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Locomotor Dysfunction and Pain: The Scylla and Charybdis of Fiber Sprouting After Spinal Cord Injury

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Abstract Injury to the spinal cord (SCI) can produce a constellation of problems including chronic pain, autonomic dysreflexia, and motor dysfunction. Neuroplasticity in the form of fiber sprouting or the lack thereof is an important phenomenon that can contribute to the deleterious effects of SCI. Aberrant sprouting of primary afferent fibers and synaptogenesis within incorrect dorsal horn laminae leads to the development and maintenance of chronic pain as well as autonomic dysreflexia. At the same time, interruption of connections between supraspinal motor control centers and spinal cord output cells, due to lack of successful regenerative sprouting of injured descending fiber tracts, contributes to motor deficits. Similarities in the molecular control of axonal growth of motor and sensory fibers have made the development of cogent therapies difficult. In this study, we discuss recent findings related to the degradation of inhibitory barriers and promotion of sprouting of motor fibers as a strategy for the restoration of motor function and note that this may induce primary afferent fiber sprouting that can contribute to chronic pain. We highlight the importance of careful attentiveness to off-target molecular- and circuit-level modulation of nociceptive processing while moving forward with the development of therapies that will restore motor function after SCI.

Keywords Spinal cord injury · Pain · Sprouting · Hyperexcitability · Primary afferents

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The Problem of Spinal Cord Injury and Chronic Pain

Spinal cord injury (SCI) is an event that results in a loss of motor function below the level of lesion and in the development of chronic central pain syndromes. There are approximately 400,000 spinally injured patients in the USA alone, with more than 14,000 new injuries occurring each year [1]. In both complete and partial spinal lesions, following the resolution of spinal shock, chronic central pain develops in the majority of injured patients [2], often within months following injury [3]. Epidemiological studies reveal that more than 69% suffer from chronic pain [4–7], which can become so debilitating that depression and suicide can ensue [8–10].

Chronic pain syndromes and dysesthesias can be divided into two broad categories based on the dependency of the pain to peripheral stimuli. These include: (1) pain independent of peripheral stimuli, which occurs spontaneously and increases intermittently, often described as burning and aching [11], and (2) peripherally evoked pain that occurs in response to either normally non-noxious or noxious stimuli. Each of these behavioral manifestations is associated with different mechanistic underpinnings that represent unique targets for pharmacological intervention. Common drugs

used for pain relief that target neurochemical alterations within the spinal cord include antidepressants, anticonvulsants, opioids, calcium channel blockers, and nonsteroidal anti-inflammatory drugs; however, these agents are ineffective [2, 12]. The difficulty in obtaining relief with these agents may reflect an incomplete understanding of the complete mechanisms underlying pain, particularly with regard to structural changes that link the periphery through primary afferent fibers to central nociceptive structures in the spinal cord, brainstem, midbrain, and ultimately the cerebral cortex.

In this review, we give an overview of mechanisms underlying chronic SCI pain, particularly highlighting the involvement of plasticity in primary afferent fibers. The molecular and cellular processes involved in these structural changes are discussed. Finally, therapeutic SCI repair approaches focusing on enhancement of plasticity are discussed in the context of the possible contribution of sensory fiber sprouting to chronic SCI pain.

Modeling Chronic SCI Pain

In addition to their utility in studying motor dysfunction, rodent models of SCI also permit the study of chronic pain. Typically, these preparations are associated at least with the development of long-term allodynia (pain due to a stimulus that does not normally provoke pain) and hyperalgesia (an increased response to a stimulus that is normally painful). In one model [13], a laser-induced occlusion of spinal cord blood vessels produces spinal cord ischemia resulting in chronic pain. In another model, focal excitotoxic lesions are created within the spinal cord using quisqualic acid, leading to the development of allodynia [14–16]. After unilateral hemisection, a model of the Brown–Sequard syndrome, robust neuronal hyperexcitability and chronic pain result [17–21]. Spinal contusion lesions best parallel the injury profile described in human SCI [22, 23]. Moderate spinal contusion [24, 25] produces an incomplete SCI that is consistent in lesion volume and motor loss [26] and long-lasting chronic central pain [19, 27, 28] in as many as 87% of all injured animals [29]. Animals that exhibit both mechanical allodynia and thermal hyperalgesia also demonstrate a bilateral band of allodynia at and rostral to the segmental level of injury [27] in agreement with patient reports [30].

