# Nogo-A: Multiple Roles in CNS Development, Maintenance, and Disease

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**Abstract**

Initially discovered as a potent neurite outgrowth inhibitor in the central nervous system (CNS), Nogo-A has emerged as a multifunctional protein. Involvement of this protein has been demonstrated in numerous developmental processes, ranging from cell migration, axon guidance and fasciculation, dendritic branching and CNS plasticity to oligodendrocyte differentiation and myelination. Although initially necessary and beneficial for shaping and later maintaining CNS structure and functionality, the growth restricting properties of Nogo-A can have negative effects on nervous system injury or disease. Hence, correlating with its various neurobiological roles, Nogo-A was implicated in a range of CNS disturbances, including trauma such as spinal cord injury or stroke, neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis or multiple sclerosis, or in schizophrenia. In this review, we summarize the current state of knowledge for Nogo-A's involvement in these nervous system diseases and perturbations and discuss the possible underlying mechanisms. Furthermore, we provide a comprehensive overview on molecular signaling pathways as well as structural properties identified for Nogo-A and point to open questions in the field.

**Keywords**

Nogo-A, CNS, development, disease, spinal cord injury, stroke, ALS, Alzheimer's, schizophrenia, multiple sclerosis

## Introduction

In his book *Degeneration and Regeneration of the Nervous System*, published exactly 100 years ago, the Spanish neuroscientist Ramon Y. Cajal not only beautifully described the limited regenerative capacity of the central nervous system (CNS) but also observed that even though the CNS eventually fails to regenerate, it undergoes numerous regenerative attempts. He consequently concluded that although ineffective, these attempts merit careful study: "No matter what their significance, these productions have a positive biological interest. Besides fortifying the doctrine of neurobional autonomy, they definitely refute the fatalist concept of the essential irregenerability of central paths." This by then revolutionary idea should become the fundament of modern regenerative neurosciences. However, it took more than half a century until the Canadian neurologist Albert Aguayo provided the first experimental proof for the lifelong ability of CNS neurons to regenerate on injury. By bridging the medulla oblongata and the thoracic spinal cord using a peripheral nerve graft in adult rats, growth of different types of central axons into this nerve graft could be detected up to a distance of 30 mm (David and Aguayo 1981). The biochemical basis underlying this phenomenon was subsequently hypothesized to be the lack of neurotrophic factors in CNS tissue compared with the peripheral nervous system (PNS). This hypothesis was tested by cultivating central or peripheral neurons in contact with optic (CNS) and sciatic (PNS) nerve explants isolated from the adult rat. Although no neurite growth into the optic nerve explants was detected, the opposite was the case for sciatic nerve explants. Interestingly, also an optimal supply with neurotrophic factors failed to enable growth of neurons into the optic nerve explants (Schwab and Thoenen 1985). The source of the difference in growth observed on PNS in comparison to CNS tissue thus was postulated to be a nonpermissive factor or set of factors residing in the CNS. Interestingly, this neurite outgrowth inhibitory activity was shown to be strongest in myelin-containing white matter areas when neurons were plated on frozen sections of various regions of the CNS (Savio and Schwab 1989). Additionally, myelin extracted from spinal cords—but not from sciatic nerves of adult rats—was shown to contain the nonpermissive properties

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(Schwab and Caroni 1988). The focus thus shifted toward the isolation and identification of this putative myelin-associated inhibitory substrate. Indeed, two membrane protein fractions of 35 kDa and 250 kDa, purified from adult rat spinal cord, revealed strong inhibitory activity on neuronal outgrowth and fibroblast spreading. Treating the same cultures with antibodies raised against these membrane proteins resulted in a strong reduction in neurite outgrowth and fibroblast spreading inhibition (Caroni and Schwab 1988a). However, it took another 10 to 12 years until the protein was purified and the gene encoding for the main inhibitory protein of the myelin-derived fractions was identified and received its name: Nogo-A (Chen and others 2000; GrandPre and others 2000; Prinjha and others 2000; Spillmann and others 1998). Numerous studies have been undertaken since, further characterizing Nogo's functions in development, adulthood, and disease of the nervous system, elucidating its biochemical properties as well as demonstrating underlying signaling mechanisms. This review shall provide a comprehensive overview of the current knowledge on this protein and identify remaining open questions.

## Nogo-A: Functional Domains

Alternative splicing or different promoter usage yield three isoforms: Nogo-A, Nogo-B, and Nogo-C (Chen and others 2000; GrandPre and others 2000; Prinjha and others 2000). Typical for the reticulon family, all three isoforms share the same C-terminal reticulon homology domain (RHD), consisting of two hydrophobic membrane domains flanking a hydrophilic 66 amino acids long region, termed Nogo-66 (GrandPre and others 2000). The N-termini on the contrary exhibit a large diversity (Schwab 2010). Neither Nogo-B (which is lower expressed in oligodendrocytes) or Nogo-C (which is mainly located in peripheral tissues) nor Rtn1, Rtn2 or Rtn3 (all of which also contain a RHD) but solely Nogo-A was shown to exert strong inhibitory effects in the CNS (GrandPre and others 2000; Huber and others 2002), suggesting that an important functional domain is located in the Nogo-A-specific part of the amino-terminus. Such a region possessing neurite growth and fibroblast spreading inhibitory activity was found by screening a Nogo-A deletion construct library and was termed Nogo-A-Δ20 (Oertle and others 2003). However, also the carboxy-terminal Nogo-66 domain of Nogo-A (but not the reticulon homology domains of the other reticulon family members) was recognized to possess strong inhibitory activity for neurite growth (Fournier and others 2001). Although sufficient to exert their inhibitory functions, both Nogo-A-Δ20 as well as Nogo-66 were shown to possess even stronger activity when being part of a larger Nogo-A-derived fragment, such as Nogo-A-ext (also known as NiR-G; rat aa 1-979) or Nogo-22 (rat aa 966-1163), respectively (Huebner and others 2011; Oertle and others 2003).

