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Spinal cord injury – there is not just one way of treating it

Veronica Estrada and Hans Werner Müller*

Address: Molecular Neurobiology Laboratory, Department of Neurology, Heinrich-Heine-University Medical Center Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany

* Corresponding author: Hans Werner Müller (hanswerner.mueller@uni-duesseldorf.de)

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Abstract

In the last century, research in the field of spinal cord trauma has brought insightful knowledge which has led to a detailed understanding of mechanisms that are involved in injury- and recovery-related processes. The quest for a cure for the yet generally incurable condition as well as the exponential rise in gained information has brought about the development of numerous treatment approaches while at the same time the abundance of data has become quite unmanageable. Owing to an enormous amount of preclinical therapeutic approaches, this report highlights important trends rather than specific treatment strategies. We focus on current advances in the treatment of spinal cord injury and want to further draw attention to arising problems in spinal cord injury (SCI) research and discuss possible solutions.

Regeneration in the central nervous system

For a very long time, the generally accepted hypothesis—initially proposed in the Edwin Smith papyrus in 2,550 BCE—had been that an injury of the spinal cord is an untreatable condition. In the 1920s, Ramon y Cajal postulated that central nervous system (CNS) axons have an intrinsic ability to regrow after injury but that the lack of trophic support and the barrier function of the lesion scar resulted in the observed lack of axonal regeneration after CNS trauma [1]. Despite almost a century of intensive investigation, the progress of therapeutic interventions to treat SCI remains very limited.

Advances in spinal cord injury research

In the early 1980s, David and Aguayo reported that CNS axonal processes were able to regenerate for remarkable distances when provided the opportunity to grow through long peripheral nerve bridges circumventing a spinal cord lesion [2]. However, the respective nerve fibers did not leave the graft to re-enter the distal spinal cord, an observation that still holds for most therapeutic approaches in the field of SCI. Since then, diagnostic SCI imaging techniques have been immensely improved, and many important growth factors and receptors, signaling cascades, cellular processes, and arising mechanisms of action have been investigated and characterized. Potential drug and cell treatment approaches have been developed based on these findings, and therapeutic interventions have been invented and successfully tested in preclinical studies. A few of these innovative therapies have already been subject to clinical trials, but the promising effects that were observed in preclinical animal studies could never be achieved to comparable degrees in human subjects [3].

Improved SCI outcome has been achieved by different repair strategies in animal models; the aim of neuroprotection strategies is to counteract secondary injury processes that lead to a progressive post-traumatic destruction of spinal cord tissue [4]. Examples of neuroprotective agents that have proven effective in animal models are the phosphodiesterase-4 inhibitor rolipram [5] and the Rho inhibitor cethrin [6]. Repair via regenerative sprouting can be achieved by (1) neutralization of inhibitory factors (e.g. the myelin protein Nogo-A [7]) or (2) administration of neurotrophic factors (e.g. neurotrophins [8]) or chemokines (e.g. CXCL12/SDF-1 [9,10]) to induce the intrinsic neuronal regeneration

program promoting axon growth and plasticity. On the other hand, those factors could influence axon regeneration and guidance through activation or inhibition of signaling pathways regulating the expression or activity of chemorepellent guidance molecules [11,12]. Axon regeneration can be further promoted by inhibition of (glial/fibrotic) scarring, either via degradation or suppression of inhibitory molecules [13,14] or by bridging the injury [15,16]. Although reactive astrocytes are often regarded to be detrimental to the functional outcome of SCI, these cells also mediate important protective functions [17]. Because astrocytes can play such dual roles in SCI response, the transplantation of specifically pre-differentiated astrocytes has also been proposed as a possible treatment for SCI and has been shown to promote functional recovery in animal models [18]. The death of oligodendrocytes, the myelinating cells of the CNS, is an acute result of SCI. In addition to axonal damage, demyelination leads to loss of axonal signal conduction and therefore to functional impairment in SCI. While mature oligodendrocytes are often lost to necrotic and apoptotic injury-related processes, a rapid proliferation and migration of oligodendrocyte precursor cells, especially at the lesion borders, can be observed [19]. For this reason, protected oligodendrocytic cells or their replacement or both are additional promising targets for therapeutic intervention after SCI. Promotion of remyelination is a key point in therapy development. Remyelination can be achieved by the induction of endogenous myelinating cells or by transplantation of myelin-producing cells [20,21]. Cell transplantation therapies have been developed to stimulate regenerative axon growth [22] or to replace lost cells and thereby repair the injured spinal cord [23], and gene therapeutic approaches with genetically modified cells or *in vivo* gene therapy can further support spinal cord repair [24]. Through transplantation of neural stem cells, lost glial and neuronal cells could be replaced, leading to remyelination [25] and axon regeneration [26] in animal models of SCI.