Nonstructural Mechanisms

Experimental SCI induces electrophysiological changes in the excitability of dorsal horn sensory neurons in response to the same stimuli that previously evoked relatively weaker responses. Since stimuli do not change, in vivo mechanisms must account for alterations in stimulus processing. Changes in expression of ion channels, neurotransmitters, and receptors and activation of microglia all contribute to altered sensory processing intrinsic to the dorsal horn and therefore are candidate contributors to SCI pain.

Ion Channel Dysregulation

Mid-thoracic SCI results in the development of sustained hyperexcitability of lumbar dorsal horn sensory neurons, many of which comprise the spinothalamic tract [31, 32]. Extracellular recordings obtained in various models of acute and chronic SCI reveal changes in electrophysiologic properties of sensory neurons at multiple spinal levels [33–38]. These changes include shifts in proportions of cells responding to noxious stimulation, increases and irregularity in spontaneous background activity, increased evoked activity to (formerly) innocuous and noxious stimuli, and increases in after-discharge activity following stimulation. Patch-clamp recordings of lumbar dorsal horn neurons after T9 SCI revealed a shift in steady-state activation and inactivation of the sodium current toward more depolarized potentials, enhanced ramp currents, and increased persistent currents [39] consistent with alterations in sodium channel expression (see [36, 40, 41]).

At the most fundamental level, action potential generation and propagation by sensory neurons relies on voltage-gated ion channels, and the selective expression of ensembles of sodium channels tunes the biophysical properties of each neuron. In the adult spinal cord, Nav1.3 is expressed at very low levels [42], but after SCI, the expression of Nav1.3 is upregulated in lumbar dorsal horn nociceptive neurons [36]. Nav1.3 produces a rapidly repriming tetrodotoxin-sensitive sodium current that permits neuronal firing at higher-than-normal frequencies [40, 43, 44]. Similar changes occur in thalamic nociceptive nuclei [44–47].

Neurotransmitter Systems

Neurotransmitter molecules modulate the excitability of primary afferent fibers as well as second-order neurons of the dorsal horn. In particular, serotonin (5-HT) plays a key role in dorsal horn pain processing. SCI results in a loss of the supply of 5-HT within the spinal cord caudal to the level of injury through the interruption of descending projections from midline raphe nuclei traveling via raphe–spinal projections located within the dorsal lateral funiculus [20]. The replacement of 5-HT after injury restores local inhibitory tone and can reduce pain phenomenology after SCI [20, 48].

Reductions in spinal levels of gamma-aminobutyric acid (GABA), which is present in up to 30% of inhibitory dorsal horn neurons [49], also support central pain after SCI by decreasing the modulation of nociceptive processing within spinal circuitry [35, 50–52]. After SCI, reduced GABAergic inhibition, through the impairment of GABA production, release, and/or loss of GABA-releasing cells, results in abnormally exaggerated evoked and spontaneous neuronal firing.

Another transmitter-based mechanism for maintained hyperexcitability of dorsal horn neurons involves changes in the expression of metabotropic glutamate receptors (mGluRs). Following SCI, mGluR1 expression increases at the level of injury, and mGluR2/3 expression levels are chronically decreased in and around the lesion site. Following SCI, there is a chronic increase in all laminae for mGluR1 and a decrease in laminae IIi, III, IV, and V for mGluR2/3 [26]. SCI produces an increase in mGluR1 expression on spinothalamic tract neurons [53].

Neuroimmune Activation

Recently, microglial activation after clinical [54] and experimental SCI [36–38, 47, 55–61] has been linked to the maintenance of chronic pain. After SCI, there is a dramatic shift in microglial status from a resting to an activated state in the lumbar spinal cord [60, 61] and thalamus [47] at a time when dorsal horn pain-processing neurons fire at very high rates in response to stimulation of peripheral receptive fields of the skin and pain-related behaviors such as mechanical allodynia and thermal hyperalgesia are evident [36–38, 41]. Microglia produce a number of neuroactive substances and cytokines (see [62]), which influence the excitability of neurons, including excitatory amino acids [63], interleukin (IL)-1β [64], brain-derived neurotrophic factor (BDNF) [65], and prostaglandin E_2 (PGE_2) [66–68]. PGE_2 can induce central sensitization of spinal neurons [69, 70], and extracellular signal-regulated kinases 1 and 2 (ERK1/2), an upstream effector of PGE_2 biosynthesis, is activated in stimulated microglia [66]. Indeed, SCI-induced PGE_2 release by activated microglia is regulated by ERK1/2 [61]. Remote microglial activation after SCI is triggered, at least in part, by the chemokine CCL21 and/or IL-6 [47]. The inhibition of microglial activation after SCI can alleviate pain-related phenomena [47, 60, 61].