## Topology and Structure

Again typical for reticulons are the long transmembrane regions of Nogo-A. These allow at least two conformations in the plasma membrane, as they can either span the whole membrane or fold into a hairpin as depicted in Figure 1A (Schwab 2010). Importantly, both active domains, Nogo-66 as well as Nogo-A-Δ20, were detected on the surface of oligodendrocytes (Dodd and others 2005; GrandPre and others 2000; Oertle and others 2003) and thus are able to engage in trans signaling processes. Furthermore, in the tubular endoplasmatic reticulum (ER), membrane curvature was suggested to depend on Nogo-A being available in two possible topologies (as demonstrated in Fig. 1A): N- and C-termini are found in the cytosol and only Nogo-66 can be localized to the ER lumen (Voeltz and others 2006). Given the intriguing topology, there is a strong interest in better understanding the overall structure of Nogo-A. A detailed structural analysis, however, has been proven unsuccessful so far. This is most likely due to the strong disordered character of the reticulon protein. Neural network–based prediction of disordered regions in Nogo-A using the VL3H predictor (Sickmeier and others 2007) suggests the amino-terminus of Nogo-A to be mainly disordered, whereas the reticulon homology domain is predicted to possess a more ordered structure (Fig. 1B). Indeed it was possible to resolve the structure of Nogo-66 when purified separately from the rest of the protein and consequently predict residues 28 to 58 to be available for binding to NgR1 (Vasudevan and others 2010). However, surprisingly a membrane mimetic in the form of dodecylphosphocholine (DPC) micelles or dimyristoyl-phosphatidylcholine (DMPC) liposomes was required for Nogo-66 to fold into its final conformation and make the transition from disordered to ordered (Fig. 1C) (Vasudevan and others 2010). As Nogo-A-Δ20 as well as NiR-G were also proven experimentally to be highly disordered in solution (Li and others 2004a; Li and Song 2007) and because circular dichroism spectroscopy did not show any structural enhancement on the co-incubation with 100-nm sized DMPC liposomes (unpublished observations), it is possible that the N-terminal part of Nogo-A is also disordered under physiological conditions. This would not come as a surprise, because intrinsically disordered proteins or regions of proteins are well known for their involvement in a high number of biological processes, such as signal transduction, regulation, and control. Thereby they were shown to be able to enhance multiple binding of one protein to many partners as well as

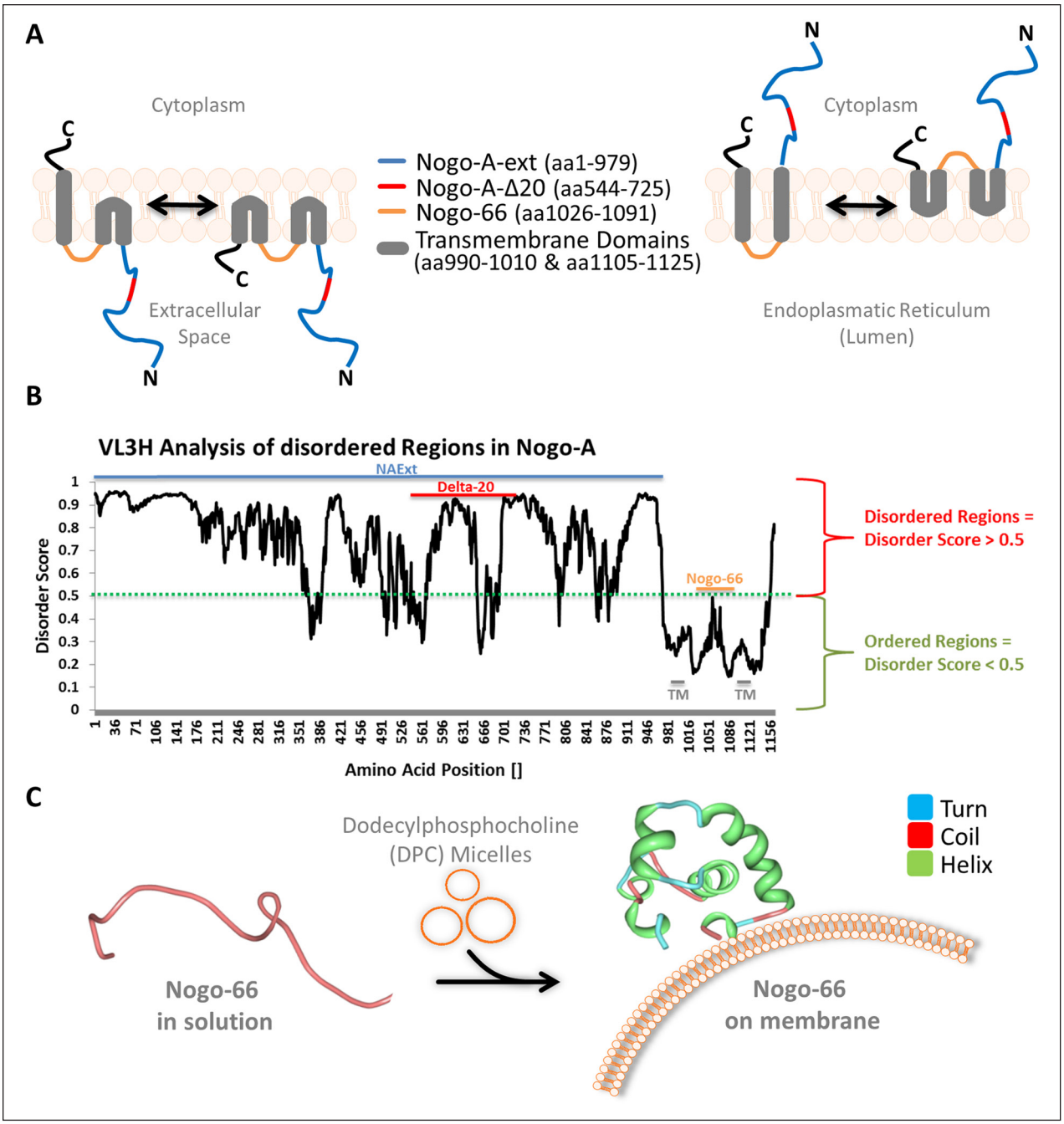


**Figure 1.** Functional domains, topologies, and structure of Nogo-A. (A) Several topologies for Nogo-A in the plasma membrane are possible as shown on the left. The C-terminal transmembrane domain can either span the whole membrane or fold into a hairpin. In either case, both functional domains, the C-terminal Nogo-66 region as well as the Nogo-A-Δ20 domain incorporating N-terminal Nogo-A-ext region, can be detected on the extracellular membrane surface. In the tubular endoplasmatic reticulum (ER), membrane curvature was suggested to depend on Nogo-A being available in two possible topologies (as depicted on the right): N- and C-termini are found in the cytosol and only Nogo-66 can be localized to the ER lumen! The different domains of Nogo-A correspond to the rat amino acid (aa) sequence. (B) Intrinsic disorder prediction by VL3H for Nogo-A suggests Nogo-A-ext to be highly disordered. (C) Nogo-66 requires a membrane or membrane mimetic like dodecylphosphocholine (DPC) in order to make the transition from a disordered to an ordered protein. Membrane-assisted folding was not detected for Nogo-A-Δ20 so far, as measured by circular dichroism spectroscopy (unpublished observations).

high-specificity low-affinity interactions (Sickmeier and others 2007). Future studies will reveal whether these highly specific low-affinity bindings as well as the existence of multiple binding partners are also characteristic for signaling of the Nogo-A-specific functional domain.

