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Axon Regeneration in the Peripheral and Central Nervous Systems

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Abstract

Axon regeneration in the mature mammalian central nervous system (CNS) is extremely limited after injury. Consequently, functional deficits persist after spinal cord injury (SCI), traumatic brain injury, stroke, and related conditions that involve axonal disconnection. This situation differs from that in the mammalian peripheral nervous system (PNS), where long- distance axon regeneration and substantial functional recovery can occur in the adult. Both extracellular molecules and the intrinsic growth capacity of the neuron influence regenerative success. This chapter discusses determinants of axon regeneration in the PNS and CNS.

1 Introduction

Central nervous system (CNS) axons do not spontaneously regenerate after injury in adult mammals. In contrast, peripheral nervous system (PNS) axons readily regenerate, allowing recovery of function after peripheral nerve damage. Aguayo and colleagues demonstrated that at least some mature CNS neurons retain the capacity to regenerate when provided with a permissive peripheral nerve graft (Richardson et al. 1980, 1984; David and Aguayo, 1981; Benfey and Aguayo, 1982). This work suggested that the PNS environment is stimulatory and/or that the CNS environment is inhibitory for axon growth. Subsequent studies identified both growth- promoting factors in the PNS and growth- inhibiting factors in the CNS. Inhibitors of regeneration include specific proteins in CNS myelin and molecules associated with the astroglial scar. In addition, slower debris clearance in the CNS relative to the PNS may impede axonal re-growth. The cell-autonomous failure of the cell of axotomized CNS neurons to induce those growth- promoting genes, which are highly upregulated by injured PNS neurons also limits brain and spinal cord repair. An understanding of factors which influence axon growth is critical for the development of therapeutics to promote CNS regeneration.

2 Axon Regeneration in the Peripheral Nervous System

2.1 Overview of Peripheral Nervous System Regeneration

After peripheral nerve injury, axons readily regenerate. The distal portion of the axon, which is disconnected from the cell body, undergoes Wallerian degeneration. This active process results in fragmentation and disintegration of the axon. Debris is removed by glial cells, predominantly macrophages. Proximal axons can then regenerate and re-innervate their targets, allowing recovery of function.

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2.2 Regeneration-Associated Genes

Following axotomy, PNS neurons upregulate numerous regeneration-associated genes (RAGs). Some of these genes have a direct role in axon regeneration, while others do not. A number of RAGs have been shown to be important for neurite outgrowth and/or regeneration. These include c-Jun (Raivich et al. 2004), activating transcription factor-3 (ATF-3) (Seijffers et al. 2006), SRY-box containing gene 11 (Sox11) (Jankowski et al. 2009), small proline-repeat protein 1A (SPRR1A) (Bonilla et al. 2002), growth-associated protein-43 (GAP-43) and CAP-23 (Bomze et al. 2001).

One strategy to identify RAGs involves injuring a peripheral nerve, and then observing gene expression changes in the corresponding cell bodies (Bonilla et al. 2002; Tanabe et al. 2003; Costigan et al. 2002). A number of such studies have used gene profiling technology to examine gene expression changes in sensory neurons following axotomy. For example, Bonilla et al. (2002) demonstrated that SPRR1A is highly induced in dorsal root ganglion (DRG) neurons one week after sciatic nerve transection (protein increased more than 60-fold from whole DRGs). Immunohistochemistry demonstrated expression of SPRR1A in DRG neuronal cell bodies and regenerating peripheral axons. SPRR1A expression is also increased after sciatic nerve injury in the ventral horn motor neuron cell bodies and sensory fibers within the spinal cord (Fig. 1). Herpes simplex virus-mediated overexpression of SPRR1A in embryonic chick DRG neurons promotes neurite outgrowth. The association of SPRR1A expression with regeneration and its ability to promote neurite outgrowth suggest that it may have a role in axon regeneration.

ATF-3 is a transcriptional factor induced in sensory neurons after injury (Tanabe et al. 2003; Boeshore et al. 2004). Over expression of ATF-3 promotes neurite outgrowth (Seijffers et al. 2006). Sox11 and c-Jun are injury-induced transcription factors and are required for efficient nerve regeneration (Jankowski et al. 2009; Raivich et al. 2004). Transcriptional factors associated with regeneration, such as c-Jun, appear to induce the expression of other RAGs and thereby may promote a growth state (Raivich et al. 2004).