Single-treatment approaches

Effective therapies are available for several SCI symptoms: brain stimulation can be used to treat neuropathic pain [27], and pharmacological treatments can act as neuroprotectants [28] or can reduce spasticity [29,30] or detrimental inflammation at the injury site [31]. Furthermore, therapeutic approaches to achieve improvements in quality of life by regaining breathing function [32], bladder/bowel function [33,34], or hand function [35] have proven quite successful in animal models of SCI. Existing treatment strategies as well as the majority of animal models generally target distinct symptoms of SCI, thereby neglecting the complexity of a wide range of additional parameters. However, many of these approaches have delivered important insight into SCI pathology and have helped bring SCI therapies closer to feasibility. Examples are numerous approaches targeting the injury scar [13,14] to make it more permissive for regenerative axon growth [7,13,14,36,37], influencing inflammatory processes [38-40], peripheral nerve transplants [41-43], numerous cellular transplantation approaches [22,44-46], conditioning lesions [47], or gene therapy [48,49].

Several inhibitory molecules and some of their receptors have been identified and can be targeted by therapy. Some inhibitors of axonal growth are associated with white matter myelin (e.g. Nogo-A, myelin associated glycoprotein [MAG], and oligodendrocyte myelin glycoprotein [OMgp]) [50,51], whereas examples for scar-based inhibitory molecules which accumulate in the SCI lesion scar are members of the large class of chondroitin sulfate proteoglycans (CSPGs) [7,13]. Methods to block or disable the inhibitory function of these molecules have been developed. The myelin-associated inhibitor Nogo-A, for instance, can be neutralized by a specific antibody (IN-1)[7,52], and the glycosaminoglycan side chains of CSPGs can be degraded enzymatically by the bacterial enzyme chondroitinase ABC [7,13].

Strategies to improve locomotor function have demonstrated that small numbers of regenerating nerve fibers can suffice to achieve varying degrees of locomotor functional recovery [13,14,53]. At the same time, high numbers of regenerating nerve fibers—which can be achieved by cell transplantation—do not necessarily result in a considerably improved degree of functional recovery [26] when compared with "conventional" treatments [16,22]. On the contrary, regenerative axon growth, whether at a high or a low rate, could always result in adverse effects such as plastic changes leading to neuropathic pain [54,55]. Strategies to improve locomotor function have also shown that intrinsic spinal neuronal networks such as central pattern generators (CPGs) mediate certain aspects of locomotion even in the absence of sensory feedback [56,57]. CPGs are also important for functions like swallowing and breathing. Finally, (personalized) neuroprosthetics can aid in restoring locomotion even in the absence of axon regeneration and re-synaptogenesis. Therefore, such devices are very promising for future clinical applications [58-61].

