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Review

Disinhibition of neurite growth to repair the injured adult CNS: Focusing on Nogo

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Abstract. Investigations into mechanisms that restrict the recovery of functions after an injury to the brain or the spinal cord have led to the discovery of specific neurite growth inhibitory factors in the adult central nervous system (CNS) of mammals. Blocking their growth-suppressive function resulted in disinhibition of axonal growth, i.e. growth of cultured neurons on inhibitory CNS tissue *in vitro* and regeneration of injured axons *in vivo*. The enhanced regenerative and compensatory fibre growth was often accompanied by a substantial improvement in the functional recovery after CNS injury. The first clinical studies to assess the therapeutic potential of compounds that neutralize growth inhibitors or interfere with their downstream signalling are currently in progress. This review discusses recent advances in the understanding of how the 'founder molecule' Nogo-A and other glial-derived growth inhibitors restrict the regeneration and repair of disrupted neuronal circuits, thus limiting the functional recovery after CNS injuries.

Keywords. Regeneration, plasticity, myelin, CNS repair, spinal cord injury, stroke.

Introduction

In mammals, an injury to the adult central nervous system leads to irreversible functional impairments. For example, after a cervical spinal cord injury (SCI), the ability to walk or to grasp an object is impaired and there is little recovery of these motor functions following the acute phase after large injuries. Similarly, after stroke, various functions are impaired depending on which brain regions are damaged. After large strokes, substantial recovery is rare and functional deficits usually persist for the rest of life. This lack of significant functional recovery after CNS injury corresponds with the failure of mature central neurons to effectively regenerate axons. Lesioned nerve fibres usually retract and form dystrophic end bulbs [1]. Occasionally, the proximal stumps of cut axons start to grow short sprouts but this sprouting response comes to a halt. The sprouting collaterals are not able to grow significantly and often retract [1, 2]. This is in sharp contrast to the response of injured axons in the peripheral nervous system, which regenerate vigorously over long distances and re-establish functioning synaptic contacts with peripheral muscles, a process which can lead to functional restoration.
This observation inspired the landmark experiments of Aguayo and colleagues in the early 1980s [3]: they showed that after spinal cord injury, CNS axons readily grew into a peripheral nerve graft transplanted

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into the wound. This demonstrated, for the first time, that adult, injured central neurons are able to regenerate long axons under favourable conditions (including basal lamina tubes and Schwann-cell-derived trophic factors) of the peripheral-nerve microenvironment.

In the late 1980s, our laboratory undertook experiments to investigate the molecular differences between central and peripheral nerve tissue. We found that explanted, cultured dorsal root ganglion neurons grew into explants of sciatic nerves, but not into optic nerves despite the presence of high concentrations of trophic factors [4]. Subsequently, myelin extracted from peripheral nerves was shown to be growth permissive whereas CNS myelin strongly inhibited nerve growth [5]. We went on to isolate a membrane protein from CNS myelin that strongly inhibited neurite growth, 'IN-250', which is now called Nogo-A [5–7]. Antibodies raised against this inhibitory protein neutralized the growth-restricting properties of oligodendrocyte myelin *in vitro* [8]. However, the most encouraging results achieved with these antibodies was the substantial regeneration of cut fibre tracts *in vivo* [9]. Importantly, this increased regeneration was accompanied by an impressive recovery of lost motor function [10, 11].

The discovery and characterization of myelin-associated neurite growth inhibitory proteins, in particular Nogo-A, has opened the door to a new field in regeneration research. In the wake of this breakthrough, other molecules were found to suppress neurite growth in the adult CNS. Most of them are located in the myelin sheaths of oligodendrocytes or are secreted into the extracellular matrix after injury.

Nogo-A

Nogo-A, -B and -C are splice variants of the nogo gene that was identified on the basis of peptide sequences of IN-220/250, isolated from CNS myelin [6, 7, 12, 13]. All three Nogo isoforms share a common carboxyl terminus of 188 amino acids which contains two long hydrophobic domains and a short loop of 66 amino acids between the two hydrophobic domains, called Nogo-66. The common C-terminus is a reticulon homology domain (RHD) and assigns the Nogo gene to the Reticulon protein family, with Nogo being Reticulon 4 (RTN4). However, the common Nogo-A/B N-terminus and the large, 800-amino-acid-long Nogo-A-specific region are unique to Nogo and have no homology to the RTN genes. Reticulons are highly conserved, and reticulon-like genes occur in all eukaryotes. Nogo-A, like other reticulons, contains an endoplasmatic reticulum (ER) retention motif and is highly enriched in the ER, in addition to its location in the cell membrane [7, 8, 12–14]. A recent report suggests that Nogo/RTN4 might be involved in shaping the tubular morphology of the ER [15].

Although a large part of Nogo-A is found intracellularly, it is also present on the cell surface and at least three active sites are exposed to the extracellular space: the Nogo-66 domain, which is close to the C-terminus and common to all three Nogo isoforms, inhibits neurite growth and induces growth cone collaps [12, 16]. A second active site (also called the central inhibitory domain) is located within the large 800-amino-acid Nogo-A-specific domain and strongly inhibits neurite outgrowth and cell spreading and induces growth cone collapse [16]. The third active site is found in the Nogo-A/B-specific N-terminus which inhibits spreading of cultured fibroblast [16] and was recently shown to promote adhesion of vascular cells and to stimulate endothelial cell migration [17, 18].

The glycoprotein NgR, which is widely expressed in many neurons, has been characterized as a receptor subunit that binds to the Nogo-66 site [19–21]. NgR is a GPI-linked cell surface protein that lacks an intracellular domain and requires either p75 [22, 23] or TROY [24, 25] as co-receptors to mediate signal transduction across the cell membrane. Both are transmembrane proteins of the tumour necrosis factor receptor (TNFR) family. Another co-receptor, LINGO-1, acts as an adaptor protein and seems to be required for Nogo-A signalling [26]. Interestingly, two other myelin-associated growth inhibitors, MAG and OMgp, bind to NgR with high affinity as well. This means that three structurally unrelated myelin-associated inhibitory molecules, Nogo-A, MAG and OMgp, converge on a single receptor complex and share a common intracellular signalling pathway [22, 27–30].