## Signaling

Different receptors and coreceptors have been described for Nogo-A (Fig. 2). Nogo-66, next to the two other structurally unrelated myelin-associated proteins, oligodendrocyte-myelin glycoprotein (OMgp) and myelin-associated glycoprotein (MAG), was shown to directly bind to two neuronal receptors: the Nogo-66 receptor NgR1 and the paired immunoglobulin-like receptor B (PirB) (Atwal and others 2008; Domeniconi and others 2002; Fournier and others 2001; Wang and others 2002b). Although little is known about PirB so far, NgR1 has been extensively studied since its discovery more than a decade ago. It is well accepted today that this Nogo-66 receptor acts in concert with different coreceptors. This is necessary, given the fact that NgR1, being a glycosylphosphatidylinositol (GPI) anchored membrane protein, does not contain a cytosolic domain. To convert extracellular ligand-encoded information into intracellular signaling events, NgR1 thus interacts with the leucine-rich repeat and Ig domain-containing Nogo receptor-interacting protein LINGO-1 (Mi and others 2004). Furthermore, this receptor complex was shown to either contain the low-affinity neurotrophin receptor $p75^{NTR}$ (Wang and others 2002a) or the related tumor necrosis factor-α receptor superfamily member 19, also known as TROY (Park and others 2005). The nature of the Nogo-A-Δ20-specific receptor has been difficult to identify. Whereas integrins seem to be indirectly involved in signaling of the amino-terminal part of Nogo-A (Hu and Strittmatter 2008), a direct interaction could not be detected so far. However, at least three indications suggest the existence of a neuronal Nogo-A-specific receptor. First, Nogo-A-Δ20 was demonstrated to not only bind to the surface of neurons but also to be endocytosed in a pincher-dependent manner (Joset and others 2010). Second, Nogo-A-Δ20 is able to induce a wide range of intracellular changes (Kempf and Schwab 2013). Third, this Nogo-A-specific domain is able to inhibit spreading of 3T3 fibroblasts independent of the Nogo-66 receptor, as these cells do not express NgR1 (Oertle and others 2003).

Although both active Nogo-A domains are thought to target distinct receptors, they were demonstrated to modulate the same intracellular signaling pathway: They both activate the small GTPase RhoA (Nash and others 2009; Niederost and others 2002). Being activated, RhoA is able to bind to the Rho binding domain (RBD) of the Rho-associated coiled-coil-containing protein kinase (ROCK), subsequently resulting in activation of this kinase (Schmandke and others 2007). Many effectors are known to be phosphorylated by ROCK, mainly resulting in rearrangement of the cytoskeleton (Schmandke and others 2007). Three of these effectors, the LIM-domain (Lin11, Isl1, Mec3)-containing protein kinase (LIMK), Myosin Light Chain 2 (MLC2), and Collapsin Response Mediator Protein 2 (CRMP2), have been shown to primarily account for the functional effects observed in neurons on exposure to Nogo-A (Fig. 2). Phosphorylation of LIMK enables this enzyme to phosphorylate and thus inactivate cofilin at an early timepoint after stimulation with Nogo-A. Interestingly, a delayed activation of slingshot phosphatase (SHH) was demonstrated, subsequently to LIMK activation, resulting again in dephosphorylation of cofilin and LIMK (Hsieh and others 2006). These temporal changes in cofilin activation correspond to its actin severing activity: First, actin turnover is diminished resulting in reduced growth of filaments since less momomers are being incorporated; later SHH dependent activation induces actin filament dissolution increasing growth cone collapse activity. MLC2 phosphorylation on the other hand was demonstrated to modulate actomyosin contraction. It thus does not come to a surprise that both LIMK as well as MLC2 have been implicated to play a central role in highly actin-dependent processes such as growth cone collapse and neurite outgrowth inhibition (Aizawa and others 2001; Amano and others 1998; Nash and others 2009). Further contributing to these morphological perturbations is the ROCK-mediated phosphorylation of CRMP2, resulting in an increased destabilization of microtubules (Mimura and others 2006).

Apart from the RhoA-ROCK signaling pathway, not much is known for Nogo-A in terms of intracellular signaling cascades. Although it is still unclear whether and if so by what domain Nogo-A induces intracellular calcium increase, first evidence was provided for transcriptional changes, induced by Nogo-A-Δ20 (Joset and others 2010). Despite the intriguing observation of reduced levels of phosphorylated cyclic AMP response element-binding (pCREB) in response to Nogo-A-Δ20 (Joset and others 2010), very little is known about direct transcriptional changes induced by Nogo-A in neurons. Proteomic analysis of spinal cord tissue from Nogo-A null versus wild type mice showed regulation of cytoskeleton-, transport-, and signaling growth-related proteins (Montani and others 2009). However, the cellular basis of these changes and the role that transcriptional mechanisms play in these regulations remain to be determined. A comprehensive analysis, employing powerful nucleic acid detection methods, such as deep-sequencing in combination with in-depth bioinformatics, will be helpful to shed light on a range of Nogo-A-induced transcriptional effects such as