3 Axon Regeneration in the Central Nervous System

3.1 Overview of Central Nervous System Regeneration

Pioneering work by Aguayo and colleagues demonstrated that adult mammalian CNS neurons, which normally do not regenerate, are able to grow for long distances into the permissive environment of a peripheral nerve graft (Richardson et al. 1980, 1984; David and Aguayo 1981; Benfey and Aguayo 1982). These studies demonstrated that the environment is a critical determinant of axon regeneration. Subsequently, numerous molecules were identified within the CNS that limit regeneration.

The two major classes of CNS regeneration inhibitors are the myelin-associated inhibitors (MAIs) and the chondroitin sulfate proteoglycans (CSPGs). These molecules limit axon regeneration, and, by interfering with their function, some degree of growth in the adult CNS is achieved.

Cell-autonomous factors are also important determinants of CNS regeneration failure. CNS neurons do not upregulate growth-associated genes to the same extent as do PNS neurons. Consequently, their ability to regenerate is limited even in the absence of inhibitors. Increasing the intrinsic growth capacity of neurons allows modest axon regeneration within the CNS (Bomze et al. 2001; Neumann and Woolf 1999).

Axon regeneration is one of many factors influencing recovery after CNS damage. Sprouting of uninjured axons can also contribute dramatically to functional improvements. Additionally,

plasticity at the synaptic level may underlie a certain degree of recovery seen even in the absence of treatments (i.e., learning to use spared neuronal circuitry in new ways). CNS regeneration studies do not always distinguish between these different mechanisms, and, for the purpose of this discussion, they will be considered together. Replacement of lost neuronal cell bodies, a prominent component of many CNS disorders, is beyond the scope of this chapter.

3.2 Myelin-Associated Inhibitors

MAIs are proteins expressed by oligodendrocytes as components of CNS myelin. MAIs impair neurite outgrowth in vitro and are thought to limit axon growth in vivo after CNS damage. MAIs include Nogo-A (Chen et al. 2000; GrandPre et al., 2000), myelin-associated glycoprotein (MAG) (McKerracher et al., 1994), oligodendrocyte myelin glycoprotein (OMgp) (Kottis et al. 2002), ephrin-B3 (Benson et al. 2005) and Semaphorin 4D (Sema4D) (Moreau-Fauvarque et al. 2003). Three of these (Nogo-A, MAG and OMgp) interact with a neuronal Nogo-66 receptor 1 (NgR1) to limit axon growth. These three structurally unrelated ligands also show affinity for a second axon growth-inhibiting receptor, paired immunoglobulin-like receptor B (PirB) (Atwal et al. 2008). For the most part, MAIs are not found in PNS myelin, which is produced by Schwann cells rather than oligodendrocytes. An exception is MAG, which is present in PNS myelin but is cleared much more rapidly by glial cells in the periphery than in the brain and spinal cord.

One of the most well- characterized MAIs is Nogo-A. Genetic deletion of Nogo-A promotes corticospinal (Fig. 2) and raphespinal tract growth and enhances functional recovery after SCI, although this phenotype is modulated by strain background, age and axonal tract (Kim et al. 2003b;Simonen et al. 2003;Zheng et al. 2003;Dimou et al., 2006). Even after controlling for these factors, certain targeted mutations create a greater axon growth response than others (Cafferty et al. 2007b). However, even the least growth-promoting mutation of the Nogo gene has an enhanced growth phenotype after pyramidotomy (Cafferty and Strittmatter 2006). In addition, antibodies that target Nogo-A promote axonal growth and functional recovery after CNS injury (Z'Graggen et al., 2000;Wiessner et al. 2003;Seymour et al. 2005). An anti-Nogo-A antibody has advanced to clinical trials for SCI.

Two inhibitory portions of Nogo-A have been identified. The first, termed Nogo-66, is a 66 amino acid fragment which interacts with NgR1 on the neuronal membrane (Fournier et al. 2001). An adjacent 24 amino acid sequence, although not inhibitory in itself, facilitates picomolar-affinity binding of the Nogo-66 to NgR1 (Hu et al. 2005). The Nogo-66 domain can also interact directly with a secondary receptor, PirB, on the surface of neurons (Atwal et al. 2008). The other inhibitory portion of Nogo-A Amino-Nogo, acts via an independent mechanism to disrupt neuronal integrin function (Hu and Strittmatter 2008).

