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REVIEW

Neurotrophins: Potential Therapeutic Tools for the Treatment of Spinal Cord Injury

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Abstract Spinal cord injury permanently disrupts neuroanatomical circuitry and can result in severe functional deficits. These functional deficits, however, are not immutable and spontaneous recovery occurs in some patients. It is highly likely that this recovery is dependent upon spared tissue and the endogenous plasticity of the central nervous system. Neurotrophic factors are mediators of neuronal plasticity throughout development and into adulthood, affecting proliferation of neuronal precursors, neuronal survival, axonal growth, dendritic arborization and synapse formation. Neurotrophic factors are therefore excellent candidates for enhancing axonal plasticity and regeneration after spinal cord injury. Understanding growth factor effects on axonal growth and utilizing them to alter the intrinsic limitations on regenerative growth will provide potent tools for the development of translational therapeutic interventions for spinal cord injury.

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Human Spinal Cord Injury

Traumatic injury of the spinal cord can produce a range of debilitating effects and permanently alter the capabilities and quality of life of its surviving victims. Damage to the central nervous system (CNS) in general results in destruction of neuronal circuitry. Contusion, compression, and penetration injuries of the spinal cord can interrupt the flow of sensory and motor information between the brain and periphery [1]. Depending on the location and severity of the injury, deficits can range from weakness of limb movement to total paralysis and ventilator-assisted respiration. Spontaneous functional recovery is limited, but can and often does occur in patients with initial sparing of sensorimotor function [2]. This recovery, which plateaus between 12 to 18 months, is very likely due to sparing and sprouting of axons within the zone of partial preservation, an area where some motor function remains intact, immediately adjacent to the lesion site [2].

Approximately 40% of humans that sustain spinal cord injury (SCI) exhibit improvement from their early post-injury baseline, and this spontaneous recovery can range from modest to extensive [2]. Spontaneous recovery primarily appears to depend on the extent of tissue sparing at the injury site, allowing compensatory axonal sprouting and systems reorganization at levels ranging from the spinal cord to the cerebral cortex [3–10]. However, in cases of more severe injuries, means of enhancing endogenous levels of axonal sprouting and inducing true axonal regeneration are required to enhance functional outcomes.

Clinical Treatment

As there are no current clinical treatments that increase plasticity or regeneration of axons, the clinical field is restricted to attempting to limit the amount of secondary damage that follows SCI. The main goals of this approach are to stabilize the spinal column and minimize the secondary neural degeneration brought on by numerous factors including edema, hypoxia, ischemia, excitotoxicity, free radical damage, lipid peroxidation, inflammation, and activation of apoptosis [11, 12]. Acute spinal surgery, within the first 24 h following SCI, to alleviate mechanical shearing and compression forces is used to restrict primary damage to the cord, as well as secondary damage that can result from extended periods of compression [13]. In addition to spinal cord stabilization, arterial oxygenation and maintenance of mean arterial blood pressure between 85 and 90 mm Hg following acute SCI is vital in reducing secondary damage due to ischemia and hypoxia, and improving functional outcome [11, 14–18]. Hypothermia is also currently in clinical testing as a means of limiting secondary damage immediately following injury [19, 20]. However, progress in the translation of pre-clinical treatments aimed at promoting regenerative growth has been slow [21].

Mechanisms Underlying the Failure of CNS Regeneration

There are several obstacles hindering the functional regeneration of CNS circuitry. These include both neuron-dependent intrinsic and neuron-independent extrinsic mechanisms. Neuron-intrinsic mechanisms that contribute to regeneration failure include the absence of appropriate expression levels or localization of receptors capable of transducing growth signals, the modulation of growth factor signaling cascades, and the lack of expression of regeneration-associated genes, such as growth-associated protein 43 (GAP-43), which are indicative of an active axonal growth state [22–26].