Structural Mechanisms Underlying Chronic SCI Pain

In addition to changes in ion channels, neurotransmitter systems, and activation of microglia, the less-understood phenomena of primary afferent fiber plasticity is an important contributor to post-SCI pain. Structural rewiring of the termination patterns of primary afferents in the form of aberrant sprouting [71] is vital in the development of chronic pain. The resulting synaptogenesis contributes to abnormal processing of sensory information by central neurons resulting in the generation and amplification of nociceptive signals. Hence, sprouting may contribute not only to the limited degree of functional recovery but also to the development of chronic pain after SCI.

Rewiring of Local Dorsal Horn Circuitry

The dorsal horn receives somatosensory inputs from the periphery via low- and high-threshold primary afferent fibers (see [72]). Large myelinated Aα fibers convey signals from the skeletal muscle and provide information to the nervous system regarding spatial positioning (proprioception). Medium-diameter myelinated Aβ fibers transmit non-noxious information such as touch received from cutaneous mechanoreceptors and enter the spinal cord and either ascend toward the brain via the dorsal column or synapse within the dorsal horn. Small diameter, thinly myelinated Aδ fibers transmit information from peripheral nociceptors about noxious stimuli such as temperature and sharp pain. Very thin unmyelinated C fibers transmit information from cutaneous nociceptors regarding temperature and burning pain. C fibers make their primary synaptic terminations in lamina II (substantia gelatinosa), which is a major pain-specific relay region of the spinal cord. Aδ and C fibers also synapse on neurons in laminae III–VI.

The central projections of dorsal root ganglion neurons utilize a number of small molecule and peptide neurotransmitters in their communication with second-order neurons such as calcitonin gene-related peptide (CGRP), substance P, and glutamate. CGRP colocalizes with substance P in small-diameter afferent fibers [73, 74] and is released following noxious peripheral stimulation [75] and/or inflammation [50, 51, 76]. CGRP release results in direct enhancement of dorsal horn nociceptive neuron excitability [77–79] and nociceptive behaviors [80, 81]. Substance P also plays an important role in feed-forward inhibitory activity in the spinal cord, whereby behavioral sensitization can occur if substance P-driven feed-forward signaling is compromised [82, 83].

Projection neurons of the dorsal horn receive and integrate inputs from interneurons and/or directly from afferent fibers and then transmit sensory information supraspinally via the spinothalamic tract to make primary connections in the brainstem, thalamus, amygdala, and cortical structures involved in the interpretation and conscious perception of pain [84]. In intact animals, neurons conveying information related to touch normally

project upward via the dorsal column system, bypassing spinal cord circuitry altogether. There is evidence that supraspinal structures also undergo changes in pain processing after SCI [85–87], and this remains a promising area of research.

Dorsal horn sensory neurons are functionally divided into categories according to their responses to mechanical and thermal stimuli. Those responding best to brushing of their peripheral receptive fields are classified as low-threshold cells. Neurons with a preferential response to noxious pinch and little (<10%) or none to brush are high threshold cells. Multireceptive or wide-dynamic range neurons respond to a range of both noxious and non-noxious stimuli. After SCI, the proportions of these cells shift such that more neurons exhibit a multireceptive phenotype [37].

New Targets for Primary Afferents

Structural changes in primary afferent projections and synapses have now also been identified as major players in post-SCI allodynia. The inappropriate sprouting of primary afferent fibers carrying non-noxious stimuli (such as Aβ fibers), as well increased density of projection from nociceptive fibers (Aδ and C), onto the secondary dorsal column and spinothalamic projection neurons represents a structural basis for the unchecked transmission of both types of inputs as "pain" signals described as allodynia and hyperalgesia. It has been known for more than 15 years that after peripheral nerve injury, the central terminals of axotomized myelinated afferents, including the large Aβ fibers, sprout into lamina II, contributing to the modification of sensory input to the central nervous system and allodynia [88–91].