Several *in vitro* and *in vivo* observations indicate that another yet unknown receptor mechanism may mediate Nogo-A-specific signalling. Although the Nogo-A-specific central region does not bind to NgR, it inhibits neurite outgrowth and prevents spreading of different cell types [16]. Moreover, corticospinal tract neurons of $ngr^{-/-}$ or $p75^{-/-}$ mice do not regenerate after SCI [31–33] but regenerate vigorously after application of antibodies directed against the Nogo-A-specific domain *in vivo* (see below), indicating that another receptor or an additional receptor subunit may be of importance for the *in vivo* suppression of axonal growth.

Nogo-A is expressed in oligodendrocyte myelin and in some subpopulations of neurons

Nogo-A is highly expressed in oligodendrocytes of higher vertebrates, where it localizes mainly to the outer and innermost adaxonal myelin sheath (i.e. at the axon-oligodendrocyte contact zone) and to synaptic sites [34, 35].

The time of myelination of different pathways coincides with the age at which their regenerative capability is lost, pointing to the crucial contribution of the myelin-associated inhibitors such as Nogo-A in forming the growth-suppressive environment of the adult CNS [36]. During development, oligodendrocyte Nogo-A expression follows the course of myelination: in the developing cerebellum, for example, nogo-a mRNA first appears in oligodendrocytes in deep cerebellar regions at P5 and later on, at P9, Nogo-A-positive oligodendrocytes are found towards the distal ends of the folia in the white matter, correlating with the course of myelination [34, 37].

During development, Nogo-A is also expressed in subpopulations of neurons [34, 38–43], whereas in the adult CNS, neuronal Nogo-A is down-regulated in most of these regions. Neuronal expression of Nogo-A is tightly regulated during development; for example, olfactory receptor neurons and cerebellar granule cells were shown to have high levels of Nogo-A protein or mRNA during differentiation and migration, but after maturation, Nogo-A was virtually absent [34, 39]. In growing axons, Nogo-A preferentially localizes to the growth cone and to axonal branching points [39, 41, 43, 44]. Furthermore, radial glia cells, which are crucial for cortical development, express high levels of Nogo-A [43].

In contrast to mammals, Nogo-A is not found in the CNS myelin of lower vertebrates like fish or salamander [45, 46], whose CNS has a much higher regenerative potential [47–51]. Salamander, for example, can completely regenerate an injured spinal cord with full restoration of functions [50]. In contrast, frogs do express Nogo-A in myelin [46]. Accordingly, their regenerative potential is limited, and adult frogs do not recover from spinal cord transection [52].

Interestingly, Nogo-A expression levels are also known to be altered in a number of CNS diseases. For example, in amyotrophic lateral sclerosis (ALS), Nogo-A is up-regulated in muscles and spinal cord motoneurons [53] and might be involved in the pathophysiology of the disease [54]. The expression of Nogo-A in muscle tissue could also be used as an early diagnostic [53] and prognostic [55] marker for ALS. Furthermore, soluble Nogo-A fragments are found in the cerebrospinal fluid of patients with multiple sclerosis (MS) [56, 57]. In experimental autoimmune encephalomyelitis (EAE), a widely used animal model for MS, vaccination against a Nogo-A fragment or passive immunization with anti-Nogo-A antibodies attenuate clinical signs, demyelination and axonal damage [58, 59].

After brain or spinal cord trauma, overall Nogo-A protein or mRNA levels are mostly unaltered [34, 38, 41]. After the Wallerian degeneration of axons distal to an injury site, the myelin sheaths persist for a long time in the CNS. Indeed, Nogo-A was still detectable in degenerated fibre tracts of human spinal cord 3 years after spinal cord injury [60].

The intracellular signalling pathways of Nogo-A involve RhoA and Ca^{2+}

CNS neurons respond to Nogo-A with growth cone collapse and the arrest of neurite growth, suggesting an intracellular signalling mechanism that ultimately acts on cytoskeletal dynamics. Activation of RhoA seems to be a major downstream signalling mechanism of Nogo-A [61–64]. RhoA is a GTPase of the Rho family and is known for its central role in the signal transduction of axonal guidance molecules during development. Rho-A together with two other members of the same family, Rac1 and Cdc42, interact with a series of downstream effectors to regulate the dynamics of the actin cytoskeleton [for reviews see refs. 65–68]. Active RhoA activates Rho kinase (ROCK) which in turn can phosphorylate several other effectors. Injured axons are able to grow on an inhibitory myelin substrate when RhoA or ROCK are inactivated [62–64]. Further downstream signalling may involve the phosphorylation of cofilin by LIM kinase [69].

Nogo-A also initiates a rise in intracellular calcium, which mediates collapse of growth cones [23, 70]. Two additional signal mediators were found to be activated as well: protein kinase C (PKC) [71, 72] and epidermal growth factor receptor (EGFR) [73]. These pathways may act in parallel or in sequence with RhoA.

Interestingly, Nogo-A shares some of its downstream effectors with other myelin associated inhibitors of neurite growth as well as with chondroitin sulphate proteoglycans (see below) [73–76]. Targeting these downstream effectors of Nogo-A with specific blocking compounds therefore prevents the signalling of a number of different neurite growth inhibitors.

Several other myelin-associated molecules also suppress neurite growth

Several components of CNS myelin have been shown to inhibit regrowth of injured neurons. Myelin-associated glycoprotein (MAG) [77, 78] and oligodendrocyte myelin glycoprotein (OMgp) [27] are enriched in

oligodendrocytes. Although both are structurally unrelated to Nogo-A, they can bind to the NgR/p75/Lingo-1 receptor complex. The blockade of this pathway promotes neurite growth *in vitro*, but there is no evidence so far that acute *in vivo* neutralization of MAG or OMgp or gene knockout leads to regeneration or improves functional recovery. Versican V2 and brevican, both CSPGs, are constitutively present in myelin and also suppress neurite growth [79, 80]. In addition, some repulsive axon guidance cues that play a role in development continue to be expressed in oligodendrocytes in adult animals and have been implicated as inhibitors of axonal regeneration. Ephrin B3, best known for its function as a midline repellent for growing corticospinal tract (CST) fibres during development, is expressed in myelinating oligodendrocytes in adult mammals and strongly inhibits axonal growth *in vitro* [81]. Mice which lack EphA4, a receptor for Ephrin B3, show increased axonal regeneration *in vivo* [82]. Another regulator of axonal pathfinding during development, Semaphorin 4D, is also present in myelinating oligodendrocytes and inhibits neurite growth [83].