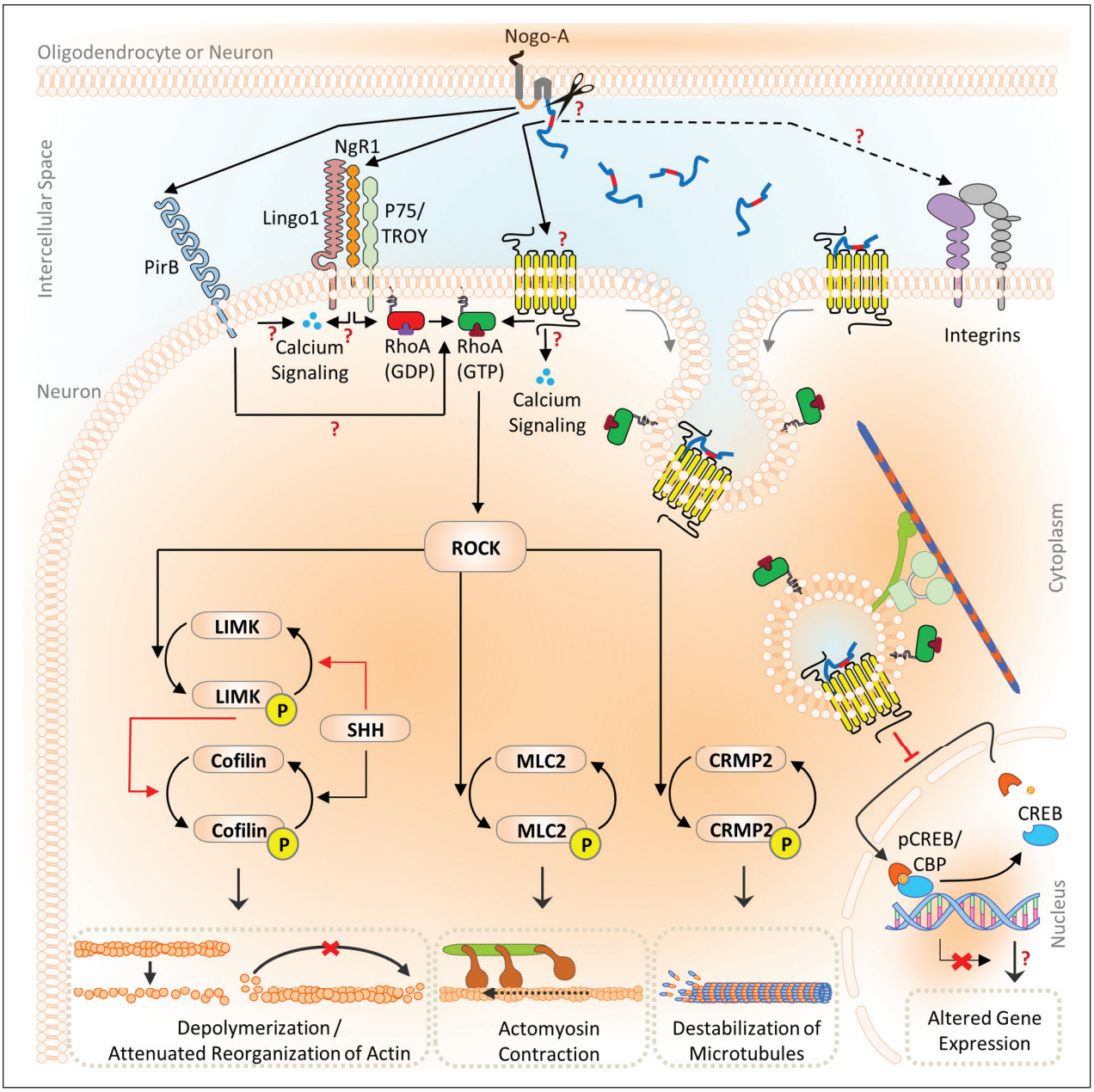


**Figure 2.** Nogo-A receptors and signaling. The main signaling pathways targeted by Nogo-A. Nogo-A-Δ20 and Nogo-66 both are known to activate the RhoA/ROCK pathway, resulting in depolymerization or attenuated reorganization of the actin cytoskeleton, increased actomyosin contraction, as well as reduced stabilization of microtubules. Furthermore, Nogo-A-Δ20 was demonstrated to inactivate CREB on pincher-mediated endocytosis, possibly affecting gene expression. Additionally, the Nogo-A-Δ20 domain is implicated in negative regulation of integrin activation. Two different receptors have been described for Nogo-66 (PirB and the NgR1-Lingo1-p75/Troy-receptor complex); the functional receptor(s) for Nogo-A-Δ20 remain to be characterized. Furthermore, it is still unclear whether and if so what part of Nogo-A is involved in modulation of intracellular calcium transients as suggested by earlier studies using purified myelin proteins with neurite outgrowth inhibitory activity. Finally, given the fact that Nogo-A-Δ20 signaling was demonstrated to be highly dependent on endocytosis in vitro, it will be crucial to investigate the existence of soluble Nogo-A fragments in vivo and, if so, identify underlying mechanisms and/or Nogo-A-specific proteases. For full names of the depicted proteins please refer to the main text.

gene expression, modulation of alternative splicing, or direct and indirect transcription factor modulation. Finally, given the fact that Nogo-A-Δ20 signaling was demonstrated to be highly dependent on endocytosis in vitro, it will be crucial to investigate the existence of soluble Nogo-A fragments in vivo and, if so, identify


**Figure 3.** Complexity of Nogo-A signaling. Nogo-A signaling is dependent on several variables, regulated over time (development/adulthood), space (cell type/microdomain), and disease state. The variables are partially dependent on each other. Changing one variable modulates at least one other.

underlying mechanisms and involved proteases. Figure 3 depicts the complexity in Nogo-A signaling that becomes apparent by integrating all the data as reviewed above: With up to seven interacting variables that can be modulated over time, space, and disease, study of Nogo-A signaling requires well-defined systems. It remains one of the great challenges of the near future to define the compositions and interactions of the Nogo-A multi-subunit receptor complex and its downstream effectors in various cell types, microdomains (e.g., lipid rafts), and cellular compartments (e.g., signaling endosomes) during development, in the adult and in disease.

## Roles in Development of the Nervous System

Even though initially identified as a myelin-associated inhibitor of neurite growth in the adult CNS, Nogo-A was shown to possess additional functions during development, where it was found to be primarily expressed in peripheral as well as central neurons (Huber and others 2002). Inhibition of Nogo-A in cultured dorsal root ganglia (DRG) neurons from newborn mice using a function blocking antibody directed against a part of the Nogo-A-specific N-terminus, or genetic ablation of Nogo-A in these neurons, resulted in a significant increase of growth cone area and motility, in enhanced neurite outgrowth, and in increased neurite fasciculation (Petrinovic and others 2010). Furthermore, inhibition of Nogo-A proofed to increase sprouting in the adult CNS, suggesting a continuous inhibitory role of Nogo-A on axon growth/sprouting beyond development (Buffo and others 2000). Functions in axon guidance were shown in prenatal mice. Nogo-A expressing radial glia repulse optic nerve axons in the optic chiasm, possibly via interaction with neuronal NgR1, because not only function-blocking antibodies raised against Nogo-A but also a function blocking peptide directed against the Nogo-66 receptor were able to disturb axon growth, resulting in axonal misprojections (Wang and others 2008). Similarly, Nogo-A might be involved in ventral midline repulsion of spinal cord commissural axons (Wang and others 2010). Neuronal Nogo-A expression rapidly decreases during early postnatal development—with the exception of neurons located to centers of high plasticity in the brain—whereas a strong increase in oligodendrocyte-derived Nogo-A can be observed (Huber and others 2002). Interestingly, also Nogo-A localized to oligodendrocyte myelin was observed to execute axon guidance functions during this early postnatal phase. This becomes especially apparent in the dorsal column of the spinal cord in rats, where the earlier established myelinated ascending sensory tracts channel the developmentally delayed appearing corticospinal tract (Schwab and Schnell 1991). In the PNS, Nogo-A is expressed developmentally by both DRG and motoneurons and their axons. An increase in fasciculation, possibly by loss of mutual, Nogo-A mediated repulsion, as well as a decrease in branching of peripheral neurites, was detected in vitro as well as in chicken embryos, treated with anti-Nogo-A antibodies or in embryos from Nogo-A null mice (Petrinovic and others 2010). The developing cerebellum of mice Nogo-A, which is transiently expressed in Purkinje cells during early postnatal development, was found to be important for dendritic arborization and formation of their input synapses: Genetic deletion of Nogo-A resulted in larger, more complex dendritic trees and larger and stronger parallel fiber synapses, whereas the opposite was observed for Nogo-A overexpressing Purkinje cells (Petrinovic and others 2013).