Two other Nogo isoforms exist (Nogo-B and Nogo-C), which contain the inhibitory Nogo-66 loop found in Nogo-A but lack the Amino-Nogo sequence. These isoforms are not found naturally in myelin, but transgenic overexpression of Nogo-C in Schwann cells, which normally do not express any Nogo isoform, delays peripheral nerve regeneration. This demonstrates the ability of Nogo-66 to limit axon regeneration in vivo (Kim et al. 2003a).

MAG is another inhibitory protein present in CNS myelin (McKerracher et al., 1994). MAG interacts with several neuronal receptors to limit neurite outgrowth in vitro, including NgR1 (Liu et al. 2002; Domeniconi et al. 2002), gangliosides (Vyas et al. 2002; Mehta et al. 2007), Nogo receptor 2 (NgR2) (Venkatesh et al. 2005) and PirB (Atwal et al. 2008). The relative importance of each receptor varies with neuronal type. For example, in postnatal DRG neurons, NgR1 mediates the majority of inhibition by MAG, whereas in postnatal cerebellar granule neurons, GT1b appears to be more important (Mehta et al. 2007). Although MAG inhibits neurite outgrowth in vitro, no evidence of enhanced corticospinal tract (CST) regeneration or

sprouting after SCI or optic nerve injury is observed in MAG knockout mice (Bartsch et al. 1995). Thus, MAG appears to have a less important role in limiting CNS axon growth than other inhibitors such as Nogo-A.

OMgp, another MAI that interacts with NgR1 and PirB, also limits neurite outgrowth in vitro (Kottis et al. 2002). CNS regeneration studies with OMgp knockout mice have not been described.

NgR1 is a glycosylphosphatidylinositol (GPI)-linked membrane receptor, which lacks a transmembrane or cytoplasmic domain. It interacts with coreceptors LINGO-1 (Mi et al. 2004) and p75 (Wang et al, 2002) or TAJ/TROY (Park et al. 2005; Shao et al. 2005), depending on neuronal type, to limit axon growth. Enhanced rubrospinal and raphespinal, but not corticospinal, axon regeneration is observed in NgR1 knockout mice after SCI (Kim et al. 2004). The enhanced axonal growth is correlated with improved functional recovery. Although CST regeneration is not observed after SCI in mice lacking NgR1, corticofugal axons do show enhanced growth in these mice after a stroke (Li et al. 2004) or pyramidotomy (Cafferty and Strittmatter 2006). Thus, NgR1 limits axonal growth and functional recovery after CNS damage.

NgR1 function can be blocked by a soluble form of extracellular NgR1 fused to human Fc (NgR(310)ecto-Fc). NgR(310)ecto-Fc promotes corticospinal and raphe-spinal growth and functional recovery after SCI in rats (Li et al. 2004). In addition, transgenic mice which secrete NgR(310)ecto under control of the GFAP promoter (causing reactive astrocytes to secrete high levels of the protein after CNS injury) show enhanced functional recovery after SCI (Li et al. 2005).

A competitive NgR1 antagonist, Nogo-extracellular peptide, residues 1–40 (NEP1-40), binds to, but does not activate, NgR1. NEP1-40 attenuates inhibition of neurite outgrowth by Nogo-A and CNS myelin. After SCI, NEP1-40 promotes corticospinal and raphespinal regeneration and functional recovery, even when the initiation of treatment is delayed for one week (GrandPre et al., 2002; Li and Strittmatter, 2003). Because NEP1-40 blocks Nogo-66, but not other NgR1 ligands, it is less effective than NgR(310)ecto-Fc.

The studies described above confirm the importance of NgR1 and its ligands in limiting CNS regeneration. In vivo functional studies of other MAI receptors have not yet been reported.

3.3 Chondroitin Sulfate Proteoglycans

The astroglial scar, which forms after CNS injury, is a physical barrier to regeneration, and also contains inhibitory molecules that impede axon growth. CSPGs are the main inhibitory molecules found in the glial scar (reviewed in Morgenstern et al. 2002). CSPGs are upregulated by reactive astrocytes after CNS damage and are both membrane bound and secreted into the extracellular space. Members of this class of inhibitors include neurocan (Asher et al. 2000), versican (Schmalfeldt et al., 2000), brevican (Yamada et al. 1997), phosphacan (Inatani et al. 2001), aggrecan (Carmen et al. 2007) and NG2 (Dou and Levine, 1994). A receptor for CSPGs has not been identified.