A number of neuron-extrinsic factors affect the regenerative capacity of CNS neurons. These extrinsic factors include the absence of a growth-promoting substrate, inflammation following SCI, reactive astrogliosis, inhibitory extracellular matrix proteins, myelin inhibitory proteins, induction of repulsive guidance cues, and the lack of trophic support in the injured CNS [27–33]. There are numerous experimental strategies for targeting these extrinsic mechanisms, which include providing growth-promoting substrates, mediating the inflammatory response to SCI, eliminating reactive astrogliosis, reducing inhibitory extracellular matrix and myelin proteins, attenuating repulsive guidance signals, as well as providing growth-promoting neurotrophic signals.

In examining strategies aimed at promoting axonal growth through modulation of either intrinsic or extrinsic mechanisms, plasticity of axons can be divided into 2 main categories: 1) sprouting and 2) regeneration. Regeneration refers to new axonal growth that arises at the injury site from the cut end of an axon. Sprouting, on the other hand, refers to axonal growth emerging from a spared axon adjoining the lesion site, or from a transected axon at some distance from the site of transection.

Provision of Growth-Promoting Substrates to Sites of Injury

Pre-clinical research on SCI has focused primarily on the modulation of the extrinsic cellular environment with an emphasis on the differences between the relatively nonpermissive CNS environment for growth compared to the supportive peripheral nervous system environment. It has long been known that regeneration occurs following lesions to the peripheral nervous system, so it follows that the first attempts at bridging lesions in the CNS would graft segments of potentially permissive peripheral nerve. Grafting of peripheral nerve to the CNS dates back at least as far as the work of Ramón y Cajal in 1911 [34, 35]. Sugar and Gerard [36] demonstrated anatomical and physiological evidence of regeneration in the spinal cord through peripheral nerve grafts in 1940, though it was the work of Aguayo and colleagues that demonstrated a clear capacity for spinal cord regeneration through a peripheral graft using modern tracing methods [37, 38]. These studies demonstrated that (for at least some cell populations) lesioned CNS neurons are capable of regeneration if the injured CNS is grafted with a substrate permissive to growth.

Within peripheral nerves, the principal cells are Schwann cells, which proliferate in response to injury [39]. Furthermore, the elimination of viable Schwann cells from peripheral nerve grafts abolishes the promotion of CNS regeneration [39–41]. Transplantation of Schwann cells into sites of CNS injury, including the lesioned spinal cord, mimics the effects of peripheral nerve grafts and supports axonal regeneration [42, 43]. In addition to potentially myelinating regenerated axons, Schwann cells express cell adhesion molecules, produce components of the extracellular matrix, and secrete multiple neurotrophic factors [44–53]. Whether grafted Schwann cells provide an advantage in comparision with other potential cell grafts remains to be determined; however, as the grafted cells survive poorly in the lesioned spinal cord, they are soon replaced by migrating endogenous Schwann cells [54, 55].

Due to the multi-potent nature of neural stem cells and embryonic stem cells, these progenitors have been investigated for their potential in neural tissue replacement strategies and as neurotropic and neurotrophic substrates [56]. Neural stem cells secrete trophic cytokines and neurotrophins, and when transduced to over-express neurotrophic factors, exhibit enhanced neurotropic effects on spinal axons [57, 58]. The diversity of studies using neural and embryonic stem cell transplantation after spinal cord injury is reviewed elsewhere (for more detail see Rossi and Keirstead [56]).

More readily accessible cell types available for autologous cell grafting include bone marrow stromal cells and ectoderm-derived fibroblasts. These cells can be noninvasively isolated from a patient, rapidly expanded *in vitro*, transduced to express therapeutic agents and transplanted without the need for immunosuppression. Numerous studies have used these non-neural cells as a means of bridging the lesion cavity, as well as providing extracellular matrix proteins and trophic support for regeneration [23, 59–68]. Although these cells are unable to initiate myelination of regenerated axons themselves, neurotrophin production by transplanted cells leads to robust graft infiltration by endogenous Schwann cells, which may act to promote or stabilize axonal regeneration in a secondary manner [63, 65, 69, 70].

