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INVITED REVIEW

PTEN inhibition and axon regeneration and neural repair

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Abstract

The intrinsic growth ability of all the neurons declines during development although some may grow better than others. Numerous intracellular signaling proteins and transcription factors have been shown to regulate the intrinsic growth capacity in mature neurons. Among them, PI3 kinase/Akt pathway is important for controlling axon elongation. As a negative regulator of this pathway, the tumor suppressor phosphatase and tensin homolog (PTEN) appears critical to control the regenerative ability of young and adult neurons. This review will focus on recent research progress in axon regeneration and neural repair by PTEN inhibition and therapeutic potential of blocking this phosphatase for neurological disorders. Inhibition of PTEN by deletion in conditional knockout mice, knockdown by short-hairpin RNA, or blockade by pharmacological approaches, including administration of selective PTEN antagonist peptides, stimulates various degrees of axon regrowth in juvenile or adult rodents with central nervous system injuries. Importantly, post-injury PTEN suppression could enhance axonal growth and functional recovery in adult central nervous system after injury.

Key Words: *PTEN inhibition; antagonist peptide; spinal cord injury; intrinsic growth capacity; axon regeneration; functional recovery*

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Introduction

Following central nervous system (CNS) injuries, the incapability of axons to regenerate is due to the combination of a non-permissive extrinsic CNS environment (McGee and Strittmatter, 2003; Liu et al., 2006; Busch and Silver, 2007) and a loss of intrinsic regenerative ability during development (Goldberg et al., 2002; Lu et al., 2014). A great number of studies identified various cell types and molecules that inhibit neuronal elongation in adult CNS. The components of CNS myelin, glial scar tissues and certain guidance cues inhibit axon elongation and partially contribute to the CNS regeneration failure. Removing or blocking inhibitory activities of negative molecules, such as myelin or scar associated inhibitors, induces limited degree of axon regeneration *in vivo*. On the other hand, the intrinsic growth ability of all the neurons declines during development although some neuronal types may grow better than others. Numerous factors could regulate the intrinsic growth capacity, including certain transcription factors, such as cAMP-responsive element binding protein (CREB), signal transducer and activator of transcription 3 (STAT3), nuclear factor of activated T cell (NFAT), c-Jun activating transcription factor 3 (AFT3) and Krüppel-like factors (KLFs), and intracellular signaling proteins, such as PI3 kinase, Akt, phosphatase and tensin homolog (PTEN), suppressor of cytokine signaling 3 (SOCS3), B-RAF, dual leucine zipper kinase (DLK), and insulin/insulin-like growth factor-1 (IGF-1) signaling (Moore and Goldberg, 2011; Byrne et al., 2014; Lu et al., 2014). Although targeting each of these signals could enhance axon growth (Moore and Goldberg, 2011), deletion of the tumor suppressor PTEN in conditional knockout (KO) mice appears to result in most dramatic regrowth of CNS axons after injuries (Park et al., 2008; Liu et al., 2010), suggesting that PTEN/mammalian target of rapamycin (mTOR) signaling is critical to regulate the intrinsic regenerative ability of young and adult neurons (**Figure 1**) (Park et al., 2010; Lu et al., 2014). Further studies on PTEN knockdown by short-hairpin RNA (shRNA) or blockade by pharmacological approaches demonstrate various degrees of axon regrowth in adult rodents with CNS injuries (Zukor et al., 2013; Lewandowski and Steward, 2014; Ohtake et al., 2014). This review will update recent research progress in axon regeneration and neural repair by PTEN inhibition (**Table 1**) and discuss the therapeutic potential of blocking this phosphatase for neurological disorders.

PTEN Deletion and CNS Regeneration and Neural Repair

PI3K/Akt pathway plays a critical role in regulating axon formation and extension (Zhou and Snider, 2006). Expression of