Next to its effects on neurons during development of the nervous system, Nogo-A was additionally found to be a developmental regulator of oligodendrocyte myelin formation in the cerebral cortex of mice (Chong and others 2012) as well as the optic nerve (Chong and others 2012; Pernet and others 2008). An overview of developmental processes that are regulated by Nogo-A can be found in Figure 4.

Even though Nogo-A was initially found to not only possess inhibitory functions on neurite outgrowth but

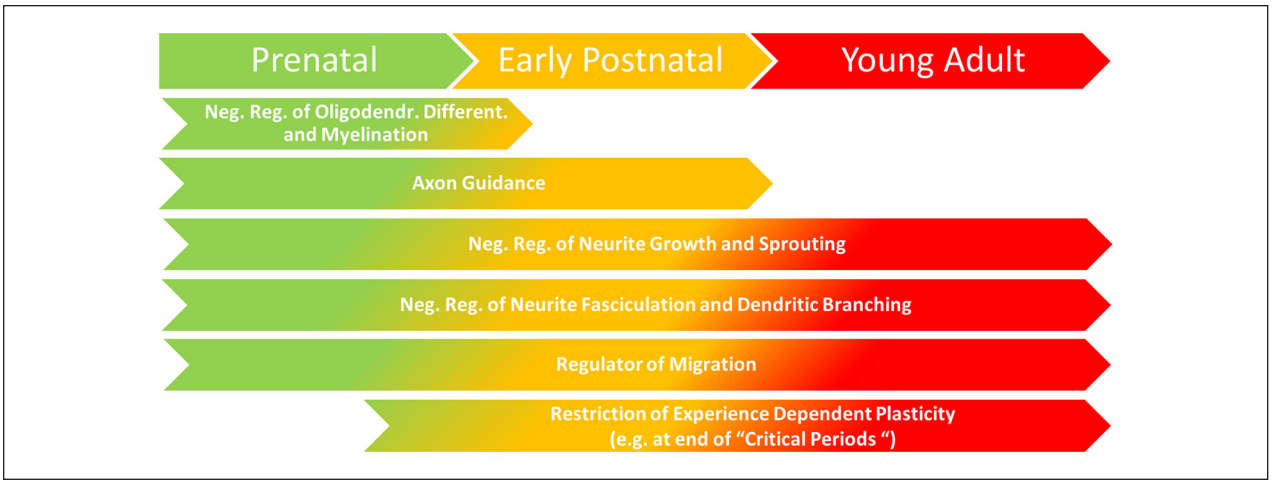


**Figure 4.** Roles of Nogo-A in nervous system development. Nervous system development requires a minute orchestration of events. Nogo-A is known to participate in this regulation. Neurodevelopmental processes modulated by Nogo-A in rodents can be detected prenatally (marked in green), during early postnatal development (marked in yellow), and up to late developmental phases (marked in red). Oligodendr. Different. = oligodendrocyte differentiation.

also on cell adhesion and spreading, not much was known for a long time concerning its involvement in adhesion-dependent processes such as migration of cells in the CNS. However, mainly in the last 6 years this property has been rediscovered and was analyzed in a range of in vitro and in vivo systems (Schmandke and others 2013a). Strikingly, the effects observed for Nogo-A on adhesion and migration are highly diverse (as summarized in Table 1). This is probably attributable to a number of variables, ranging from intrinsic and extrinsic factors such as cell type and local environment up to the mode of migration. Recent advances in systems biology (Schmandke and others 2013b) will be helpful in dissecting underlying mechanisms for Nogo-A's modulation of adhesion and cell migration.

## Nogo-A modulates synaptic plasticity in the adult CNS

Next to the roles of Nogo-A during development, it becomes more and more apparent that this molecule is also involved in the regulation of synaptic plasticity. Monocular deprivation-induced large shifts of ocular dominance, which are normally limited to a postnatal critical period between P20 and P32 in mice, were still detectable at P45 and P120 of NgR1- and Nogo-A-null animals (McGee and others 2005). Consequently, NgR1 seems to be crucial for consolidation of neural circuits, established during experience-dependent plasticity. A mechanism underlying the effects observed could possibly be linked to changes in turnover of synaptic anatomy, as recently described for the cerebral cortex (Akbik and others 2013). Nogo-A and NgR1 have been detected pre- and postsynaptically in several neuronal subpopulations within the plastic regions of the CNS (Aloy and others 2006; Lee and others 2008; Liu and others 2003b; Wang and others 2002c). In hippocampal slice cultures, acute neutralization of Nogo-A or NgR1 using function blocking antibodies increases long-term potentiation (LTP). However, long-term depression (LTD), short-term plasticity, or basal synaptic transmission are unaffected (Delekate and others 2011). Stimulation of Ngr1 with either Nogo-66 or OMgp decreases LTP (Raiker and others 2010). Whereas Nogo-A, NgR1, and PirB null mice show no significant modulation of hippocampal LTP, possibly because of compensatory mechanisms during development, LTD is only attenuated in NgR1 null mice (Delekate and others 2011; Karlen and others 2009; Lee and others 2008; Raiker and others 2010). No changes in hippocampal LTD are observed for Nogo-A or PirB null mice. Interestingly, unpublished observations from our laboratory show that similar mechanisms of modulating synaptic plasticity are present in acute slices of the rat motor cortex. Acute neutralization of Nogo-A or NgR1 increases LTP, whereas LTD is unchanged. In line with these in vitro effects, in vivo infusion of function blocking anti-Nogo-A antibodies enhance motor skill learning in adult rats.