Neurotrophic Factors

Neurotrophic factor expression is tightly linked to growth, maintenance of synapses, and survival of neurons during development. The first class of nervous system growth factors to be identified (the classic neurotrophin family) consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 [71]. Since the initial discovery of NGF more than 60 years ago, and the identification of the other neurotrophin family members in the 1980s and 1990s, several additional families of growth factors have been identified [72]. The most thoroughly studied growth factor family in models of SCI is the classic neurotrophin family, and the rest of this article will focus on these proteins. These neurotrophins have unique functions in the CNS and are differentially regulated during developmental maturation of the brain and spinal cord. All four neurotrophins are translated as proneurotrophins, which are subsequently proteolytically cleaved to produce 13 kD proteins that exist as noncovalently linked homodimers [71]. All 4 can bind the low-affinity receptor p75NTR (p75 neurotrophin receptor), which, when co-expressed with 1 of the high-affinity tropomyosin receptor kinase (trk) neurotrophin receptors, can modulate the signaling activity of trk [71].

Neurotrophin expression levels are regulated both spatially and temporally throughout development. NGF levels in the CNS decrease somewhat during postnatal development, but expression persists throughout adulthood in hippocampus, cortex, and olfactory bulb, which are all sites of neural plasticity in the adult [73]. BDNF levels exhibit a robust increase, primarily in the hippocampus where expression of both pro and mature forms peak perinatally before decreasing slightly to adult levels, whereas NT-3 expression levels decrease from neonates to adults, except in the hippocampus [73, 74]. In the adult spinal cord, there is a dramatic reduction in levels of NGF, BDNF, and NT-3 in comparison to embryonic expression levels [73].

Neurotrophins, Development, and Survival

The reduction in neurotrophin expression in the adult CNS is correlated with an apparently reduced requirement for trophic support, as well as a reduced potential for axonal plasticity. During development, availability of neurotrophins in the embryo and neonate govern the survival of neurons during a period of synaptic and neuronal elimination, with exogenously applied neurotrophins reducing normal levels of cell death [75]. The role of neurotrophins in preventing the inappropriate paring of synaptic connections in perinatal animals leaves these neurons much more susceptible to cell death following the removal of a trophic source, either through biochemical manipulations or via de-efferentation by axotomy, than neurons in adult animals [76, 77]. Sciatic lesion in neonatal mice results in a loss of approximately two-thirds of the lower motor neurons in the lumbar enlargement, which is completely ameliorated with the application of BDNF, NT-3, or insulin-like growth factor I (IGF-I) [78]. This death of neonatal motor neurons is in stark contrast to lower motor neurons that not only survive, but regenerate following adult sciatic nerve injury; sciatic injury has been shown to result in increased NGF, BDNF, IGFs, cilliary neurotrophic factor, and glial-derived neurotrophic factor secretion from Schwann cells [44–53]. Antibody depletion of Schwann cell-produced BDNF leads to decreased regeneration and deficits in myelination of lower motor neurons and sensory neurons [79–81].

There are other nuclei in the adult CNS that maintain a requirement for trophic support as evidenced by somal atrophy or cell death following axotomy, although cell loss does not occur at the same rate or to the same extent as in neonatal animals. Axotomy of medial septal cholinergic neurons results in cell atrophy and eventual death that is ameliorated by NGF delivery within the first week [82–84]. Delayed NGF treatment cannot completely prevent cell loss, although it can restore cell size and neurotransmitter

expression in a large proportion of medial septal cholinergic neurons [82, 83, 85].

Cortical and brainstem neurons involved in motor control pathways have demonstrated a somewhat reduced requirement for neurotrophic stimulation in the adult. During development, neonatal animals exhibit a critical period for axonal plasticity where lesioned and spared corticospinal, as well as rubrospinal motor axons may sprout following SCI [86–92]. Despite this capacity to sprout, the neurotrophic requirements of neonatal rubrospinal neurons lead to massive cell loss following rubrospinal tract lesion, which can be rescued with BDNF administration [91–93]. In contrast, rubrospinal tract lesion in the adult results in significant atrophy of motor neurons in the red nucleus but limited cell death; this atrophy is fully reversible with BDNF delivery even for as much as 1 year after SCI [94–97]. In addition, BDNF administration to either the red nucleus or the spinal cord following rubrospinal tract lesion results in up-regulation of growth associated genes and promotes axonal growth [67, 94–96, 98, 99].