Table 1 Summary of PTEN inhibition on axon growth and neuroprotection

Reference	Approach	Model	Major finding
Chadborn et al. (2006)	Expression of dominant negative PTEN	Chick dorsal root ganglion explant	Antagonize Sema3A-induced growth cone collapse
Park et al. (2008)	Deletion by intravitreal AAV Cre injection into conditional knockout neonates	Optic nerve crush injury	Enhance RGC survival and axon regeneration of injured optic nerve axons
Drinjakovic et al. (2010)	Down-regulation by overexpressing Nedd4 protein	Embryonic Xenopus RGC cultures	Increase RGC axon branching
Ning et al. (2010)	siRNA or AAV-siRNA	Purified motor neuronal cultures and SMN-deficient mice	Increase growth cones size *in vitro* and motor neuron survival *in vitro* and *in vivo* in SMN-deficient mice
Christie et al. (2010)	siRNA or bpV	Sciatic nerve transection	Enhance PNS axon growth independent of mTOR pathway
Liu et al. (2010)	Deletion by AAV Cre injection into the sensorimotor cortex in neonates or juvenile mice	Dorsal transection and crush spinal cord injury at T_8	Robust corticospinal tract regeneration into the caudal spinal cord
Kurimoto et al. (2010)	Deletion by intravitreal AAV Cre injection combined with oncomodulin and cAMP treatments	Optic nerve crush injury in conditional knockout mice	Induce long-distance optic axon regeneration
Sun et al. (2011)	Deletion of PTEN and SOCS3 by intravitreal AAV Cre injections into neonates	Optic nerve crush injury in single or double knockout mice	Double deletion induces robust and sustained axon regeneration
Walker et al. (2012)	Systemic bpV starting post injury in adult rats	Cervical unilateral contusive spinal cord injury	Activate Akt/mTOR, reduce autophagy and enhance recovery
Zhang et al. (2012)	Deletion in dopamine neurons	Transplantation into dopamine-depleted striata in MitoPark mice	PTEN-deleted dopamine neurons become less susceptible to cell death and have increased axon outgrowth
de Lima et al. (2012)	Deletion combined with Zymosan and CPT-cAMP treatments	Optic nerve crush injury in conditional knockout mice	Induce long-distance axon regeneration and partial functional recovery
Zukor et al. (2013)	AAV shRNA applied to sensorimotor cortex in neonates	Crush spinal cord injury at T_8 (induced 6–8.5 week old mice)	Enhance regeneration of corticospinal tract axons into the caudal spinal cord using reactive astrocytes as bridging tissue
Inoue et al. (2013)	Deletion of PTEN and Atg-7	Midbrain dopamine neurons in knockout mice	Deletion of both PTEN and Atg7 further enlarges size of axon terminals
Zhao et al. (2013)	Pretreatment with bpV	Oxygen-glucose deprivation in cultured rat cortical neurons	Reduce neuronal apoptosis and enhance vesicle recycling in axons
Mao et al. (2013)	One-day delayed bpV treatments for 14 days	Middle cerebral artery occlusionin adult mice	Not alter infarction size in acute phase, but enhance long-term functional recovery
Ohtake et al. (2014)	Selective antagonistpeptides targeting PTEN functional domains	Dorsal over-transection spinal cord injury at T_7 in adult mice	Promote remarkable 5-hydroxytryptamine axon regrowth and moderate corticospinal tract regrowth, and significant locomotor recovery
Singh et al. (2014)	Knockdown with siRNA	Crush injury of neuropathic sciatic nerves in chronic diabetic models	Improve axon regeneration and conduction function
Lewandowski and Steward (2014)	Pre-injury injections of AAV shRNA into sensorimotor cortex, with/without delivery of salmon fibrin into the injury site	Cervical dorsal hemisection spinal cord injury in rats	PTEN knockdown combined with salmon fibrin injection into the lesion site enhances corticospinal tract growth and motor function, but not AAV shRNA alone
O'Donovan et al. (2014)	Deletion by intravitreal AAV Cre injections combined withoverexpression of activated B-RAF in transgenic mice	Optic nerve crush injury	PTEN deletion plus expression of activated B-RAF promotes additional optic nerve axon regeneration
Walker and Xu (2014)	Post-injury systemic bpV treatments	Cervical hemi-contusion spinal cord injury	Reduce tissue damage, neuron death, and promote functional recovery
Byrne et al. (2014)	PTEN mutants	Young and aged C. Elegans	Loss of PTEN (daf-18) increases regeneration in aged C. Elegans

PTEN: Phosphatase and tensin homolog; AAV: adeno-associated virus; siRNA: small interfering RNA; bpV: bisperoxovanadium; SMN: survival of motor neuron; RGC: retinal ganglion cells; PNS: peripheral nervous system; mTOR: mammalian target of rapamycin; shRNA: short-hairpin RNA; SOCS3: suppressor of cytokine signaling 3; CPT: chlorophenylthio; B-RAF: B-Raf proto-oncogene.