Interfering with CSPG function promotes axon regeneration in the CNS. CPSGs contain core proteins with attached glycosaminoglycan (GAG) side chains, which can be cleaved by the bacterial enzyme Chondroitinase ABC. This enzyme reduces the inhibitory activity of CSPGs in vitro (McKeon et al. 1995; Carmen et al. 2007). Moreover, when Chondroitinase ABC is administered after spinal contusion in rats, regeneration of both descending CST and ascending sensory fibers can be detected (Bradbury et al. 2002). This axonal growth is accompanied by enhanced recovery of associated locomotor and proprioceptive functions. Several other studies

have confirmed that Chondrotinase ABC promotes axonal growth after CNS injury (Barritt et al. 2006; Massey et al. 2006; Cafferty et al. 2007a).

3.4 Other Axon Regeneration Inhibitors

Axon regeneration inhibitors (ARIs) found in the CNS that are not present in myelin or the glial scar include repulsive guidance molecule (RGM) and semaphorin 3A (Sema3A). Evidence that these molecules limit CNS regeneration include studies demonstrating that an anti-RGMa antibody (Hata et al. 2006) or a small molecule inhibitor of Sema3A (Kaneko et al. 2007) promote functional recovery after SCI in rats.

3.5 Inhibitory Signaling Pathways

Multiple ARIs have been shown to activate the small GTPase ras homolog gene family, member A (RhoA) (Niederost et al. 2002; Fournier et al. 2003; Shao et al. 2005). Activated RhoA, in turn, activates Rho-associated coiled-coil containing protein kinase 2 (ROCK2), a kinase that regulates actin cytoskeletal dynamics (reviewed in Schmandke et al. 2007). Activation of ROCK2 results in cessation of neurite growth. Interfering with RhoA or ROCK2 activity promotes CNS axon regeneration and functional recovery.

Ibuprofen, which inhibits RhoA, promotes corticospinal and raphespinal sprouting after spinal contusion (Fu et al. 2007; Wang et al. 2009), as well as long- distance raphespinal axon regeneration after a complete spinal cord transection (Wang et al. 2009). Tissue sparing at the lesion site is also enhanced by ibuprofen and thus may contribute to functional recovery (Wang et al. 2009).

The ROCK2 inhibitor Y27632 promotes CST sprouting and locomotor recovery after dorsal hemi section spinal injury in rats (Fournier et al. 2003). In addition, ROCK2 knockout mice show enhanced functional recovery after SCI (Duffy PJ, Schmandke A, and Strittmatter SM, unpublished observations). Thus, ROCK2 is an important mediator of CNS regeneration failure.

Some evidence suggests that epidermal growth factor receptor (EGFR) contributes to CNS regeneration failure. One study demonstrated enhanced optic nerve regeneration after treatment with the irreversible EGFR inhibitor PD168393 (Koprivica et al. 2005). This study provides evidence that *trans-activation* of EGFR mediates inhibition of neurite outgrowth by MAIs and CSPGs. Another study observed that PD168393 enhances sparing, and/or regeneration of 5-hydroxytryptophan-immunoreactive (serotonergic) fibers caudal to a spinal cord lesion (Erschbamer et al. 2007). Thus, EGFR activation appears to limit recovery after CNS trauma.

Other molecules that have been implicated in ARI- signaling include protein kinase C, (Sivasankaran et al. 2004), LIM kinase, Slingshot phosphatase and cofilin (Hsieh et al. 2006).

3.6 Intrinsic Growth State of the Neuron

In contrast to the PNS, the upregulation of peripheral RAGs (see Sect. 2.2) is relatively modest in the CNS after injury (Fernandes et al. 1999; Marklund et al. 2006). This paucity of RAG expression appears to be partially responsible for the limited ability of CNS neurons to regenerate. Increasing RAG expression in CNS neurons improves their regenerative ability. For example, Bomze et al. (2001) demonstrated that overexpressing GAP-43 and CAP-23 together promotes sensory axon regeneration after SCI.

DRG neurons have a peripheral process and a central process. Injury to the peripheral process results in robust upregulation of RAGs, as described above. However, injury to the central process by dorsal rhizotomy or spinal cord dorsal hemi section does not induce nearly as robust

of a regenerative response, and central processes fail to regenerate in the CNS. Injury of peripheral axons one week prior to central injury (termed a conditioning lesion) allows some degree of sensory fiber regeneration within the spinal cord (Neumann and Woolf 1999). The conditioning lesion appears to enhance the growth state of the neuron such that its central process is able to regenerate in the CNS environment.