Following adult SCI, corticospinal motor neurons exhibit somal atrophy but little if any cell loss; cortical atrophy can be prevented by BDNF administration to the spinal cord injury site [100, 101]. Axotomy proximal to the cell body at the level of the internal capsule, however, results in a loss of approximately 50% of lesioned corticospinal motor neurons and atrophy of the surviving neurons [102]; this cell death and atrophy are completely prevented by high levels of BDNF or NT-3 treatment [23, 102, 103].

Neurotrophins and Spinal Cord Regeneration

Neurotrophin delivery to the injured spinal cord supports the growth of a number of discrete neuronal populations (Table 1). NGF promotes the sprouting and regeneration of cholinergic local motor axons, primary nociceptive sensory axons, and cerulospinal axons [104, 105]. BDNF-secreting bone marrow stromal cell grafts promote regeneration of a number of neuronal populations including raphaespinal, cerulospinal, rubrospinal, local motor and propprioceptive sensory axons [63, 67, 94, 96]. NT-3 expression, similar to BDNF, promotes the regeneration of ascending sensory neurons across the dorsal root entry zone and within the dorsal columns [60, 64, 106–109].

Graded expression of NT-3 has been used to induce chemotropic regeneration of ascending sensory axons [60, 110]. In animals with low levels of NT-3 expression within a permissive dorsal column graft and higher levels in the spinal cord beyond the lesion, sensory axons are able to regenerate through the site of injury and reconstitute damaged neuronal circuitry (Fig. 1) [60, 110]. Once sensory axons have re-entered host tissue, they can be guided to NT-3-secreting nuclei several millimeters away and form synapses on neurons in the appropriate target nucleus [110]. These synapses in nucleus gracilis are indistinguishable from intact synapses at the ultrastructural level, containing clusters of synaptic vesicles. However, the newly formed regenerated projections are not electrophysiologically active, possibly due in part to a failure of remyelination [110].

Table 1 Classic neurotrophins induce regeneration of distinct spinal cord axon populations

Growth factor	Central axon populations affected	References
NGF	$ChAT^+$ motor $CGRP^+$ sensory TH^+ coerulospinal	[62, 104, 105]
BDNF	$5\text{-}HT^+$ raphaespinal TH^+ coerulospinal $NF200^+$ proprioceptive sensory Rubrospinal	[63, 67, 94, 96, 112]
NT-3	$5\text{-}HT^+$ raphaespinal $NF200^+$ proprioceptive sensory Corticospinal motor (axon plasticity only)	[60, 61, 64, 106–113]
NT-4	$5\text{-}HT^+$ raphaespinal TH^+ coerulospinal	[112]

BDNF = brain-derived neurotrophic factor; NGF = nerve growth factor; NT-3 = neurotrophin-3; NT-4 = neurotrophin-4; $5\text{-}HT^+$ = (serotonergic) raphaespinal; TH^+ (tyrosine hydroxylase expressing) coerulospinal

Provision of growth factor gradients can promote regeneration, even at chronic time periods after injury. When treatment with NT-3 is delayed as much as 15 months after SCI, dorsal column proprioceptive axons are able to initiate a regenerative response and bridge into, and beyond, cell grafts placed in the chronic lesion site [111]. This regeneration of chronically injured neurons is possible only when coupled with modulation of the intrinsic growth state by peripheral conditioning lesion (discussed in detail as follows) [111].