Mechanical (or tactile) allodynia, whereby pain is induced by light touch/pressure or brushing of the skin, may represent inappropriate sprouting of Aβ fibers directly onto dorsal horn nociceptive neurons. In this new configuration, mechanoreceptors can now transmit signals that are interpreted as painful. Thermal hyperalgesia may reflect an increase in the density of Aδ/C fiber sprouting onto dorsal horn nociceptive neurons.

Nociceptive Network Plasticity

Early evidence for pathological SCI-induced sprouting of primary afferent fibers was presented by Weaver et al. [92] in the context of autonomic dysreflexia. They showed that SCI triggered growth-associated protein 43 (GAP-43) upregulation typically associated with growth or sprouting axons in a reticular network of immunoreactive fibers that extended throughout the intermediate gray matter from days 14 to 30 postinjury, at a time when virtually all supraspinal inputs had been eliminated. GAP-43-positive sprouting of Aδ, Aβ, and C fiber populations was later verified using confocal techniques within deeper laminae of the dorsal horn [93]. Measurement of small-diameter afferent arbors revealed increases in area ranging from 20% to 27% in thoracolumbar segments caudal to the injury within dorsal horn laminae III–VII [92].

After hemisection SCI, where at- and below-level mechanical and thermal allodynia robustly develops, the analysis of CGRP and GAP-43 levels was performed to assay for neurite sprouting [71]. In spinal segments C8 and L5, increases in CGRP occur in lamina III and increases in GAP-43 at C8, T13, and L5 segments in lamina I through IV, at 3 days postinjury. The increased area and density of the GAP-43 signal is consistent with neurite sprouting, and the colocalization with CGRP indicates that some of the sprouting neurites are nociceptive primary afferents. These findings support the development and maintenance of the dysfunctional state of allodynia and hyperalgesia [71]. It should be noted that there may be a differential susceptibility of certain classes of C fiber primary afferents to sprouting rostral to cord transection [94]. The analysis of human tissue corroborates these findings, showing a significant increase in CGRP immunoreactivity in the dorsal horns of individuals with chronic SCI [95]. Consistent with these results, antagonism of CGRP signaling alleviates mechanical and thermal allodynia after SCI [96].

Mechanisms Involved in Nociceptive Plasticity

The occurrence of neuroplasticity per se likely depends on the balance between the intrinsic ability of axons to initiate a growth response and the permissiveness of the spinal cord environment [97–99]. In the injured spinal cord, the molecular balance between growth-promoting and growth-inhibiting factors turns out negative for motor axon sprouting. Nevertheless, a limited number of axons do traverse the interface between intact parenchyma and injured spinal tissue [100]. Primary afferents containing CGRP or substance P form a subpopulation of these sprouting fibers. After SCI, these fibers associate with a non-neuronal framework that is formed in the lesion site by invading Schwann cells and leptomeningeal cells [100]. Schwann cells in particular are known to evoke a regenerative response of CGRP and substance P fibers [101, 102]. Knowledge about the exact mechanisms underlying the Schwann cell-mediated response of primary afferents remains incomplete, although there are indications of a role for the cell adhesion molecule (CAM) L1. The non-neuronal framework that forms in the spinal lesion sites and supports primary afferent fiber ingrowth is very rich in L1 CAM. In mice lacking L1, the lesion site remains almost completely devoid of CGRP-positive fibers, despite

the formation of a non-neuronal framework [103]. Further evidence supporting a role of L1 CAM in sensory axon growth is available. The glia limitans present at the dorsal root entry zone is nonpermissive to regrowth of primary afferents, which show clear preference for the peripheral Schwann cell environment over the central astrocytic environment [104]. However, when central astrocytes were genetically modified to express L1 CAM, a robust increase in primary afferent sprouting was observed from Schwann cell to astrocyte territories [105].

Besides a role for L1 CAM, enhanced nociceptive input to pain transmission neurons by sprouting of nociceptive afferents expressing CGRP has also been reported to require nerve growth factor (NGF) [4, 5]. Virtually all CGRP-positive dorsal root ganglion cells express the high-affinity receptor for NGF, tyrosine-kinase receptor A (trkA) [106]. Prolonged treatment with antibodies against NGF alleviated the SCI-induced upregulation of CGRP fiber sprouting in the spinal cord dorsal horn [4, 5], as was mechanical responsiveness of wide-dynamic range neurons and of below-injury-level mechanical allodynia [107]. Thus, NGF plays an important role in SCI-induced CGRP fiber sprouting and subsequent chronic pain development.

