Cell Atlas. Nat. Biotechnol. 2021, 39, 149–153.
23. Lindeboom, R.G.; Regev, A.; Teichmann, S.A. Towards a Human Cell Atlas: Taking Notes from the Past. Trends Genet. 2021, 37, 625–630.

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