Intrinsic Capacity to Regenerate

Sensory neurons in the dorsal root ganglia demonstrate a robust change in regenerative potential of the central axon in the spinal cord following a "conditioning" crush lesion of the peripheral branch of the neuron [114, 115]. This increase in regenerative potential of the neuron is accompanied by regulated changes in thousands of genes in the dorsal root ganglia [47, 116]. Collectively, these changes in transcriptional programs represent a change in the intrinsic regenerative state of the neuron. Among the many changes activated by a conditioning lesion are increases in BDNF

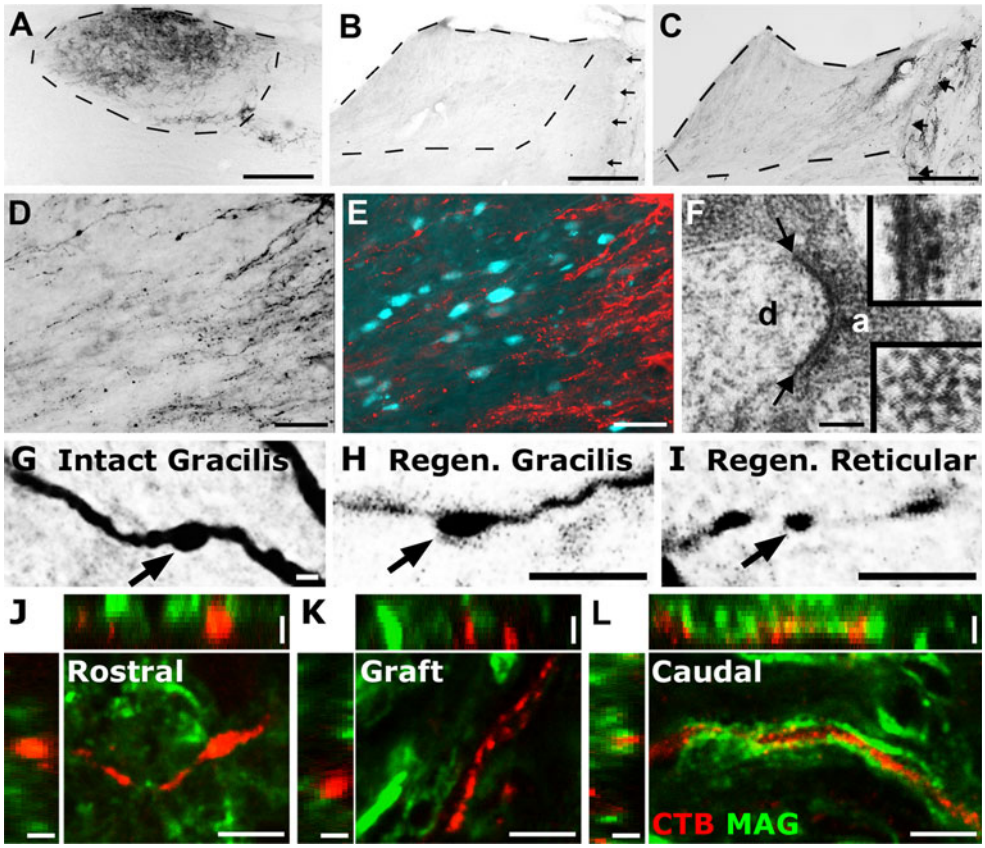

Fig. 1 Expression of neurotrophin-3 (NT-3) gradients can induce sensory regeneration and synapse formation in target nuclei. (**a**) The transganglionic tracer cholera toxin B subunit (CTB) labels ascending sensory neurons in nucleus gracilis in an intact animal. (**b**) Control animals receiving green fluorescent protein (GFP) expressing lentivirus in the nucleus gracilis do not exhibit axonal regeneration into the nucleus. (**c**) NT-3 expression in nucleus gracilis, as well as the lesion site facilitates reinnervation of the appropriate target nucleus. (**d**, **e**) CTB-labeled sensory axons approach secondary sensory neurons in nucleus gracilis (labeled retrogradely by flourogold injection to the ventro-posterolateral nucleus of the thalamus). (**f**) Electron microscopy reveals pre-synaptic structures (between arrows) in regenerated, CTB-labeled sensory axons (**a**) in nucleus gracilis on a dendritic process (**d**) with asymmetric synaptic specializations (top inset) with CTB surrounded by electron-dense synaptic vesicles (bottom inset). (**g-i**) Axons in intact (**g**), re-innervated target nucleus gracilis (**h**), and newly innervated nontarget areas (reticular formation); (**i**) labeled with CTB display bouton-like structures resembling synapses. (**j-l**) Despite reinnervation of target nuclei, regenerated axons are not electrophysiologically active and lack remyelination both in and beyond grafted NT-3 secreting more readily accessible cell types available for autologous cell grafting, include bone marrow stromal cells 1 month after central injury. Scale bars 250 μm (A-C), 50 μm (D, E), 0.4 μm (F), 5 μm (G-I), (J-L) main panels), and 2.5 μm (J-L) z-stack side panels

expression. Indeed, blockade of BDNF both *in vivo* and in neuronal cultures attenuates neurite outgrowth after conditioning lesions [80, 81]. Priming dorsal root ganglia with neurotrophins *in vitro* results in elevated cyclic adenosine monophosphate (cAMP) levels and protein kinase A (PKA) activation, which similar to conditioning lesion attenuates the neurite outgrowth-inhibitory effects of central myelin [117]. Similarly, conditioning lesions elevate cAMP levels in dorsal root ganglia [118], and conditioning effects can be partly replicated by cAMP injections into dorsal root ganglia (DRG) neurons [118, 119].