Similar to other inhibitory molecules such as ephrins or semaphorins, Nogo-A has been speculated to modulate synaptic function via the pre- and/or postsynaptic cytoskeleton through activation of RhoA/ROCK and subsequent activation of LimK and cofilin (Delekate and others 2011). Several findings support this hypothesis: Whereas

**Table 1.** Nogo-A's Diverse Roles in Adhesion and Migration.

| System | Perturbation | Effect | Reference |
|---|---|---|---|
| Spreading of 3T3 fibroblasts (in vitro) | Cells are plated on membrane protein fractions containing Nogo-A | Spreading inhibition | (Caroni and Schwab 1988b) |
| Spreading of 3T3 fibroblasts, CHO cells, primary neurons (in vitro) | Cells are plated on recombinant Nogo-A-Δ20 | Spreading inhibition | (Oertle and others 2003) |
| Spreading and migration of primary brain microvascular endothelial cells (in vitro) | Cells are plated on recombinant Nogo-A-Δ20 | Inhibition of spreading and migration | (Walchli and others 2013) |
| Neuroblast migration along the rostral migratory stream in the adult mouse brain | Intraventricular infusion with anti-Nogo-A antibody "11C7" for 7 days | Reduced neuroblast migration toward the olfactory bulb | (Rolando and others 2012) |
| Adhesion and motility of embryonic neuronal precursors from cortices of Nogo-A null mice (in vitro) | Comparison of wild type vs. Nogo-A null precursors | Decreased adhesion and increased motility on Nogo-A deletion | (Mathis and others 2010) |
| Adhesion and motility of neurospheres derived from cortices of embryonic mice (in vitro) | Neurospheres are treated with anti-Nogo-A, -NgR1, or -Lingo-1 | Decreased adhesion and increased motility | (Mathis and others 2010) |
| Radial migration of neuronal precursors in the cortex of embryonic mice | Comparison of wild type vs. Nogo-A null mice | Nogo-A deletion → Loss of transient accumulation of radially migrating precursors at E17.5; disturbed migration to upper cortical layers at E19 | (Mathis and others 2010) |
| Tangential migration of cortical neurons in E12.5 mice | Comparison of wild type vs. Nogo-A/B/C null mice | Nogo-A/B/C deletion → Delay in the tangential migration of E12.5 cortical neurons | (Mingorance-Le Meur and others 2007) |
| Adhesion and migration of olfactory ensheathing cells (in vitro) | Stimulation with recombinant Nogo-66 | Reduced adhesion and migration | (Su and others 2007) |
| Implanted olfactory ensheathing cells in a spinal cord hemisection injury model | Treatment with anti-NgR1 | Facilitated migration of implanted olfactory ensheathing cells | (Su and others 2007) |
| Adhesion of myeloid dendritic cells (in vitro) | Mature (high NgR1/2 levels) vs. immature (lower NgR1/2 levels) dendritic cells are plated on myelin or recombinant Nogo-66 | Down-regulation of NgR1/2 promotes adhesion of dendritic cells to myelin/ Nogo-66 | (McDonald and others 2011) |
| Leukocyte infiltration into the central nervous system | Comparison of NgR1/2 double null vs. wild type mice | NgR1/2 null mice: increased leukocyte infiltration into the central nervous system | (Steinbach and others 2011) |
| Adhesion and migration of microglia (in vitro) | Stimulation with recombinant Nogo-66 | Inhibition of adhesion and migration | (Yan and others 2012) |

A detailed discussion of Nogo-A's functions in these processes as well as the results of an investigation of Nogo-A's long hypothesized involvement in cerebellar granule neuron migration has been published recently (Schmandke and others 2013a).

Nogo-A is known to activate the Rho-A/ROCK pathway (Figure 2), the amount of postsynaptic densities (PSDs) that are positive for phosphocofilin increases after LTP induction (Rex and others 2009). Furthermore, an abnormal spine morphology and increased LTP as well as impaired spatial learning is detected in limk null mice (Meng and others 2002). Taken together, these results suggest a role for Nogo-A in mature neuronal networks. Whereas Nogo-A might serve as negative regulator of functional and structural plasticity, acute blockade of

either Nogo-A or NgR1 might increase plasticity and promote learning at a circuit level (Delekate and others 2011).

## Functions in Disease/Trauma of the Nervous System

Nogo-A has been implicated in a range of diseases and disturbances of the nervous system, from trauma such as spinal cord injury or stroke to neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and psychiatric diseases. The current state of knowledge for Nogo-A's involvement in these nervous system diseases and perturbations shall be summarized below. Key mechanisms, central to functions of Nogo-A in these diseases, are depicted in Figure 5. Intriguingly, developmentally beneficial properties of the protein could have negative consequences for regenerative or plastic events after injury or in disease: Outgrowth inhibition and neurite repulsion terminate critical, highly plastic developmental periods and stabilized the CNS wiring, but they also inhibit axonal regrowth and compensatory sprouting in the injured adult system (Schwab 2010). Nogo-A can hinder myelination and remyelination of regenerating axons as well as newly formed fibers (Chong and others 2012), and restriction of synaptic plasticity could prevent establishment of new functional circuits (Kempf and Schwab 2013).

### *Spinal Cord Injury*

Since more than two decades, the role of Nogo-A has been studied in spinal cord injury (SCI). Initially found to enhance regeneration of lesioned axons in the spinal cord (Schnell and Schwab 1990), anti-Nogo-A antibodies and later developed tools, such as NgR1 receptor blockers (e.g., NgR blocking peptide NEP1-40, soluble NgR-Fc, Lingo-Fc fusion proteins), as well as mutant animals (e.g., Nogo-A-null, NgR1-null mice, Nogo-A knock down rats, ROCKII-null mice), have been used extensively to further investigate Nogo-A's impact on the CNS on injury (Duffy and others 2009; GrandPre and others 2002; Kim and others 2004; Li and others 2004b; Zorner and Schwab 2010). Today it becomes increasingly obvious that next to an increase in regenerative growth (Schnell and Schwab 1990) and regenerative sprouting of injured axons (Liebscher and others 2005), functional improvements on blockade of Nogo-A signaling additionally rely on compensatory sprouting of unlesioned fibers. That even anatomically distinct systems can functionally compensate for lesion-induced defects has been demonstrated in anti-Nogo-A antibody-treated rats. On pyramidal lesion of both cortico-spinal tracts (CSTs), rubrospinal fibers of these animals were shown to partially compensate for lesion-induced defects by sprouting into the deafferented spinal gray matter (Raineteau and others 2001). Because of the promising effects observed in animal SCI models including macaques on anti-Nogo-A antibody treatment, a human antibody was developed in collaboration with Novartis (ATI 355). A clinical trial investigating the effects of ATI 355 intrathecal application in acute functionally complete or incomplete SCI patients (ASIA A-C) with thoracic and cervical injuries has been started in 2006. Clinical trial Phase I has been completed and revealed excellent safety and tolerance of the antibody treatment.