The glial scar also contains growth-inhibitory molecules that impede the regeneration of cut axons through the lesion site

Myelin is not the only source of neurite growth inhibition in the adult CNS. CNS injuries trigger a cascade of cellular, vascular and molecular events that eventually lead to the formation of a glial scar: the disruption of the blood-brain barrier results in the recruitment of inflammatory cells, neutrophils and macrophages that invade the disrupted tissue and, together with activated resident microglia cells, start to phagocytose cell debris. They release a wealth of inflammatory mediators such as cytokines and prostaglandins, which in turn attract more inflammatory cells, including T cells, to the injury site and together produce a complex concert of cellular and molecular factors that can be supportive or inhibitory for neurite growth [for reviews on inflammation and regeneration see refs. 36, 84].

At the same time, glial cells, notably activated astrocytes and oligodendrocyte precursor cells, together with invading meningeal cells start to produce chondroitin sulphate proteoglycans (CSPGs) and release them into the extracellular space [85]. Different species of CSPGs, such as NG2, neurocan, versican, phosphacan and brevican [79, 86–90] are strong inhibitors of neurite growth and accumulate at and around the lesion site within days after an injury. These secreted CSPGs are an important component of the glial scar and may persist for months [91, 92], impeding sprouting and regenerating axons from crossing the lesion site.

Accumulated CSPGs can be enzymatically degraded by repeatedly injecting bacterial chondroitinase ABC into the injured tissue [93]. This elimination of inhibitory CSPGs was shown to increase effectively the regeneration of cut axons through the glial scar and thus improve the recovery of motor and sensory functions [93]. Using the GFAP promotor to transgenically express chondroitinase ABC in astrocytes led to increased growth of CST axons into the lesion site but did not yield an improved recovery of motor functions [94] [The role of CSPGs after CNS injury is reviewed in refs. 85, 95].

Myelin-associated inhibitors and CSPGs stabilize existing connections and suppress plasticity in the mature CNS

The occurrence of different inhibitory molecules in the CNS of adult mammals suggests that they play a vital role. Increasing evidence indicates that myelin and its associated inhibitors of axonal growth control and restrict fibre growth in the adult CNS. For example, the onset of myelination correlates with the postnatal decline in the plastic potential in various axonal pathways as shown by the decline of the plasticity marker GAP-43 concurrently with myelination [96]. Moreover, the CNS remains permissive for neurite growth if myelination is blocked by neonatal X-ray irradiation [97].

Myelin and myelin-associated inhibitors appear in the CNS after the completion of axon growth. Intriguingly, they might actually be involved in terminating the neurite growth phase during postnatal CNS development. Following axonal pathfinding and initial circuit formation in early development, a second, activity-dependent process adjusts and fine-tunes the neuronal circuits in 'critical periods' during early postnatal life. These critical periods, characterized by a high plasticity of connections, are restricted to well-defined time windows in early life. For example, ocular dominance columns in the visual cortex are fine-tuned during a short postnatal time period: during this critical period, monocular deprivation by experimentally closing one eye leads to the expansion of the ocular dominance columns of the contralateral, non-deprived eye [98].

Two papers have shown that Nogo-A, via its receptor NgR, and CSPGs are involved in closing the critical period for ocular dominance in the visual cortex. Enzymatic degradation of CSPGs with chondroitinase ABC was shown to restitute plasticity for monocular

deprivation in adult rats, leading to a shift of ocular dominance to the non-deprived eye after unilateral lid suture [99]. Genetic deletion of Nogo-A/B or the Nogo receptor subunit NgR was found to extend the closure of the critical period for monocular deprivation in young adult mice [100]. It seems, therefore, that Nogo and CSPGs actively contribute to the consolidation of neuronal circuits during CNS maturation. They restrict plasticity and may prevent axons from aberrant growth in the adult CNS [96, 101, 102]. The lack of axonal regeneration would therefore be the price to pay for the stabilization of a complex nervous system [96, 102–104].

Blocking Nogo-A function after SCI

The consequences of SCI are complex: vast numbers of axons that carry sensory information from the spinal cord to the brain and motor and autonomic system commands from the brain to the spinal cord are partly or, in rare cases, completely disconnected from their specific targets. At the level of the injury, interneurons and motoneurons are destroyed. Yet, about half of spinal-cord-injured patients in western countries show some limited recovery in the first months after the injury [105]. Patients with lesions that do not completely interrupt all ascending and descending pathways are more likely to spontaneously recover some of the lost functions. These functional improvements, however, are variable and depend on the lesion anatomy. Most patients have to cope with permanent functional deficits. Depending on the level and the severity of the injury, many patients suffer from motor and sensory deficits and malfunctions such as pain and spasticity for the rest of their life. Often, apparently small functional improvements, e.g. regaining some hand function or being able to stand up from the wheelchair and support the own weight, can mean a lot in the daily life of a victim of SCI and may decide between complete dependence or living in autonomy.

Such spontaneous functional improvements are largely due to adaptive changes in the neuronal circuitries of the brain and the spinal cord. Axotomized neurons around the lesion were shown to up-regulate growth proteins such as GAP-43, and some transected axons may sprout and grow collaterals and may form new functional connections [106, 107].

However, reorganization of the injured CNS is limited, due in part to restrictions imposed by the inhibitory CNS environment. Attempts of axons to regenerate are transitory and abortive; they eventually form dystrophic endbulbs and growth-associated proteins are down-regulated after a few days [36]. Such observations have led to the conclusion that the lack of substantial functional recovery after large brain or spinal cord injuries is caused by ineffective regeneration of lesioned axons, the regeneration being limited by neurite growth inhibitors. The immediate questions brought about by the discovery of inhibitory factors and in particular the protein Nogo-A were: (1) Would the functional blockade of Nogo-A signalling after CNS injury increase the otherwise abortive regenerative response and allow axons to regenerate over longer distances? (2) Could regeneration together with the potential increase in compensatory fibre growth and circuit plasticity lead to improved functional recovery?