Hematogenous immune cells and activated glial cells, including Schwann cells, microglia, and astrocytes, have been identified as cellular sources of NGF after SCI [108]. Although primary afferents express the trkA receptor [106], the effects of NGF on CGRP fiber sprouting may also be indirectly mediated via an effect of NGF on glial cells. Schwann cells, which can stimulate CGRP fiber sprouting as described above, for example, upregulate their expression of trkA upon injury [109] and may thereby be stimulated to invade the spinal lesion site.

Considerations of Neuroplasticity-enhancing Repair Strategies

Since, after SCI, there is limited motor recovery in humans (it should be noted, however, that after rodent SCI, there is a greater degree of spontaneous motor recovery), the goal of most SCI therapies is to induce specific sprouting of spinal cord motor axons and fibers through nonpermissive growth regions (see [110]). In most cases, the intended fibers are corticospinal and/or rubrospinal motor fibers, which after successful regeneration should carry commands to spinal central pattern generator or motor output neurons directly. On the other hand, unintended induction of sprouting of sensory fibers represents a deleterious consequence of these therapies. Thus, skillful navigation between the Scylla of paralysis and the Charybdis of chronic pain represents a goal of high importance that must be met to achieve satisfactory results from strategies aimed at inducing sprouting after SCI (Fig. 1).

One set of SCI repair strategies attempts to overcome the negative balance between growth promotion and growth inhibition by neutralizing or degrading growth inhibitory cues associated with central myelin and the fibroglial scar that develops at the interface between intact neural parenchyma and damaged spinal tissue [111–114]. However, some of these strategies have also included the introduction of cellular and/or molecular growth-promoting factors [115, 116]. It is not our intention to give a detailed description of each SCI repair strategy aiming at enhancement of neuroplasticity; rather, we will discuss how neuroplasticity-enhancing strategies can nonspecifically affect severed and spared motor fibers and induce plasticity in sensory fibers.

Regenerative Therapies—Inhibitory Molecules and Sprouting

Nearly two decades ago, central myelin was found to be inhibitory to the outgrowth of neurites [117–119]. Today, a molecular profile has been characterized that better describes the inhibitory nature of central myelin [120–122]. Growth inhibitory molecules exert their inhibitory effects through the activation of a receptor complex and a downstream signaling cascade, which influences the cytoskeleton [123–127]. Pharmacological interference with the inhibitory effects of central myelin has been reported to boost plasticity of injured motor fibers [124, 128], although these results have also been challenged [129]. It is important to note that SCI repair strategies that manipulate central myelin do not seem to affect primary afferent fibers. For example, mice lacking the Nogo receptor do not show alterations in termination patterns [130]. In support of this, central myelin has been reported noninhibitory on the regrowth of dorsal root ganglion neurons, which were microtransplanted into intact and injured rat spinal cords [131, 132]. Conversely, dorsal root ganglion neurites were found to halt their growth in areas rich in chondroitin sulfate proteoglycans (CSPGs) [132].

CSPGs are part of the extracellular matrix, and particularly, high expression levels are detected in the fibroglial scar after SCI [133–135]. The inhibitory nature of CSPG has been linked to multiple regions within the molecule [135–138]. Manipulation of the growth inhibitory fibroglial scar has been achieved by enzymatic degradation of CSPG via prolonged treatment with the bacterial enzyme chondroitinase ABC [139]. Following treatment, injured motor fibers regrow, and motor abilities significantly improve [139]. It is important to note, however, that CGRP fibers were also found to sprout into aberrant locations following chondroitinase ABC. Although the authors reported no