Questions of age and timing

Regeneration studies are generally performed in young adult animals, whereas the SCI epidemiology shows that there is an increased incidence at older ages [62] in

human patients. Older age seems to impair axonal plasticity rather than axon regeneration [63,64]. This finding could be of importance because it suggests that effective therapies to promote axon regeneration are still feasible for elderly patients, but it also suggests that different efficacies must be expected for treatments in young and aged patients. Additionally and very importantly, many therapies are being developed in acute injury models. However, a successful treatment for acute SCI may not be equally effective in sub-acute or even chronic SCI. The fibrous SCI scar develops in the first week after the insult [65]; therefore, many treatments target the lesion scar because it is a major physical and molecular barrier to regenerative axon growth. For a large number of treatments, the existing scar at the site of injury is an obstacle that needs to be overcome, especially in sub-acute and chronic SCI. There are different ways of approaching this matter: cellular or acellular matrices, filaments, or channels can be inserted, which function as bridging or guidance structures (or both) or deliver pharmaceutically active substances [15,16,66-69]. A very innovative treatment tool for this purpose is a recently described mechanical microconnector system [70], which actively reconnects severed spinal cord tissue stumps and can further deliver fluid pharmaceuticals into the lesion center cross-section, which is generally not well accessible for continuous *in situ* treatment. With this microconnector system, as with all experimental treatments, a major challenge will be the translation into large animal models up to the potential future clinical application where spinal defects will be of considerably larger size than in rodents. From a clinical point of view, a sub-acute therapy might be the most reasonable because patients with SCI might be reluctant to undergo further invasive interventions once they have come to terms with their situation. In this context, psychological care is absolutely vital to help the patient to accept his or her fate [71]. Regarding SCI in general and sub-acute and chronic SCI in particular, rehabilitative training requires a mention: it can increase neuronal plasticity and is one of the most successful current treatments [72] and, unlike most other SCI therapies, has made its way from the application in patients into experimental animal research (bedside-to-bench) and not *vice versa*. In the long term, locomotor training is of importance because, owing to muscle atrophy over time, axonal regeneration may not be as effective since respective functions must be re-learned. This makes rehabilitation an essential factor for chronic SCI research and treatment. Rehabilitation can be provided as either "passive exercise" or "active exercise". For passive exercise, volitional control is not mandatory. Repetitive training by passive exercise can modulate the caudal spinal circuitry to "normalize" specific spinal reflexes in the absence of supraspinal control and thereby can reduce spasticity [73]. Active exercise can promote recovery by mediating plasticity at multiple levels of the neuraxis [73]. Active exercise requires varying degrees of supraspinal or spinal control or both. Unlike passive exercise, active exercise is, therefore, appropriate only after incomplete SCI. Whereas passive training can activate and increase joint motion, active exercise can improve motor recovery by further activating the muscles and multiple modes of afferent stimulation, possibly by changing the expression of inhibitory or supporting factors (or both) [74] or by altering electrophysiological properties in the lumbar enlargement [75].

Combinatory treatments on the rise

Aside from obvious differences (e.g. spinal level, nature of the injury, and gross classification of the severity), no two cases of SCI are alike. Some single treatments can have multiple (additive or synergistic) effects (e.g. cell transplantation strategies [76,77], the administration of neurotrophic factors [78], or modulation of the SCI scar [13-15,79]). The multitude of research foci reflects the diversity of SCI. Therefore, the current trend is moving from single treatments to more holistic combinatory approaches [80]. As an example for a scar-modulating therapy, the bacterial enzyme chondroitinase ABC has been applied initially as a single treatment in rodents and currently is used in different small and large experimental animal studies [13,32,33,81,82] and also in numerous combinatory approaches [32,33,83-87]. At present, there are also numerous attempts to combine available pharmacological treatments with training in order to maximize the treatment effects. However, such combinatory strategies raise many new questions regarding, for example, the right timing (delay) to start the training, the intensity of the training sessions, or possible adverse effects [72]. Generally, a holistic combinatory SCI therapy should address as many aspects as possible, including neuroprotection (at early post-injury phases), the promotion of axonal growth, and modulating the lesion scar to make it more permissive for growing axons. Regular rehabilitative training should be a self-evident component of any SCI treatment. The major challenge in designing effective strategies will be the potential negative effects of the combination of generally beneficial single approaches. The development of such a comprehensive treatment requires intensive research and careful considerations to reduce the currently unmanageable number of potential treatment strategies.