Experiments from various laboratories over more than 10 years suggest that the answer to both questions is yes. Neutralizing Nogo-A either by applying function-blocking antibodies directed against the N-terminal region of Nogo-A or by interfering with Nogo-A receptors or signalling pathways boosts the regenerative response of injured adult CNS tracts, stimulates compensatory fibre growth and improves the recovery of lost functions [9–11, 62, 108–111].

Four different lines of transgenic animals lacking Nogo-A, Nogo-A and -B or Nogo-A, -B and -C generated by three independent laboratories yielded somewhat conflicting results [112]. Whereas the Nogo-A [113] and the Nogo-A and -B [114] knockout lines showed an increased regenerative phenotype, with an increased number of CST fibres growing from the end of the severed CST towards the lesion site in the former, and fibres regenerating into distal cord segments in the latter, the Nogo-A and -B and Nogo-A, -B and -C knockout mice of the third laboratory did not seem to show increased regeneration [115]. Follow-up studies showed that the genetic background of different mouse lines [116], compensatory up-regulation of other Nogo proteins [113] and the lesion paradigms used [117] may account for some of the discrepancies in the findings between the different lines.

Recently, Steward et al. [118] argued that the increased regeneration in the Nogo-A/B knockout mice described by Kim et al. [114] might in part be based on artefactual labelling of axons due to accidental injection or leakage of the tracer into the cerebrospinal fluid in the cerebral ventricle. In response, Cafferty et al. [119] pointed out that this labelling artefact was rare (5% of traced mice) and the vast majority of the Nogo-A/B knockout mice used for their study bore no resemblance to the labelling pattern of Steward. If the rare mice with such a pattern were excluded from the axon counts, the same statistically valid conclusions remained [119]. In our laboratory, such artefactual labelling of

axons resulting from incorrect tracing techniques has never been observed.

After large but incomplete SCI and treatment with anti-Nogo-A antibodies, two principal axonal repair mechanisms were observed. Using reconstructions from uninterrupted serial section series, cut axons were seen to *regenerate* around and beyond the lesion site and to grow through the denervated spinal cord for long distances (typically more than 1–2 mm). They crossed the injury site on bridges of spared tissue and could form extensive terminal arbours in the caudal spinal cord. Corticospinal and serotonergic fibres were studied most intensively [9, 10, 108, 120, 121] (Fig. 1).

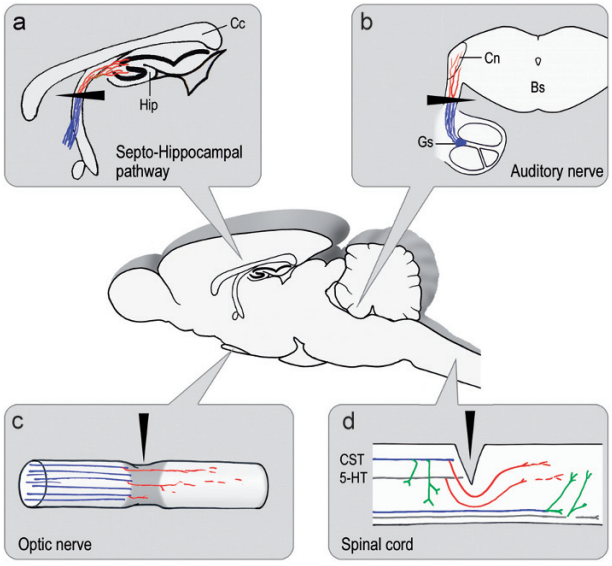

Figure 1. Regenerative axon growth after different CNS lesion paradigms is increased after anti-Nogo-A antibody or NgR antagonist treatment. Lesion sites are indicated with black arrow heads. Red = regenerated axons. (*a*) Cholinergic axons regenerate after damage to the septo-hippocampal projection and reinervate their original terminal areas in the hippocampus (Hip) [124]. Blue = cut axons; Cc, corpus callosum. (*b*) Cochlear fibres, originating from the ganglion spirale (Gs) in the cochlea, regenerate after an auditory nerve transection; some fibres reach their correct target nuclei in the brainstem (Bs) [127]. Blue = cut axons; Cn, cochlear nuclei. (*c*) Retinal ganglion cell axons regenerate after a freeze-crush lesion of the optic nerve after combined fibroblast growth factor or brain-derived neurotrophic factor and anti-Nogo-A antibody treatment [126] or after suppressing NgR activity with a dominant-negative construct transfected into retinal ganglion cell axons [125]. Blue = cut axons. (*d*) Spinal cord: after dorsal bilateral hemisection of the thoracic spinal cord, cut corticospinal tract axons (blue) regenerate through bridges of spared tissue and grow 1–2 cm below the lesion site and spared CST axons sprout collaterals below the lesion site after treatment with anti-Nogo-A antibodies [9, 120, 121] or blocking NgR [133] or blocking RhoA and ROCK [62, 111]; lesioned and/or spared 5-HT fibres (grey) regenerate/sprout vigorously below the injury site [10, 133]. Blue = spared and intact CST axons; green = sprouted fibres; 5-HT, serotonergic (5-hydroxytryptamine) raphespinal tract.

Alternatively, damaged and/or spared axons were observed to sprout collaterals above and below the injury site. These fibres are typically short (up to 1 mm) and can innervate nearby targets, e.g. areas that were denervated by the lesion. This repair mechanism is referred to as *collateral* or *compensatory sprouting* (Fig. 2). Below we describe in more detail the recovery process mediated by the neutralization of Nogo-A.

Damaged CNS fibres regenerate after blocking Nogo-A function

In 1990, Schnell and Schwab [9] reported that neutralizing Nogo-A with function-blocking monoclonal antibodies in rats after an incomplete experimental SCI increased the regeneration of cut axons. They implanted anti-Nogo-A-antibody-producing hybridoma cells into the brain of young, adult rats and transected the dorsal two-thirds of the thoracic spinal cord, including the CST. As a consequence of the treatment, the CST, a major motor and sensory pathway that originates in the sensorimotor cortex and projects to the spinal cord, regenerated up to 11 mm beyond the injury site (Fig. 1d). In contrast, control animals, treated with antibodies against an unrelated protein, rarely regenerated their CST fibres beyond 0.5–1 mm.