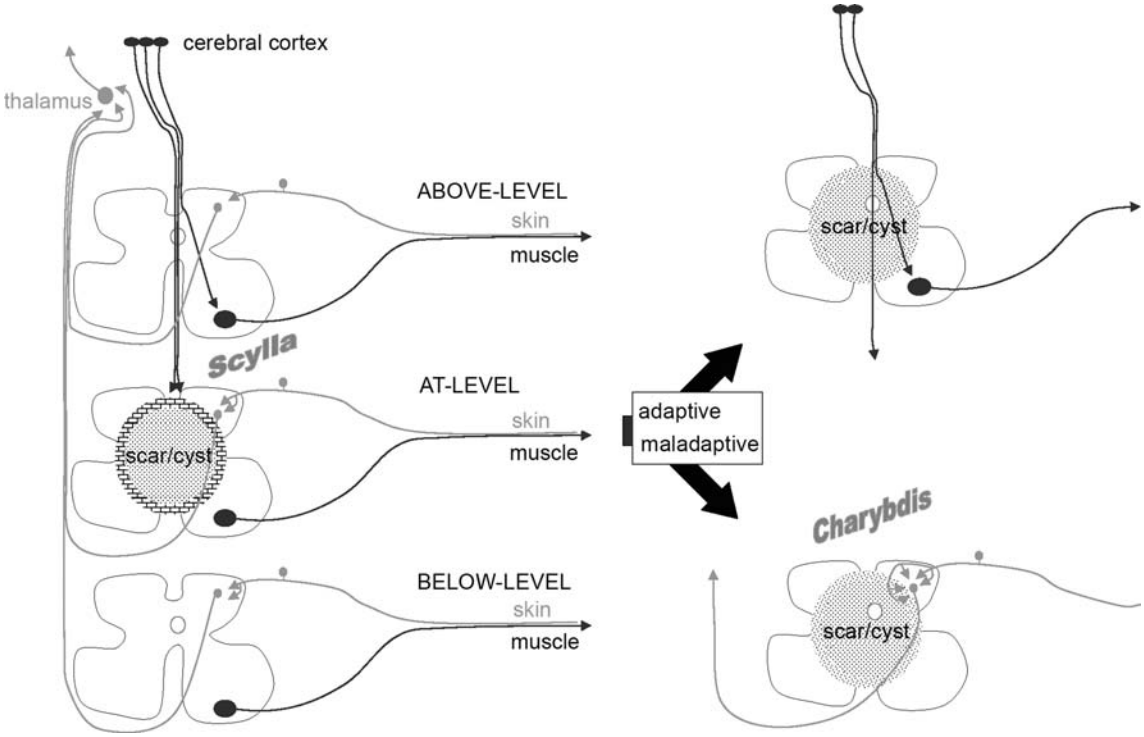

Fig. 1 The highly restricted sprouting of descending motor fibers after SCI is represented by the mythological monster of Scylla. Upon injury, a number of local factors inhibit damaged motor fibers from regenerating into and/or through the lesion site, with the fibroglial scar playing a key role in this inhibition. Attempts at overcoming this growth inhibitory barrier with the goal of enhancing plasticity have been somewhat successful. However, an unwanted side effect of these therapies is the induction of unspecific sensory fiber sprouting, represented here by Charybdis, resulting in the structural development of chronic central pain syndromes and dysesthesia. Enhanced sprouting of primary afferent fibers entering the spinal cord results in an increase in the absolute number of sensory inputs reaching the dorsal horn, as well as the formation of new and inappropriate synapses onto nociceptive relay neurons. From a clinical perspective, it is therefore of high importance to carefully navigate between the two monsters of fiber sprouting to achieve gain of motor function without pain

enhancement in mechanical or thermal hyperalgesia [140], pain behaviors were not measured at locations corresponding to the spinal levels, which showed enhanced CGRP fiber sprouting.

Manipulation of the fibroglial scar has also been achieved via antisemaphorin-3A treatment. Like CSPG, semaphorins are extracellular matrix proteins present in the fibroglial scar. Semaphorin-3A is abundantly expressed by fibroblasts invading spinal lesion sites from the meninges [141] and can exert growth inhibitory effects by binding to the neuropilin-1 receptor (NP-1). When rats with complete cord transection received prolonged treatment with the selective semaphorin-3A inhibitor xantofulvin, there was growth of motor fibers, and animals regained some motor ability [142]. However, CGRP-positive fibers also express NP-1 [143] and might therefore be sensitive to the xantofulvin treatment. Indeed, CGRP fiber sprouting was observed after the blockade of semaphorin-3A signaling. Since semaphorin-3A has been reported to prevent NGF-induced CGRP fiber sprouting [144], prolonged interference with semaphorin-3A potentially unmasks a semaphorin-3A-induced restriction of CGRP fiber sprouting after SCI. Although the authors reported no development of thermal hyperalgesia [142], it is unknown whether the enhanced CGRP-positive fiber sprouting after prolonged semaphorin-3A inhibition resulted in any other form of neuropathic pain. Because SCI animals receiving treatment to modify the fibroglial scar have shown enhanced CGRP sprouting, they are at potential risk for enhanced pain development.