Cyclic adenosine monophosphate (cAMP) is a second messenger molecule which influences the growth state of the neuron. cAMP levels are increased by a peripheral conditioning lesion (Qiu et al. 2002). Elevation of cAMP levels by intra-ganglionic injection of a membrane-permeable cAMP analog, dibutyryl cAMP (db-cAMP), mimics the growth-promoting effects of a conditioning lesion, promoting regeneration of sensory axons within the spinal cord (Neumann et al. 2002; Qiu et al. 2002). In vivo injection of db-cAMP prior to DRG removal also improves the ability of dissociated DRG cultures to grow on MAG or CNS myelin in vitro, indicating that cAMP elevation can promote growth in the presence of MAIs (Qiu et al. 2002).

Rolipram, a phosphodiesterase 4 inhibitor, increases cAMP by interfering with its hydrolysis. When delivered 2 weeks after spinal cord hemisection, rolipram increases serotonergic axon regeneration into embryonic spinal tissue grafts implanted at the lesion site at the time of injury (Nikulina et al. 2004). Reactive gliosis is reduced by rolipram, and this might contribute to the functional recovery observed. Additionally, enhanced axonal sparing and myelination are induced by cAMP elevation in combination with Schwann cell grafts after SCI, compared to Schwann cell grafts alone (Pearse et al. 2004), suggesting additional mechanisms by which cAMP elevation could lead to functional improvements. Nonetheless, the demonstration of serotonergic axon growth into grafts at the lesion site in both of these studies indicates that cAMP elevation can induce CNS axon regeneration.

cAMP elevation activates protein kinase A (PKA) and induces CREB-mediated transcription of various growth-associated genes, including IL-6 and arginase I. Subsequent synthesis of polyamines by arginase I has been proposed as a possible mechanism by which cAMP increases neurite growth (Cai et al. 2002).

4 Conclusion

Regeneration of the injured mammalian CNS was once thought to be an unachievable goal. Recent advances in our understanding of factors which limit CNS regeneration and those which facilitate PNS regeneration have lead to therapies which allow some degree of recovery from brain and SCI in animal models. These findings open the possibility of promoting regeneration of the damaged human CNS.

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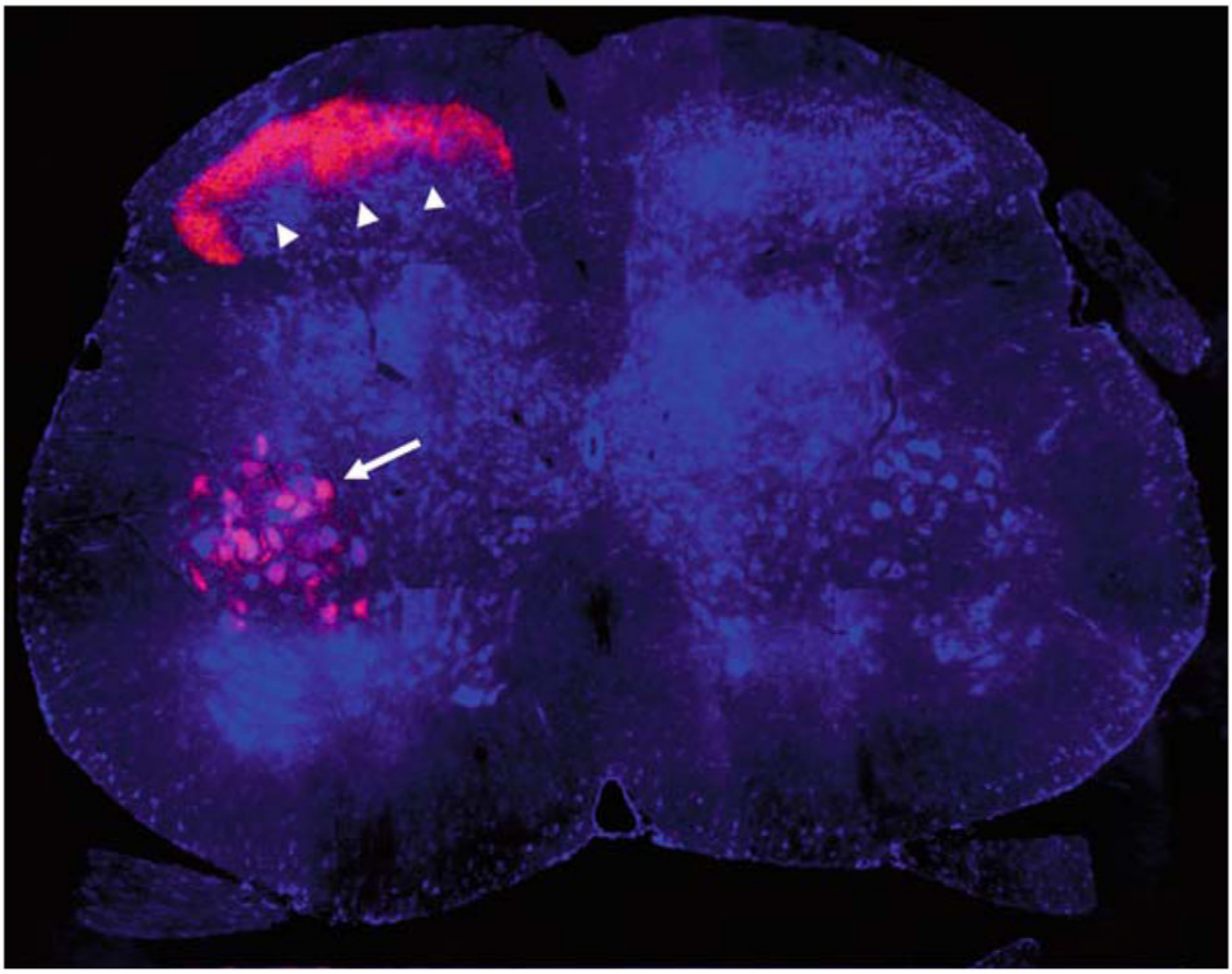