These experiments were repeated in a more clinically relevant setting. Specifically, highly purified monoclonal antibodies directed against the N-terminal region of Nogo-A were applied via a small intrathecal lumbar catheter directly into the cerebrospinal fluid. The results were similar: the number of regenerated CST fibres was much higher in anti-Nogo-A-antibody-treated animals than in control animals [120]. The antibodies that have been used in these studies specifically recognize the Nogo-A-specific domain in the middle of the Nogo-A molecule, thereby blocking the binding of Nogo-A with a putative Nogo-A-specific receptor (see above). Due to the large size of IgG antibodies, steric blockade of the Nogo-A-NgR interaction could occur as well. In addition, antibody-induced internalization and subsequent degradation of cell surface Nogo-A decreases the total tissue levels of Nogo-A and may indirectly contribute to the plasticity-enhancing effects of intrathecally applied anti-Nogo-A antibodies in CNS-injured animals [122].

Other approaches to block Nogo functions, e.g. by blocking NgR with a blocking peptide (NEP1–40) or by targeting downstream effectors that are shared by other neurite growth inhibitors, e.g. RhoA and ROCK, with blocking compounds yielded comparable results with respect to CST regeneration [62, 108, 111] (Fig. 1d).

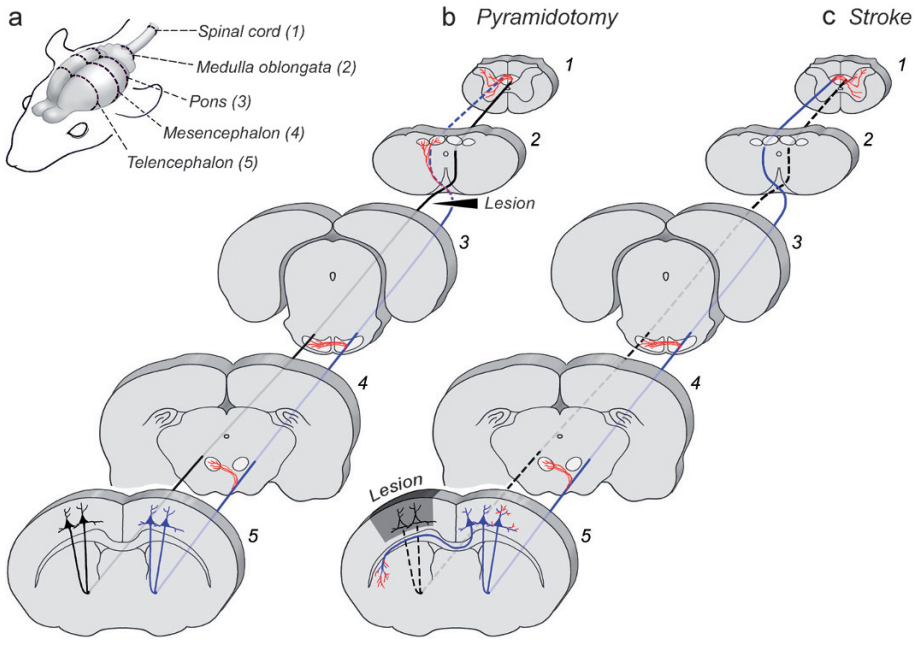

Figure 2. Plastic changes in corticofugal projections that are induced or increased by anti-Nogo-A antibody treatment after spinal cord injury (*b*) and stroke (*c*). (*a*) The overview shows the location of the coronal brain and spinal cord sections. The CST and corticostriatal fibres originating in the left cortex and descending (mainly) in the right half of the spinal cord are in blue, the opposite CST is in black. Dashed lines indicate the degenerated CST below the disruption site. Red, sprouting axons (*b/c 1–5*) and dendrites (*c5*). (*b*) Pyramidotomy: a unilateral pyramidotomy (black arrowhead) interrupts selectively the CST on one side at the level of the medulla oblongata (*b2*) before it decussates. Above the lesion, the affected CST grows midline crossing collaterals to the red nucleus (*b4*) and the basilar pontine nuclei (*b3*) [11, 130, 131]. In the medulla (*b2*), the dorsal column nuclei are reinervated [11]. The unlesioned CST sprouts across the midline in the spinal cord (*b1*) and reinervates the grey matter after anti-Nogo-A antibody treatment [11]. Similar results were found in $ngr^{-/-}$ and nogo-a/$b^{-/-}$ mice [117]. (*c*) stroke: spared corticospinal tract fibres are seen to sprout to the contralateral side that was denervated by the stroke at several levels. In the mesencephalon (*c4*) they grow to the contralateral red nucleus, in the pons to the contralateral basilar pontine nuclei (*c3*), and in the spinal cord to the contralateral grey matter (*c1*) [109, 110, 140, 141, 155]. In the telencephalon (*c5*), corticofugal fibres increase the innervation of the contralateral dorsal striatum [154]. Apical and basilar dendrites of contralesional layer V pyramidal neurons arbourize to a greater degree [157].

So far most studies have focused on the regeneration of CST neurons because their origin, the sensorimotor cortex, is readily accessible for neuroanatomical tract tracing. However, the regenerative potential may not be equal for different spinal tracts.

Another descending pathway with crucial modulatory function for motor, sensory and autonomic circuits in the spinal cord, the serotonergic raphespinal tracts, also responded vigorously to Nogo-A blocking treatment after a large partial spinal cord lesion: the density of 5-HT fibres below the injury site recovered substantially, reaching normal, preinjury levels in some studies [10, 108, 123] (Fig. 1d). Many fibres may have regenerated but some may also have sprouted from intact fibres that were not interrupted by the injury. Other descending pathways originating from the brainstem, such as the vestibulospinal and reticulospinal tract, are crucial for locomotor functions, yet their response to Nogo-A inactivation has not been studied.