Managing the data overflow

The list of varying parameters and protocols in SCI research is already daunting (e.g. different injury models

in different species, strains, and sub-strains of experimental animals), and additionally taking into account the timing of treatment (acute, sub-acute, and chronic) and the recent trend toward combinatory treatments results in tremendous amounts of data, which are impossible to follow up by standard methods. This data overflow has recently led to an inevitable new focus in the field of SCI and in medicine in general: structuring, evaluating, and grading existent data in standardized ways. In this context, an international group of SCI researchers has joined to design new software and knowledge databases that allow the users to structure, manage, evaluate, and grade published data. Important examples are surveys, a grading system, and systematic reviews by Kwon and Tetzlaff and colleagues [88-91]; the Facilities of Research Excellence-Spinal Cord Injury (FORE-SCI) [92]; the Center for Neuronal Regeneration (CNR) [93]; and the reporting standard initiative Minimal Information About a Spinal Cord Injury Experiment (MIASCI) [94]. These initiatives have clearly demonstrated several problems in SCI research which result in a general lack of reproducibility. Problems in inter-lab reproducibility, presumably resulting from the above-mentioned varying protocols, have recently been disclosed. Influencing factors include small sample sizes (especially in many preclinical studies); lack of appropriate controls, of blinding, and of reliable outcome measures; and a general lack of transparency. On these grounds, the aforementioned initiatives address existing problems and try to bring potential solutions to the attention of the scientific community as well as the public. Furthermore, researchers are understandably reluctant to publish negative data. This leads to a serious lack of data availability. Overcoming this restraint could significantly accelerate the development of clinical therapies because it could prevent superfluous, time-consuming, and costly reproductions of negative data.

Clinical trials – neuroprotection, functional repair, and regeneration

In addition to a network of scientific (see above) and clinical databases, e.g. the European Multicenter Study about Spinal Cord Injury (EM-SCI [95]), the successful translation of preclinical animal models requires the enforcement of strict criteria, which are established by regulatory agencies. Recently, various clinical trials based on innovative and novel experimental approaches have shown an efficacy in preclinical animal studies and safety in SCI patients but failed to show significant and reproducible efficacy [96]. One of the early clinical SCI trials was conducted by Proneuron Biotechnologies [97]. It comprised the transplantation of autologous (the patient's own) activated macrophages as a treatment for acute SCI. The phase II study was suspended prematurely (supposedly not because of clinical or safety concerns). Some current/planned early-phase (phase I and II) clinical trials include conventional drug and molecule therapies such as the anti-NOGO A antibody therapy (antibody directed against an axon growth inhibitory protein in CNS myelin; desired effects: neuroprotection, axonal sprouting, and regeneration [98-100]) or cethrin treatment (cethrin acts as a C3 Rho inhibitor; desired effects: neuroprotection, axonal sprouting, and regeneration [101-103]). Cell transplantation approaches like the transplantation of autologous olfactory ensheathing glia (desired effects: axonal sprouting and regeneration [104,105]), of autologous bone marrow cells (desired effect: functional repair [20,106-109]), and of autologous Schwann cells (desired effect: functional repair [20,110,111]) are also very promising. However, in contrast to the transplantation of the latter cells, clinical approval of embryonic stem cells (ESCs) remains highly questionable because of the tumorigenic potential of ESC or ESC-derived precursor cells [112] in spite of potential beneficial treatment effects.

Perspective

This short summary describing SCI symptoms, recent research approaches, and treatments up to current clinical applications is far from being complete. It highlights certain facets of a very complex disease pattern and outlines some attempts of aiding the patients' recovery. The hope remains that GLP (good laboratory practice) standardization of SCI studies, the availability and management of necessary data, and well-conducted clinical trials will eventually lead to the development of effective and, most likely, combinatorial treatments from which SCI patients can benefit.

Abbreviations

CNS, central nervous system; CPG, central pattern generator; CSPG, chondroitin sulfate proteoglycan; ESC, embryonic stem cell; SCI, spinal cord injury.

Disclosures

The authors declare that they have no disclosures.

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