Developmental down-regulation of growth-associated genes is a potential reason for the lack of regeneration in the adult CNS. GAP-43 is highly expressed in the embryonic and early postnatal spinal cord with almost undetectable levels by P29 [120]. Following peripheral conditioning lesions, lower motor neurons and dorsal root ganglia sensory neurons dramatically upregulate GAP-43 mRNA and levels remain elevated for 5 to 10 weeks [121]. This increase in GAP-43 expression does not occur following lesion of the central branch of dorsal root ganglia sensory neurons, suggesting a potential role for GAP-43 in the regenerative response, which occurs specifically following peripheral lesion [122].

Electrical stimulation of lesioned femoral nerve promotes regeneration of lower motor neurons [123, 124]. Brief stimulation of lesioned femoral nerves for 1 hour leads to a rapid increase in messenger RNA (mRNA) levels of BDNF and its complementary high affinity receptor trkB in the motor neurons that peaks 2 days poststimulation with maximum sixfold and fourfold increases, respectively, in comparison to contralateral intact motor neurons [25].

Temporally following increases in BDNF and trkB expression is an increase in mRNA of the growth-associated genes Tα1-tubulin (Talpha1-tubulin) and GAP-43 [26]. Interestingly, electrical stimulation of the intact sciatic nerve for 1 h increases cAMP levels in the dorsal root ganglia to levels found 24 h following sciatic nerve conditioning lesion [125]. Similar to cAMP elevation via direct injection of the membrane-permeable analog db-cAMP, electrical stimulation of the sciatic nerve also promotes significant sensory axonal regeneration both in cultured dissociated adult dorsal root ganglia neurons and *in vivo* following a central lesion [125]. Electrical stimulation may therefore activate a similar cascade of events as peripheral conditioning lesions, and could potentially be used to promote regeneration.

Although peripheral conditioning promotes regeneration of sensory neurons through modulation of intrinsic signaling pathways, there is no correlate mechanism for stimulating regeneration of central motor pathways. Corticospinal motor neurons are perhaps the most refractory of neuronal systems in response to therapeutic intervention following injury. Corticospinal neurons extend axons in response to IGF-I during development; however, in the adult IGF-I has no effect on corticospinal axons potentially due to a combination of a lack of receptor trafficking to the axon and a developmental increase in expression of the inhibitory IGF-binding proteins [24, 126, 127]. NT-3 promotes sprouting of corticospinal axons into gray matter surrounding spinal cord lesion sites, but these axons do not regenerate into cell grafts placed into lesion sites [61, 113, 128, 129].