constitutively active Akt in embryonic chick dorsal root ganglion (DRG) neurons increases axon branching, cell hypertrophy and growth cone expansion (Grider et al., 2009). Overexpression of active Akt by adeno-associated virus (AAV) vector remarkably promotes regrowth and reinnervation of lesioned dopaminergic axons and partial behavioral recovery *in vivo* (Kim et al., 2011). Activating Akt signaling also enhances axon regeneration of Drosophila CNS neurons (Song et al., 2012).

Given that PTEN negatively mediates Akt activity by dephosphorylating phosphoinositide substrates, PTEN

suppression is likely to increase axon growth by enhancing activity of PI3K/Akt signaling. Recent studies on neuronal PTEN inactivation by transgenic deletion demonstrate enhanced regeneration of lesioned CNS axons. Intravitreal injection of AAV Cre recombinase enhanced survival of retinal ganglion cells (RGCs) and promoted considerable regeneration of injured optic nerve axons in juvenile mice (Park et al., 2008). Deletion of PTEN by injection of AAV-Cre into the sensorimotor cortex in conditional KO mice induces substantial regrowth of lesioned corticospinal tract (CST) axons and formation of synapse-like structures in the caudal spinal cord of juvenile or adult mice with spinal cord injury (SCI) (Liu et al., 2010). Because treatment with rapamycin, an mTOR inhibitor, abolishes the growth promoting-effect of PTEN deletion (Park et al., 2010), mTOR activation appears critical to control axon growth downstream of PTEN. Simultaneous deletion of PTEN and SOCS3, a negative regulator of Janus kinase (JAK)/STAT pathway, results in more robust and sustained axon regeneration, suggesting that two proteins regulate regenerative programs through distinct mechanisms (Sun et al., 2011). PTEN and SOCS3 double deletion upregulates mTOR activators, such as small GTPaseRheb and IGF-1, in injured RGCs. PTEN deletion combined with overexpression of an active form of B-RAF kinase, a known signal downstream of neurotrophic factors, stimulates additive regeneration of lesioned optic axons (O'Donovan et al., 2014). In addition, simultaneous deletion of PTEN with autophagy-related protein 7 (Atg7), which regulates vacuole transport and autophagy in cytoplasm, increases axon terminal enlargement in midbrain dopamine neurons compared to Atg7 deletion alone (Inoue et al., 2013). Transplanted PTEN-deficient dopamine neurons into mice with Parkinson's disease models were less susceptible to cell death and extended longer axons than control grafts (Zhang et al., 2012). Together, PTEN appears important to restrict regeneration of mature neurons and its inactivation may have therapeutic potential for CNS disorders characterized by axonal damages.

PTEN Knockdown with shRNA and CNS Regeneration

shRNA makes a tight hairpin turn and is frequently used to silence target gene expression by RNA interference. Injections of AAV vector encoding shRNA-PTEN into the motor cortex in neonatal mice significantly reduced expression of PTEN protein and enhanced levels of phosphorylated S-6 kinase, a downstream signal of mTOR in neurons (Zukor et al., 2013). Injections of viral shRNA-PTEN into the sensorimotor cortex of neonates could sufficiently enhance the intrinsic growth of CST neurons and induce CST regrowth in the caudal spinal cord of mice with a crush injury at T_8 (induced at 6–8.5 weeks old). Some CST axons crossed the lesion area using reactive astrocytic tissues as the bridging tissue although CST sprouts avoided dense clusters of fibroblasts and macrophages around the lesion. The other group generated a similar viral shRNA-PTEN and efficiently knocked down PTEN protein (Lewandowski and Steward, 2014). Injection of AAV shRNA-PTEN into the motor cortex in adult rats 1 week before a dorsal hemisection injury at C_6 did not significantly promote CST regrowth in the caudal spinal cord and locomotor function recovery although some biotinylated dextran amine (BDA)-traced CST axons reached the lesion edge in shRNA-PTEN treated animals. However, shRNA-PTEN plus delivery of salmon fibrin into the injury area significantly increased the number of BDA-labeled CST axons in the caudal spinal cord and forelimb-reaching scores.