Approaches to Enhance SCI Plasticity—Transplantation

Several cell types have been identified as suitable candidates to promote SCI repair. More than a decade ago, olfactory ensheathing cells (OECs) received special attention because they are reported to be responsible for the natural olfactory axon regeneration, which occurs throughout mammalian life [145–147]. The transplantation of OEC preparations has impressively stimulated motor fiber regrowth in many [148–151] but not all SCI models [152–155]. Besides the model used, also other determinants have been proposed accounting for the variable efficacy of OECs in promoting fiber regrowth including the source of OECs,

the age of the animals from which OECs are obtained, OEC-culturing methods, and transplantation paradigms [156]. Recently, it was reported that OEC transplantation also evoked a sprouting response of CGRP-positive fibers in the tissue surrounding spinal lesion sites [157, 158]. Notably, in OEC-treated animals, this response was paralleled by an autotomy of the hindlimbs, which is regarded as a behavioral sign of spontaneous pain [14, 159]. The authors, unfortunately, did not include any other pain assays in their studies [157]. The mechanisms underlying the OEC-mediated CGRP sprouting are unknown, but there are indications that invading Schwann cells may be involved. OEC transplantation is known to robustly attract Schwann cells from peripheral nerves into spinal lesion sites [160, 161]. This process may involve NGF because OEC-induced Schwann cell migration can be blocked by the neutralization of NGF [162].

The use of stem cells and progenitor cells, which can be obtained from a wide range of tissues, is considered to be a promising avenue for repair of motor functions after SCI, since these cells have the intrinsic ability to replace lost cells, re-establish functional connections, and remyelinate axons [163–165]. Although it has been shown that stem cells originating from blood can differentiate into neural cells [166], the finding of stem cells in the neural tissue itself has opened exciting possibilities for SCI repair. The transplantation of a murine neural stem cell line elicited plasticity of motor fibers but also CGRP fibers [166]. The enhanced plasticity could be due to elevated expression of neurotrophic factors such as NGF, BDNF, and glial cell line-derived neurotrophic factor detected after transplantation [167]. Notably, animals treated with these neural stem cells developed above-spinal-injury-level mechanical and thermal allodynia [167]. It remains unknown how the neural stem cells induced this CGRP fiber sprouting, but the differentiation profile of the transplanted cells (i.e., differentiation primarily into astrocytes) may play an important role. This is suggested by the observations of Hofstetter et al. [168], who transplanted naïve neural stem cells derived from adult rat spinal cord into thoracic spinal cord contusion lesions and observed improved motor outcome but also above-spinal-injury-level allodynia to both mechanical and cold stimulations. The allodynia was not only paralleled by increased CGRP fiber sprouting into lamina III of the dorsal horn above the level of injury, but there was a strong correlation between these two parameters. In this experiment, naïve stem cells primarily differentiated into astrocytes, but when cells were transduced with the neurogenin-2 transcription factor, the differentiation profile of the cells shifted in favor of oligodendrocytes and neurons instead of astrocytes following transplantation into the contused spinal cord [168]. With this pretreatment, CGRP fiber sprouting and the development of mechanical and cold allodynia were prevented. It is not known how astrocytes contribute to chronic pain after SCI, but there are indications that transplantation of type II but not type I astrocytes evokes sprouting and pain after SCI [169]. SCI repair interventions involving astrocytes [170] should be explored with care.

Conclusion

The indiscriminate promotion of sprouting of fibers within the spinal cord after injury will almost certainly result in the formation of new and inappropriate connections between primary afferent fibers conveying both noxious and non-noxious sensory information and hyperexcitable dorsal horn nociceptive neurons. Recent advances in our understanding of molecular inhibitors and promoters of selective sprouting of tract- and class-specific fibers have improved the navigability of the strait of SCI repair, avoiding the monsters of paralysis (Scylla) and chronic pain (Charybdis). A careful convergence in these two fields is now needed more than ever, and will certainly put us closer to the desired endpoint where therapeutics will achieve gain without pain.

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