As the corticospinal motor neurons cannot be conditioned to regenerate, alternative means must be used to enhance their intrinsic growth state. Viral delivery has been used to deliver integrin receptors and retinoic acid receptors to sensory neurons to enhance axonal growth from the transduced neurons [130, 131]. These studies focused on manipulation of the cellular response in neurons that are already able to regenerate; however, a similar approach has also been used to alter the response of the more refractory corticospinal motor neurons. Viral delivery of the high affinity BDNF neurotrophin receptor trkB to the motor cortex, resulting in over-expression of trkB, can alter the response of cortical neurons and corticospinal motor neurons in particular to BDNF-secreting grafts [132]. Over-expressed trkB is trafficked into the axonal compartment of identified corticospinal neurons and results in regeneration of transduced neurons into subcortical BDNF-secreting grafts through Erk/Map kinase pathways [132]. Trafficking of the receptor is limited, however, as virally expressed trkB is undetectable in the spinal cord [132]. One of the downstream mediators of neurotrophin signaling is phosphoinositide 3-kinase, which signals through the serine-threonine kinase Akt, a process inhibited by phosphotase and tensin homologue (PTEN) [133–135]. Mice lacking PTEN are able to regenerate axons following optic nerve crush and exhibit sprouting of corticospinal axons after injury, similar to observations after NT-3 delivery to the injured spinal cord [136, 137]. Studies with NT-3 and PTEN underscore that attempts to promote corticospinal regeneration may require not only modulation of the injured environment, but also the intrinsic growth state of injured neurons [132, 136].

Translation of Pre-Clinical Rodent Studies to Potential Therapies

The vast majority of pre-clinical research undertaken on spinal cord injury is performed in mice and rats. One of the key steps in translating these therapies to the clinic will be to understand the response of motor and sensory systems to injury in primate species. Perhaps the most crucial example of interspecies variation in function and response to injury is the corticospinal tract. Regeneration of the corticospinal system is of crucial importance for the restoration of voluntary motor function after injury in both human and nonhuman primates, whereas rodents are capable of driving a broad repertoire of motor activities completely independent of a functional corticospinal circuit [138]. Recently, it has been demonstrated that some of the spontaneous functional recovery seen after injury in humans may have a correlate in nonhuman primates at both the behavioral level, and perhaps more significantly at the neuroanatomical level, at which the primate corticospinal tract exhibits remarkable spontaneous sprouting after incomplete SCI [10]. As in rodents, neurotrophins can reduce atrophy of corticospinal neurons following injury in nonhuman primates, yet it remains to be seen whether neurotrophins can enhance the endogenous plasticity of corticospinal axons in primates [101].

As with any potential therapy, the off-target effects of neurotrophin treatment must be considered. Intracerebroventricular infusion of NGF to treat Alzheimer's disease was halted in a trial of 3 individuals due to the induction of pain and weight loss during the course of treatment [139]. In this case, the induction of neuropathic pain and the effects on the hypothalamus were consistent with the pre-clinical literature on intracerebroventricular infusion of NGF [140]. Many of the off-target effects of neurotrophin treatment can be avoided through targeted delivery of neurotrophins through *ex vivo* cell therapy or localized expression by viral transduction, as used in many of the studies previously described [140].

Conclusion

Neurotrophins have been used to both induce axon growth and prevent atrophy and death of a number of distinct

neuronal populations after adult SCI. Cellular responses to neurotrophin stimulation likely depend on the intrinsic modulation of receptor expression and trafficking, as well as control of growth-associated genetic programs. As these responses change, along with the maturation of the nervous system, an understanding of the associated developmental changes may lead to future strategies to promote functional regeneration. Importantly, injury studies have shown discrepancies in the response to SCI between rodents and primates; this demonstrates that in some cases successful translation of regeneration strategies may be optimized by primate or other larger animal studies. Administration of growth factors is likely to constitute an important component of future combinatorial treatment strategies for SCI.

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