Fig. 1.

SPRR1A upregulation in the central process of primary afferent sensory neurons and in motoneurons after sciatic nerve injury. The sciatic nerve was crushed at the mid-thigh on one side of an adult mouse. Seven days later, the animal was sacrificed, and L5 spinal cord transverse sections were processed for anti-SPRR1A immunohistology (*red*) and for Nissl Stain (*blue*). Note the intense SPRR1A protein upregulation in afferent terminals in the dorsal horn (*arrowheads*) and in ventral horn motoneurons (*arrow*). Upregulation is confined to the injured side (*left*) with very low levels of SPRR1A on the intact side (*right*). Dorsal is *up*. Methods as in Bonilla et al. (2002). Image courtesy of Dr. William B. Cafferty

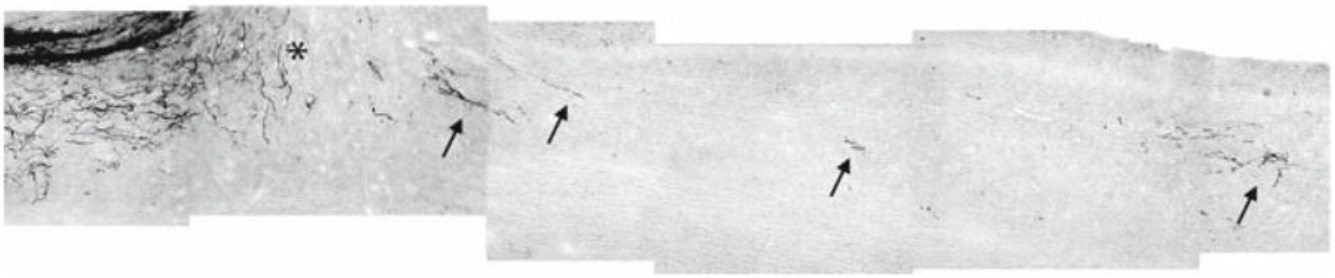

Fig. 2.

Corticospinal tract (CST) axonal tracing in mice lacking Nogo-A/B after mid-thoracic spinal cord dorsal hemisection. A parasagittal section of thoracic spinal cord from a mouse with a mutation in the Nogo gene that prevents Nogo-A and Nogo-B expression. The CST is traced from a cortical biotin dextran amine (BDA) injection after dorsal hemisection. Rostral is *left*; dorsal is *up*. The lesion is indicated by the *asterisk*. Note the evidence of CST fiber growth caudal to the lesion site (*arrows*). Significantly less BDA tracing is present caudal to the lesion in control animals (not shown). This photographic montage is a different image from the same mice described in Kim et al. (2003b)