Other important CNS pathways have been studied for their potential to regenerate after Nogo-A neutralization. In a paradigm for axonal injury in the hippocampus, the regeneration of cut cholinergic septo-hippocampal axons was boosted substantially by anti-Nogo-A antibodies [124] (Fig. 1a). Similar results were found after a crush lesion of the optic nerve. Suppressing NgR activity with a dominant-negative NgR construct transfected into retinal ganglion cells led to an enhanced regeneration of retinal ganglion cell axons when combined with stimulation by macrophage-derived factors [125]. Increased regeneration of retinal ganglion cells was also seen after application of anti-Nogo-A antibodies combined with brain-derived neurotrophic factor [126] (Fig. 1c). Equivalent effects were seen with a recombinant Fab fragment of an anti-Nogo-A antibody after cochlear nerve lesion: cochlear fibres regenerated substantially, and some fibres reached their correct target nuclei in the brainstem. In contrast, control-antibody-treated animals did not show any comparable recovery [127] (Fig. 1b).

These studies show that Nogo-A inactivation promotes axonal regeneration of various types of CNS neurons. Whether qualitative or quantitative differences exist between neurons and tracts with regard

to Nogo-A suppression remains to be studied in detail.

However, regenerated axons as such are effectively worthless unless they form functional synaptic contacts with appropriate target neurons and integrate correctly into the deafferentiated circuitries below the lesion. Indeed, following dorsal bilateral hemisection and anti-Nogo-A antibody treatment, regenerated axons branched extensively in the grey matter and formed terminal arbours with numerous varicosities, indicating strongly that they established synaptic contacts to target neurons below the injury site [121].

Nevertheless, the often small proportion (typically 5–10%) of interrupted fibres that eventually by-passed the lesion site and their variable length (a few millimeters to 1–2 cm in the rat) indicate that other factors, like the lack of trophic support or the inhibitory glial scar, play additional important roles in preventing axons from regenerating successfully. At the same time, it suggests that other mechanisms, especially compensatory ones, may contribute significantly to functional recovery after large SCIs.

Damaged and spared fibres sprout above and below the SCI site after blocking Nogo-A function

Most SCIs are incomplete and leave a proportion of axonal projections intact. In young postnatal animals, these spared fibres sprout and form collateral branches below the injury site and may connect to targets that have been left denervated by the SCI [128]. Such new connections are thought to compensate for the lost connections and thereby contribute to the spontaneous functional recovery. The ability to form new collateral connections declines soon after early postnatal life and may be related to myelination (see above) [96, 129]. Blocking a major inhibitory component of myelin, Nogo-A, in adult animals, increased the ability to sprout new collaterals after SCI (Fig. 2). After a unilateral transection of the CST at the level of the medulla oblongata (pyramidotomy), the contralateral spared CST sprouted and grew into the denervated side of the spinal cord after treatment with anti-Nogo-A antibodies [11] or if nogo-a/b or ngr [117] was genetically deleted (Fig. 2b). Corticoefferent fibres from the affected side also sprouted across the midline and innervated motor and sensory areas in the contralateral brainstem, including the red nucleus, basilar pontine nuclei and dorsal column nuclei [11, 130, 131] and formed new synaptic contacts [131] (Fig. 2b).

If the CST was transected bilaterally (bilateral pyramidotomy), another descending projection, the rubrospinal tract, originating in the mesencephalic red nucleus, started to form new collateral sprouts in the cervical spinal cord in response to antibodies against Nogo-A [132]. Red nucleus microstimulation confirmed the functionality of these new rubrospinal connections.

Blocking Nogo-A function improves the recovery of motor functions after SCI

The increased fibre growth in the lesioned CNS after therapeutic interventions is promising, but even more hopeful is the improvement in the recovery of motor function that is correlated with treatments.

Adult rats show some spontaneous recovery after large but incomplete spinal cord lesions, which reaches a plateau after 4–6 weeks. A dorsal bilateral hemisection of the thoracic spinal cord, for example, severely affects hindlimb functions, and the functional recovery is limited. However, if rats were treated with Nogo-A antibodies, these impaired functions recovered faster and to a larger extent, in particular in precision tests, e.g. walking on a narrow beam or crossing a unevenly spaced horizontal ladder. Their ability to swim or to climb a rope was also reported to be improved [10, 120, 121]. Similar results were found when the Nogo receptor subunit NgR was blocked by the small peptide antagonist NEP 1–40, or when Nogo-A was blocked by NgR(319)ecto [108, 133, 134], or by a soluble antagonist of the NgR co-receptor LINGO-1 [135]. Targeting intracellular mediators of Nogo-A signalling was equally effective: blocking RhoA with C3 transferase or ROCK with a competitive inhibitor (Y-27632) increased the functional recovery after SCI [111]. The effects of blocking these downstream effectors may reflect the consequence of inhibiting several neurite growth inhibitors whose signalling pathways seem to converge to a certain degree.

Substantial improvements in the CST-dependent skilled forelimb use after unilateral pyramidotomy and Nogo-A antibody treatment or knockout have been observed as well [11, 117] (Fig. 3a).

Importantly, common malfunctions after SCI, like pain or spasticity or disturbances in behaviour have not been observed in animals treated with reagents that block the Nogo-Nogo receptor pathway [33, 120, 136, 137].

Blocking Nogo-A function after stroke and traumatic brain injury

Equally promising are results gained with animal models for ischaemic stroke. Neutralizing the growth-inhibitory environment of the CNS by blocking Nogo-A function after experimental stroke increased greatly the functional recovery in adult