Together, PTEN knockdown by pre-injury injection of shRNA stimulates regrowth of injured CST axons in SCI mice, but it has minimal effect in SCI rats. PTEN inhibition combined with other strategies, such as those targeting other intracellular signals or extrinsic factors responsible for regeneration failure, may become more efficient for promoting axon elongation. Notably, it is very important to study whether knockdown of PTEN by viral shRNA-PTEN delivered post-injury stimulates axon regrowth and improves functional recovery after CNS injury because the pre-injury viral vector applications used in previous studies are not clinically translational.

Pharmacological PTEN Inhibition and Neuroprotection and Axon Regeneration

PTEN genetic deletion in KO mice and knockdown by pre-injury injection of shRNA are not feasible for clinical treatment. In contrast, suppression of PTEN by a pharmacological method is highly controllable in initiation time, application period and drug dosage. Bisperoxovanadium (bpV) compounds are inhibitors of several protein tyrosine phosphatases (PTPs) with selectivity for PTEN (IC50 = ~40 nM), but also block other PTPs (such as PTPβ) at higher nM levels. bpV treatment is neuroprotective after different CNS injuries. Systemic bpV initiated immediately after injury (for 7 days), increased spared white matter at the lesion area, numbers of oligodendrocytes and motor neuron area, and improved functional recovery in rats with contusive cervical SCI (Walker et al., 2012; Walker and Xu, 2014). bpV enhanced axon outgrowth of primary cortical neuronal cultures following oxygen-glucose deprivation. Although 1-day delayed treatment with bpV (for 14 days) did not reduce infarction size in mice with middle cerebral artery occlusion in acute stage, they significantly improved long-term functional recovery after ischemia (Mao et al., 2013). Thus, post-injury bpV treatments exhibit beneficial effects on recovery after CNS injuries although the molecular basis for bpV actions is less clear because bpVs target other PTPs as well as PTEN.

Suppressing PTEN activity is very promising for promoting CNS axon regeneration and neural repair, but transgenic approaches used in previous studies block PTEN before injuries and only target a single neuronal population by local injections of AAV-Cre/AAV-shRNA, not the diffusely-dispersed neurons, such as 5-hydroxytryptamine (5-HT) neurons or propriospinal interneurons known to contribute to functional recovery after SCI (Barbeau and Rossignol, 1991; Ribotta et al., 2000; Li et al., 2004; Courtine et al., 2008). Application of bpV may block PTEN action (Christie et al., 2010), but bpV may result in clinical side effects by interacting with