### *Stroke*

Similar to SCI, enhanced compensatory sprouting and structural plasticity is also observed after stroke in Nogo-A or NgR1-deficient mice as well as in animals treated with NgR1 receptor inhibitors or functional blocking antibodies against Nogo-A (Kartje and others 1999; Lee and others 2004; Markus and others 2005; Wiessner and others 2003). Acute as well as 1 week delayed anti-Nogo-A or NgR blocking peptide treatment of rats exposed to a unilateral photothrombotic lesion of the cortex or a middle cerebral artery occlusion (MCAO) induced compensatory sprouting of fibers from the motor cortex of the contralesional, intact hemisphere as measured by increased spinal midline crossing fibers (Lee and others 2004; Wiessner and others 2003). Intriguingly, postinjury recovery of the affected forelimb's grasping function highly correlated with the number of cervical midline crossing fibers (Wiessner and others 2003). Similar rearrangements were observed in a third stroke model. Nogo-A-antibody infusion of rats after unilateral aspiration of the sensorimotor cortex resulted in increased innervation of the ipsilesional striatum by cortical contralesionally derived projections (Kartje and others 1999). Using different lesion paradigms, Emerick and others (2003) as well as Lindau and others (Lindau et al., 2013) demonstrated that functional blockade of Nogo-A by antibodies in stroke rats led to movements of the impaired, paretic forelimb in response to microstimulation of the spared, ipsilateral cortex. Furthermore, enhanced structural plasticity was observed in anti-Nogo-A antibody treated rats after unilateral MCAO resulting in adaptive rearrangements of the somatosensory system (Markus and others 2005). Given its restrictive function on synaptic plasticity as discussed above, it is not unlikely that next to the structural plasticity observed, Nogo-A-signaling inhibition might also be beneficial for establishment of new synapses. Future studies will be needed to address this question.

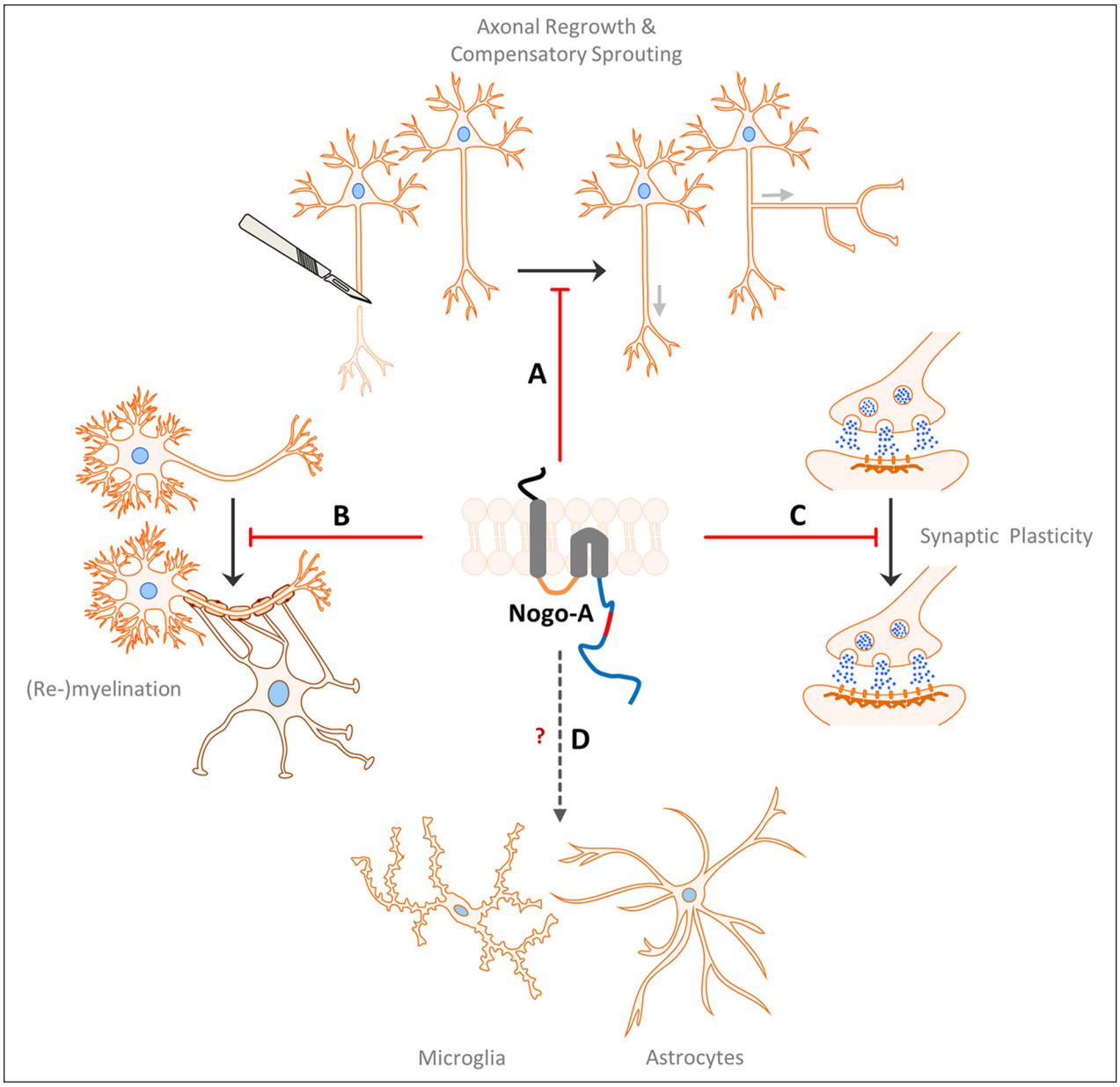


**Figure 5.** Cellular functions of Nogo-A in disease/trauma of the nervous system. Nogo-A has been implicated in a range of diseases and disturbances of the nervous system, from trauma such as spinal cord injury or stroke to neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and schizophrenia. On the cellular level, several effects of Nogo-A can be distinguished: (A) Outgrowth inhibition and repulsion of neurites inhibit axonal regeneration and compensatory sprouting. (B) Decreased myelinogenic potential induced by Nogo-A hinders myelination and remyelination. (C) Restriction of synaptic plasticity could prevent adaptation and establishment of new functional circuits. (D) Possible roles of Nogo-A for astrocytes, microglia/macrophages/inflammatory cells, for example, with regard to cell migration and recruitment to lesion site.

## *Amyotrophic Lateral Sclerosis*

In a study by Dupuis and colleagues in 2002, Nogo-A was found to be up-regulated at early stages of motoneuron disease using the transgenic G86R SOD1 mouse model (Dupuis and others 2002). These results were confirmed in postmortem biopsy samples from diagnosed ALS patients in comparison to healthy

controls. Five years later, Nogo-A expression in muscle biopsies of patients with lower motor neuron syndrome (LMNS) correctly identified patients who further progressed to ALS with 91% accuracy, 94% sensitivity, and 88% specificity (Pradat and others 2007). In these cases, Nogo-A up-regulation was detected as early as 3 months after the onset of symptoms. Whether and how Nogo-A is causally linked to disease progression is still unclear. On the one hand, Jokic and colleagues demonstrated enhanced survival and reduced muscle denervation in Nogo-A$^{-/-}$ mice crossed to G86R SOD1 mice as well as a shrinkage of the postsynapse and retraction of the presynaptic motor ending in mice overexpressing Nogo-A (Jokic and others 2006). On the other hand, Yang and colleagues later showed that Nogo-A may enhance survival in ALS mice by redistributing protein disulfide isomerase (PDI) to a subcellular compartment of uncertain identity (Yang and others 2009). This contrasting role of Nogo-A in ALS disease progression is puzzling and possibly because of the different genetic lines used for the studies. Whereas Jokic and colleagues used the Nogo-A$^{-/-}$ line, which still expresses Nogo-B and Nogo-C, Yang and colleagues performed their experiments in Nogo-A$^{-/-}$ mice in which both Nogo-A and -B isoforms were deleted. Furthermore, Yang and colleagues used another SOD1 line carrying the G93A instead of the G86R mutation. Despite this controversy, GlaxoSmithKline has developed a humanized anti-Nogo-A antibody (Ozanezumab) that has successfully passed safety tests in clinical trial phase I and is currently being tested in a 48-week, randomized, multi-center, double-blind, placebo-controlled, parallel group phase II clinical trial for efficacy and safety of intravenous application of the antibody to ALS patients.