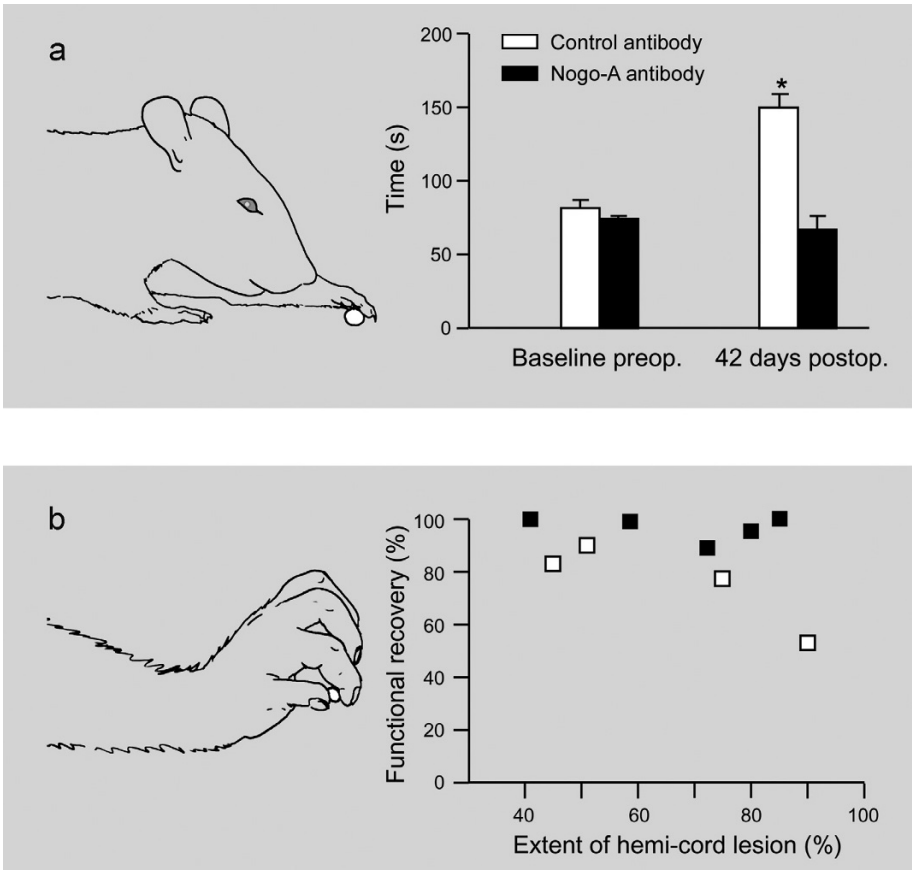

Figure 3. Functional recovery of skilled forelimb/hand use after high CST lesions in the rat (*a*) and the macaque monkey (*b*) with and without anti-Nogo-A antibody treatment. (*a*) Pellet-reaching task. Intact rats require approximately 75 s to grasp and eat 20 food pellets from a smooth surface (preoperative baseline). Forty-two days after a unilateral CST transection at the level of the pyramid (pyramidotomy), control-antibody-treated rats (white bars) required significantly more time to grasp 20 pellets with their impaired forelimb compared to the preoperative baseline. In contrast, anti-Nogo-A-antibody-treated animals (black bars) recovered to a performance level that did not differ from the preoperative baseline, indicating that the treatment had lead to a substantial functional recovery of precise forelimb usage. Error bars indicate standard error; *$p < 0.05$. Adapted by permission from Nature Neuroscience (1998) vol. 1, pp. 124–131, copyright (1998) Macmillan Publishers Ltd. (*b*) Quantitative assessment of hand dexterity after a unilateral spinal cord lesion at the C7/8 level, aimed at interrupting the main lateral CST. Macaque monkeys were trained to grasp food pellets from horizontally and vertically oriented slots. Immediately after the SCI, their ability to grasp food pellets was severely impaired. Thereafter, the animals recovered partially, reaching a plateau within 30–60 days after injury. For analysis, the average score over 10 days after a stable performance level had been reached (within 30–60 days after injury) was related to the average score over 10 prelesion testing days. The recovery in percentage relative to the prelesion baseline is plotted against the lesion size (percentage hemicord lesion). In anti-Nogo-A-antibody-treated monkeys (black squares), the recovery was complete (or nearly so) irrespective of lesion size, whereas in control-antibody-treated monkeys (white squares) the functional recovery was incomplete and appeared to correlate inversely with the lesion size. Adapted with permission from Nature Medicine (2006) vol. 12, pp. 790–792, copyright (2006) Macmillan Publishers Ltd.

rats. Middle cerebral artery occlusion (MCAO) or photothrombotic brain lesion in the sensorimotor cortex produce large unilateral strokes in rats, which lead to deficits in skilled forelimb use, for example when reaching food pellets [138, 139]. As in humans, functional deficits persist and the spontaneous recovery of motor functions after large strokes is very limited. However, this recovery was greatly increased after treatment with anti-Nogo-A antibodies [109, 140, 141] or with NgR receptor antagonists [110] in rats. Control animals reached about 50% of the preinjury performance level in tests that assess the skilled forelimb use. In contrast, Nogo-A-antibody- or NgR-antagonist-treated animals recovered up to 80–100%.

The spontaneous functional improvements after stroke probably involve the opposite intact hemisphere, which compensates for the loss of the infarcted cortical area. Several clinical and experimental studies found that plastic changes in the opposite hemisphere can facilitate motor recovery: in patients who are recovering from large strokes, movements of the paralyzed limb produce an ipsilateral activation of the intact sensorimotor cortex, which is not observed in healthy control subjects [142–145]. Similar changes in cortical activation are found after MCAO or unilat-

eral cortical ablation in rats [146–148]. Furthermore, in the unmyelinated CNS of newborn rats, unilateral lesions of the sensorimotor cortex led to a substantial increase of contralesional corticofugal projections that cross the midline to innervate denervated motor nuclei in the brainstem and spinal cord [149–153], indicating that the contralesional cortex might take over functions of the injured cortex.

In contrast, adult animals with fully myelinated corticoefferent projections show no or only a minor increase in collateral sprouting of the intact corticospinal tract across the midline after stroke. However, after neutralizing Nogo-A or blocking NgR in adult rats, the collateral sprouting to the denervated side is greatly increased, mimicking the results gained in newborn animals. The number of corticostriatal fibres projecting from the intact cortex to the contralateral dorsolateral striatum was increased in anti-Nogo-A-antibody-treated rats compared to control animals [154]. In the mesencephalon, the ipsilesional red nucleus, which had lost its ipsilateral cortical afferents, received new, crossed afferents from the intact contralateral cortex [109, 110, 140, 155]. Likewise, the basilar pontine nuclei received more fibres from the intact cortex [140]. At the level of the cervical spinal cord, the number of midline-crossing corticospinal fibres originating from the intact sensorimotor cortex increased significantly [141] and the innervation of the ispilesional medial motoneurons was augmented [156].