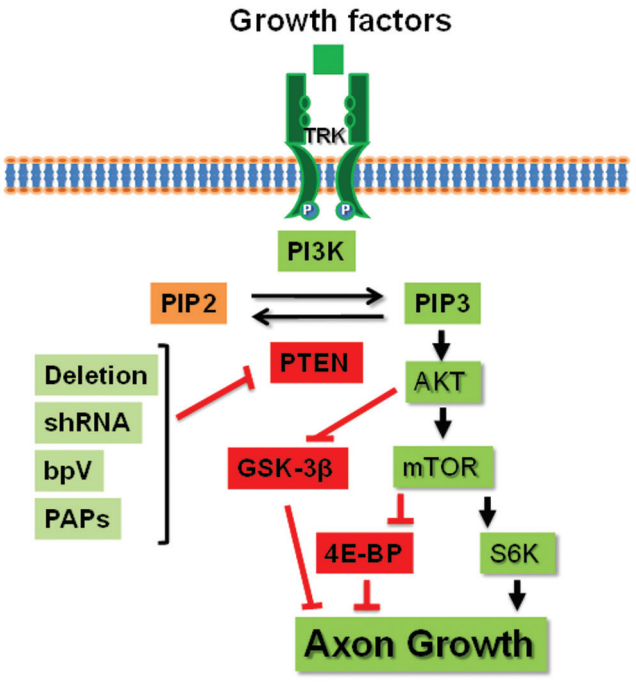

Figure 1 Schematic of Akt/PTEN pathway that regulates neuronal growth and axon regeneration by PTEN inhibition.
Various growth factors, such as nerve growth factor, activate their receptors (especially the tyrosine receptor kinases (TRK)) and PI3K pathway and stimulate neuronal growth by enchaining mTOR activity and suppressing GSK-3β signal. In contrast, intracellular PTEN phosphatase blocks axon growth by inactivating Akt signal and mTOR pathway. PTEN inhibition by a number of approaches, including deletion in knockout (KO) mice, knockdown by shRNA, or pharmacological blockade with phosphatase inhibitor bpV or selective antagonists PTEN antagonist peptides, promotes neuronal regeneration.
PTEN: Phosphatase and tensin homolog; 4E-BP: 4E-binding protein; bpV: bisperoxovanadium; PIP2: phosphatidylinositol 4,5-bisphosphate; PIP3: phosphatidylinositol 3,4,5 trisphosphate; PI3K: phosphoinositide 3-kinase; GSK-3β: glycogen synthase kinase 3β; S6K: S6 kinase; PAPs: PTEN antagonist peptides.

other PTPs (Scrivens et al., 2003), such as lowering blood glucose by activating insulin signaling (Drake and Posner, 1998). It is important to develop a pharmacological method to suppress PTEN activity efficiently and selectively. We recently identified selective antagonist peptides for PTEN by targeting its critical functional domains, including PIP2, ATP-type, PDZ and C-terminal tail domains (Ohtake et al., 2014). We demonstrated that those PTEN antagonist peptides (PAPs) bound COS7 cells that over-expressed PTEN protein, promoted neurite outgrowth *in vitro* and blocked several signals downstream of PTEN. Systemic PAP treatments by subcutaneous delivery (initiated 2 days after injury, 2-week treatment) stimulated regrowth of descending serotonergic axons in the caudal spinal cord of adult mice with dorsal over-hemisection at T7. Systemic PAPs also enhanced sprouting of CST axons rostral to the lesion and limited regrowth of CST axons in the caudal spinal cord. Importantly, systemic PAPs enhanced recovery of locomotor function several weeks after SCI by increasing BMS locomotor scores and stride length of hindlimbs and reducing grid walk errors. Thus, systemic delivery of small peptides after injury selectively blocks PTEN activity and promotes regrowth of injured multiple CNS axonal tracts. The peptide approach shows benefits in several areas where the transgenic (such as KO) and invasive approaches (such as local chondroitinase and transplants) are highly deficient and may thus facilitate development of a successful therapy for CNS axonal injuries. Constantly, our other studies demonstrated great therapeutic potential of small peptides that selectively block other axon growth inhibitory molecules (GrandPre et al., 2002; Li and Strittmatter, 2003; Fisher et al., 2011).

PTEN Suppression and Peripheral Nervous System (PNS) Regeneration and Axon Myelination

PNS axons exhibit remarked regrowth after injuries, but their regeneration may not be optimal and many patients suffer from long-term or persistent functional impairment after PNS axon lesions, including motor and sensory loss, chronic pain and inappropriate autonomic responses. PTEN is expressed in PNS neurons (such as DRGs) and contributes to their growth cone collapse and reduced axon growth (Chadborn et al., 2006). PTEN knockdown enhanced regeneration of lesioned sciatic nerve and a preconditioning lesion exhibited an additive effect. PTEN knockdown by bpV treatment or local delivery of siRNA accelerated sciatic axon outgrowth *in vivo* (Christie et al., 2010). PTEN also restricts PNS regeneration in mouse models of diabetes. Following crush of neuropathic sciatic nerves in diabetes models, local delivery of PTEN short interfering RNA increased the number of regenerating myelinated axons distal to injury site, promoted reinnervation of skin by unmyelinated epidermal axons and contributed to recovery of mechanical sensation. Inhibition of PTEN or activation of PI3K enhances growth of DRG neurons probably by mTOR-independent mechanisms because they respond to GSK-3β (also a downstream signal of PI3K) and transcription factor Smad1, but not to mTOR blockade by rapamycin (Zou et al., 2009; Christie et al., 2010; Hur et al., 2011).

PTEN and PI3K activities also regulate function of oligodendrocytes and Schwann cells and myelination during development. PTEN deletion enhanced the numbers of Schwann cells and myelinated small axons with caliber < 1 μm. PTEN deletion in oligodendrocytes induced PIP3-dependent hypermyelination of CNS axons (Goebbels et al., 2010). Interactions between PTEN and trafficking protein Dlg1 (disks large homolog 1) are able to inhibit axonal myelination and this mechanism limits myelin sheath thickness and prevents over-myelination in mouse sciatic nerves (Cotter et al., 2010).