## Alzheimer's Disease

A prominent characteristic of Alzheimer's disease (AD) is the deposition of cerebral amyloid-β (Aβ) aggregates in form of amyloid plaques (Glenner and others 1984). Interestingly, one of the main secretases involved in processing of the amyloid precursor protein (APP) to Aβ—the β-amyloid converting enzyme 1 (BACE1)—was previously shown to physically interact with reticulon proteins 1–4. Furthermore, this interaction was suggested to account for the reduced production of Aβ observed on up-regulation of reticulon proteins (He and others 2004). Surprisingly, also the Nogo-66 receptor has been implicated in the disease (Park and others 2006a; Park and others 2006b; Zhou and others 2011). However, whereas NgR1 was shown by independent groups to bind to APP, opposite effects of this interaction have been described (Park and others 2006a; Zhou and others 2011): James Park and colleagues observed decreased Aβ production on overexpression of NgR1 in neuroblastoma in vitro. Ablation of NgR1 in vivo resulted in higher Aβ levels, increased Aβ plaque depositions, as well as more dystrophic neurites in brains of AD mice. Treatment of the same mice with the soluble truncated form of the Nogo-66 receptor (NgR-FC) yielded the expected opposite effects (Park and others 2006a). Furthermore, subcutaneously delivered NgR-FC was shown to also bind to Aβ in the periphery, resulting in reduces Aβ levels in the brain of AD mice as well as improvements in spatial memory of these animals (Park and others 2006b). In contrast to these findings, the group headed by Riqiang Yan observed reduced surface expression and favored processing of APP by BACE1 on interaction of Nogo receptors 1–3. Additionally, Nogo receptor 2 (NgR2) ablation in AD mice resulted in reduced amyloid deposition (Zhou and others 2011). Hence, further data are needed to be able to understand the spectrum of roles possibly played by Nogo-A and NgR1-3 in APP and Aβ processing and a possible clinical potential of Nogo—Nogo receptor modulation for AD.

## Psychiatric Diseases

The majority of the information on Nogo-A's possible involvement in psychiatric diseases was derived from genetic association studies (Willi and Schwab 2013). Interestingly, the genes of both Nogo and NgR1 were found to be associated with schizophrenia or bipolar disease in some families. Intriguingly, Nogo is located on chromosome 2p16, a region implicated in these disorders (Lewis and others 2003; Liu and others 2003a). Additionally, postmortem analysis of frontal cerebral cortices derived from schizophrenia patients revealed increased Nogo-A mRNA levels (Novak and others 2002). Similarly, the Nogo-66 receptor NgR1 localizes to chromosome 22q11—a chromosome also known to be associated with an increased risk of psychiatric diseases (Budel and others 2008). Depending on the population assessed, mutations in NgR1 were either found to weakly but significantly correlate with the disease or did not show a significant association (Budel and others 2008). Four rare non-conservative coding sequence variants of NgR1 found in psychiatric families were demonstrated to be dysfunctional in vitro as shown by their inability to transduce myelin-induced neurite outgrowth inhibition (Budel and others 2008). Given the involvement of Nogo-A and NgR1 in structural and synaptic plasticity, it is conceivable that these mechanisms, when constitutively being impaired, may underlie the increased risk for schizophrenia observed. The importance of dysfunctional Nogo-A and NgR1 for the onset of psychiatric diseases has been supported by transgenic animal studies. Not only phenotypic abnormalities but also neurochemical

alterations have been observed in these mice, both of which are known to resemble schizophrenia (Budel and others 2008; Willi and others 2010). Schizophrenia-related endophenotypes linked to Nogo-A-null mice and Nogo-A knock down in rats include deficient sensorimotor gating, disrupted latent inhibition, perseverative and antisocial behavior, as well as increased sensitivity to amphetamine (Tews and others 2013; Willi and others 2010).

### *Multiple Sclerosis*

The idea that Nogo-A could be relevant for multiple sclerosis (MS) arose from a number of distinct observations. Most important, genetic deletion of Nogo-A/B in mice with a C57BL/6 (H-2b) background as well as Nogo-A blockade using anti-Nogo-A antibodies proved to be beneficial on experimental autoimmune encephalomyelitis (EAE) induction (Fontoura and others 2004; Karnezis and others 2004). Both the N-terminal as well as the C-terminal active domains of Nogo-A were demonstrated to underlie the effects observed (Fontoura and others 2004; Karnezis and others 2004). Thus, vaccination with an anti-Nogo-A-Δ20 peptide (directed against aa 623-640) as well as treatment with anti-Nogo-A antibody not only protected animals from MOG35-induced EAE but also led to a reduction in demyelinating lesions and axonal degeneration (Karnezis and others 2004). Next to the direct effects observed in EAE models for Nogo-A, also expression data suggest a possible involvement of Nogo-A in MS or similar diseases. Nogo-A as well as its receptor NgR1 are not only up-regulated in active demyelinating lesions (Satoh and others 2005) but also were found to correlate—regarding their expression levels in the spinal cord—with the progression of EAE (Theotokis and others 2012). Furthermore, as described above, Nogo-A has been shown to exert modulatory functions on oligodendrocyte differentiation and myelination processes that are needed to repair myelin. To what extend Nogo-A inhibition is also beneficial in humans suffering from MS is currently being investigated. Phase 1 clinical trials testing intravenously applied anti-Nogo-A antibodies (GSK1223249) in MS patients were recently conducted by GlaxoSmithKline.

## Conclusions

Initially discovered as an important neurite outgrowth inhibitor, the membrane protein Nogo-A has emerged as a multifunctional protein in the CNS. Next to its many roles in development and beyond, Nogo-A appears to be implicated in a number of different neurological diseases. Future studies will help further elucidate the underlying mechanisms as well as the functional relevance and therapeutic potential of targeting Nogo-A in the injured or diseased CNS.

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