In addition to these changes in corticofugal projections, the dendritic arbours of layer V pyramidal neurons were observed to be altered too: after unilateral MCAO, the contralateral apical and basilar dendrites in Nogo-A-antibody-treated rats had a greater degree of arborization and higher numbers of spines than those of control-antibody-treated rats [157].

Taken together these results suggest that the intact contralesional cortex can gain control over areas denervated by the unilateral cortical lesion. The intact hemisphere forms new and detour connections by sprouting into denervated subcortical motor areas and by contacting other descending tracts that were not affected by the cortical lesion, like the rubrospinal tract. In fact, after unilateral cortical aspiration, electrical stimulation of the intact contralesional cortex resulted in increased activation of ipsilateral forelimb muscles in Nogo-A-antibody-treated animals [158].

Plastic changes are likely to be more widespread and not restricted to the contralesional side. Additional plastic changes take place, for example, in the cortical area adjacent to the infarct and the premotor areas may also be important for the restitution of proper motor functions, especially after smaller lesions [159]. It is probable that blocking Nogo-A function increases spontaneous plastic changes throughout the CNS and thereby improves the functional recovery.

Do the observed anatomical changes account for the functional recovery?

Achieving successful, i.e. functionally meaningful, regeneration is immensely difficult. New fibres have to integrate into existing, albeit dysfunctional circuitries and accurately connect to appropriate target neurons. Connecting to wrong targets might lead to malfunction with severe consequences, e.g. neurogenic pain, spasticity or epilepsies. Pain and spasticity are common sequelae of SCI and have been associated with erroneous connections that form in the injured spinal cord [160–163].

Proving a causal relationship between plastic anatomical changes and functional improvements is complex and challenging. One way to demonstrate that sprouting and regeneration do account for the enhanced recovery of functions are relesion experiments whereby newly grown connections are selectively destroyed. The concurrent loss of the regained functions would indirectly prove their specific contribution. Bregman et al. [10] showed that the complete removal of the sensorimotor cortex abolished functional improvements after a large mid-thoracic hemisection following anti-Nogo-A antibody treatment. Removing regenerated raphespinal projections with a neurotoxin that selectively kills serotonergic neurons (5,7-dihydroxytryptamine) partly abolished the functional recovery seen in NgR knockout mice [33]. Although theoretically convincing, relesion experiments have an inherent danger of producing false-positive results: selective transection of only the regrown fibres is rarely possible; most lesions are large, damage other pathways and cause a short-term conduction block by oedema and inflammation.

Another approach to prove the functionality and contribution of new connections are electrophysiological experiments. Microstimulation of the rewired rubrospinal tract, which normally does not directly innervate motoneurons projecting to proximal forelimb muscles, elicited short-latency electromyography responses in these muscles, suggesting that direct functional connections were formed [164]. Similarly, transcranial magnetic stimulation of corticospinal motoneurons after an incomplete thoracic lesion showed an increased activation of hindlimb muscles after blockade of NgR [133].

Translating experimental interventions in spinal cord research into clinical studies

A prerequisite for translating a new therapeutic approach to treat SCI from rodents to humans are studies with non-human primates [165]. Their nervous system is more like ours and may react differently to interventional therapies than that of rodents. The CST, for example, has a different anatomy and is more important in monkeys and humans than in rats. Furthermore, the tissue reaction in response to a lesion and the time course of regenerative processes may be different from rodents. Most importantly, monkeys, like humans, are very dexterous in using their hands and fingers and can be trained to do complex behavioural tasks allowing a more refined assessment of motor function. In laboratory macaques, which interact with scientist and animal caretakers very closely during extended behavioural experiments, it is also easier to detect potential side effects of Nogo-A inactivation like pain, spasticity, neuropsychiatric phenomena or changes in social behaviour.

A recent study with 12 adult macaque monkeys has confirmed the efficacy of Nogo-A antibody treatment after SCI in primates [136]. A unilateral cervical hemisection at C7 led to a substantial loss of ipsilateral manual dexterity. Motor functions in the affected hand, assessed with different tests of dexterity, recovered faster and to a larger extent in anti-Nogo-A-antibody-treated animals (Fig. 3b). No signs of pain or any other side effects were detected. Anatomically, regenerative sprouting of CST axons was observed rostral to the lesion [166].

Translating these experimental findings into clinical studies faces several challenges. The incidence of SCI is low and therefore requires a multi-centre study design to obtain a sufficient number of treated patients. This in turn requires a high level of standardization of protocols between medical centres for a precise diagnosis and the assessment and follow-up of the recovery process. As the functional recovery is a multifaceted process, clinical tests (muscle strength, sensory functions, extent of neurological deficits, neurological level of injury), functional evaluations (walking capacity, hand dexterity, bladder control, ability to live independently) and neurophysiologic assessments (motor and somatosensory evoked potentials) will have to be combined to evaluate accurately the outcome of interventional therapies [167].

Different spinal levels and variable lesion anatomy imply that the population of spinal-cord-injured patients is very heterogeneous with respect to functional deficits and expected functional recovery. This highlights the importance of standardizing the initial clinical and neurophysiological examinations that can reliably estimate the expected outcome and monitor effects of the treatment.

Effective treatment of acute diseases often requires prompt initiation of therapeutic interventions if they are to be successful. Indeed, if the onset of anti-Nogo-A antibody application after SCI is delayed for 1 or 2 weeks, the therapy is less effective in rats [168]. Accumulation of inhibitory CSPGs around the scar in the days following an injury may prevent axons from growing through or around the spinal cord lesion site. Alternatively or in addition, neurons deprived of their target-derived trophic support can become atrophic and unresponsive to neutralization of Nogo-A.

A future treatment regime for patients with severe SCI will probably require a multidisciplinary approach. After medical and surgical stabilization of the acutely injured patient, the interventional therapies may involve reagents to overcome myelin inhibition, combined with neurotrophic factors to prevent neuronal atrophy and stimulate growth, and treatments that can reduce the growth-suppressive properties of the glial scar. Intensive rehabilitative training programmes will support activity-dependent plastic processes in the CNS and help the patient to regain independence.

A multicentre clinical trial for humanized Nogo-A antibodies in acute SCI is now ongoing in several countries.

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