Molecular Targets that Regulate Axon Regeneration along Akt Pathway

Following stimulation by various extracellular growth factors, activation of the receptor tyrosine kinase and/or G-protein coupled receptor activates PI3K and subsequently Akt by increasing the generation of PIP3. Activated Akt phosphorylates tuberous sclerosis protein complex (TSC) and inhibits its activity. Through enhancing Rheb activity, suppression of TSC increases the levels of activated mTOR (Park et al.,

2010; Walker et al., 2013), which phosphorylates ribosomal protein p70S6 kinase and 4E binding protein-1 (4E-BP1) and regulatesprotein synthesis and cell growth (Proud, 2002). In particular, phosphorylated p70S6K enhances phosphorylation and activity of ribosomal protein S6 and initiates various translation activities required for cell growth. Phosphorylation of 4E-BP1 reduces its activity and its inhibition on protein synthesis and thus promotes neuronal elongation. Moreover, Akt activation critically regulates GSK-3β signaling by phosphorylating this kinase (at serine 9) and subsequently inactivating it (**Figure 1**) (Cross et al., 1995). Localized GSK-3β inactivation is required for establishing and maintaining neuronal polarity (Jiang et al., 2005; Yoshimura et al., 2005). GSK-3β inactivation at growth cone is able to stimulate axon formation and extension and to convert dendritic processes into axons in polarized neurons. Consistently, GSK-3β inhibitors enhance neurite outgrowth *in vitro* and regrowth of injured axons after CNS injury (Zhou et al., 2004; Zhou and Snider, 2005; Dill et al., 2008). Therefore, GSK-3β suppression at growth cone is essential for promoting microtubule assembly in axons (Zhou and Snider, 2006; Hur and Zhou, 2010) although inhibiting GSK-3β may also block axon growth (Alabed et al., 2010; Gobrecht et al., 2014). A further study suggests that GSK-3β inhibition can both enhance and prevent axon growth depending on the substrates involved, enhancing axon elongation if towards primed substrates (such as CRMP2 and adenomatous polyposis coli) and preventing axon growth if toward unprimed substrates (such as microtubule-associated protein 1B) (Kim et al., 2006; Hur and Zhou, 2010). Therefore, GSK-3β activity should be finely tuned to stimulate axon regeneration, including its reduced activity towards one subset of substrates and preserved activity towards other substrates.

Prospective

PI3K/Akt/PTEN pathways play critical roles in regulating neural development and PTEN suppression may have great potential for promoting CNS axon regeneration and neural repair. Many unknown issues and challenges, however, remain regarding PTEN-mediated growth inhibition and its translating potential to clinical applications. Several neuronal populations are known to be sensitive to PTEN blockade, including RGC, CST, 5-HT and DRGs. Do the other types of neurons similarly respond to PTEN inhibition? PTEN is present in both neuronal soma and axonal compartment during axon extension (including the growth cones) (Chadborn et al., 2006). Does PTEN activation in both subcellular structures mediate axon elongation? Sustained and long-distance axon regeneration is crucial for meaningful functional recovery after many CNS injuries, including SCI and optic neuropathy. PTEN deletion induces remarkable axon elongation, but axon regrowth is usually limited to < 1 mm from the lesion. PTEN suppression combined with other strategies, such as regulating inflammatory responses and activities of other signaling pathways (such as SOCS3/STAT/Erk) or transcriptional factors (such as KLFs and CREB), as well as surmounting scar-mediated inhibition, may induce more robust and distant axon regeneration. Obviously, post-injury intervention of PTEN by pharmacological approaches, including selective blockade by small peptides, is promising and highly relevant to future translation into human use. Targeting PTEN-regulating molecules, such as certain miRNAs and E3 ubiquitin protein ligase Nedd4, may also become alternatives for attenuating PTEN activity and promoting CNS regeneration. Because adult CNS appears to lack adequate guidance cues present during neurodevelopment, regulation of growing axons to make direct or indirect connections with their original targets appears also important for promoting functional recovery after axonal injuries (Luo et al., 2013). Moreover, task-specific rehabilitative training is probably required for rewiring appropriate neuronal circuits and reinforcing functionally meaningful synaptic reconnections.

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