The Nogo-66 receptor: focusing myelin inhibition of axon regeneration

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CNS myelin inhibits axonal outgrowth *in vitro* and is one of several obstacles to functional recovery following spinal cord injury. Central to our current understanding of myelin-mediated inhibition are the membrane protein Nogo and the Nogo-66 receptor (NgR). New findings implicate NgR as a point of convergence in signal transduction for several myelin-associated inhibitors. Additional studies have identified a potential coreceptor for NgR as p75[NTR], and a second-messenger pathway involving RhoA that inhibits neurite elongation. Although these findings expand our understanding of the molecular determinants of adult CNS axonal regrowth, the physiological roles of myelin-associated inhibitors in the intact adult CNS remain ill-defined.

Classic peripheral nerve graft studies illustrate that damaged axons have the capacity for regenerative outgrowth when provided with a permissive substrate [1,2]. It is not the absence of growth-promoting molecules in the CNS but, rather, the presence of axon outgrowth inhibitors in CNS astroglial 'scars' [3] and CNS myelin [4,5] that suppresses the regrowth of damaged axons. Inhibition by CNS myelin can be alleviated using antibodies directed against inhibitory components of myelin [6,7] or by trophic-factor supplements [8]. Understanding how the various factors associated with myelin contribute to repressing axon extension could provide opportunities for positive intervention to improve the regenerative response of neurons after injury. Accordingly, much recent work has focused upon the identification and characterization of factors within CNS myelin that inhibit neurite outgrowth and promote the collapse of growth cones *in vitro* and *in vivo*.

Nogo

The IN-1 monoclonal antibody was generated against a fraction of myelin enriched for inhibitory activity [7], and it improves axon outgrowth and functional recovery following injury when infused into the lesion site in several injury models [6,9,10]. Three groups identified the *Nogo* gene and the protein that corresponds to the IN-1 antigen, and demonstrated inhibition of axon growth *in vitro* with recombinant Nogo protein [11–13]. Nogo is differentially spliced to generate three proteins with alternative N termini. The longest isoform is termed Nogo-A and contains a unique sequence ('amino-Nogo') with a large

percentage of acidic residues. The C terminus of Nogo has homology to the reticulon family of proteins and contains two predicted transmembrane domains and a short extracellular loop. Northern analysis has shown the three Nogo isoforms to have overlapping distributions: Nogo-A is predominantly expressed in the CNS, Nogo-B is a minor isoform and Nogo-C is enriched in the periphery, especially skeletal muscle [14]. Nogo-A is expressed by CNS myelin-forming oligodendrocytes but not by peripheral Schwann cells [14–16], and can be observed in immunoelectron micrographs at the innermost adaxonal and outermost myelin membranes [14,15]. In addition, Nogo-A is expressed in a range of central and peripheral neurons [14–16].

Interestingly, both amino-Nogo and a 66 amino acid segment within the extracellular loop (Nogo-66) have been reported to inhibit neurite outgrowth *in vitro*. The topology of Nogo, predicted from amino acid composition, immuno-histochemistry [13] and homology to the reticulons, is such that the N terminus (containing amino-Nogo) and the C terminus are cytosolic, whereas the short 66 amino acid axon-inhibitory loop between the transmembrane domains protrudes into the lumenal or extracellular space. Selective blockade of Nogo-66 with a 40 amino acid peptide derived from the same region (the Nogo extracellular peptide, NEP1–40), partially blocks the inhibitory activity of CNS myelin, and improves locomotor activity when infused into the intrathecal space following a dorsal hemisection injury [17]. However, administration of antibodies directed against the N-terminal domain can induce axon sprouting from uninjured neurons [18] and also might promote functional recovery. One interpretation of the observation that both amino-Nogo and Nogo-66 are inhibitory is that Nogo-66 might serve to inhibit axon sprouting and outgrowth subsequent to myelination, whereas amino-Nogo is an additional inhibitory factor presented by ruptured myelin membranes after injury. Alternatively, a proportion of Nogo-A might adopt a second topology, in which amino-Nogo is extracellular, and then both of these regions could inhibit regeneration.

Nogo receptor

A protein that interacts with Nogo-66 was identified by an alkaline-phosphatase (AP)-fusion-protein expression screening strategy [19]. This protein binds with high (nanomolar) affinity to both AP and glutathione-S-transferase (GST) proteins fused to Nogo-66. Transfection of the cDNA encoding this putative receptor into retinal ganglion

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  doi:10.1016/S0166-2236(03)00062-6

cells (RGCs) at a developmental stage when they otherwise are unresponsive to Nogo-66 promotes growth cone collapse in response to exogenously applied GST–Nogo-66, demonstrating that this protein is a receptor for Nogo [20]. This Nogo receptor (NgR) is predominantly expressed in the CNS in neurons and their axons [15,21] and is attached to the outer leaflet of the plasma membrane by a glycosylphosphatidylinositol (GPI) moiety. Treatment of embryonic dorsal root ganglia with phosphatidylinositol-specific phospholipase C (PI-PLC) abolishes the growth cone collapse of these neurons in response to Nogo-66; thus, this protein and/or another GPI-linked protein mediates the majority of the inhibitory activity of Nogo-66 [22]. However, the GPI-linkage is not required for NgR function, as chimeric proteins in which the GPI-attachment consensus sequence is replaced with the transmembrane domain and C terminus of the cell adhesion molecule L1 [23] also promote growth cone collapse in transfected RGCs [22]. Because NgR lacks a cytosolic component, it would appear to require a transmembrane coreceptor to transduce an inhibitory signal. The identification of a fragment of Nogo-66 that binds to NgR as a high affinity antagonist has facilitated tests of the role of NgR in CNS regeneration *in vivo*. After spinal cord injury, the NEP1–40 antagonist peptide relieves endogenous inhibitory activity, to promote sprouting of corticospinal tract axons, long distance growth and functional recovery [17]. These data validate a significant role of the Nogo-66 receptor in limiting axon regrowth in the injured adult CNS.

MAG and OMgp are ligands for NgR

Unexpectedly, at least two other inhibitory components of myelin, myelin-associated glycoprotein (MAG) and oligodendrocyte-myelin glycoprotein (OMgp), also bind to NgR (Fig. 1). MAG was identified as an NgR-interacting protein in an expression screen for an NgR coreceptor [24] and in directed binding studies [25]. Similarly, the NgR was obtained in a screen for proteins that bind to OMgp [26]. NgR is necessary for inhibition of axon growth by MAG, OMgp and Nogo-66 *in vitro*, and expression of NgR commits insensitive neurons to a MAG-, OMgp- and Nogo-66-sensitive state [20,24,26]. By contrast, amino-Nogo does not appear to interact with NgR. All three ligands (Nogo, MAG and Omgp) are reported to bind to the region of NgR that contains the leucine-rich repeats (LRRs) and flanking regions (Fig. 1; Box 1).

OMgp was recently identified as a potent inhibitor in CNS myelin [26], although it was characterized originally as a GPI-linked protein expressed by oligodendrocytes and neurons that binds to peanut agglutinin [27–29]. MAG has been known to inhibit neurite outgrowth *in vitro* for some time [30,31], and MAG-deficient mice have been generated and characterized [32–34]. The inhibitory activity of myelin membranes from mice lacking MAG is indistinguishable from that of wild-type mice [33]. There is limited evidence that MAG 'knockout' mice have some increased regenerative capacity in the PNS but not the CNS [35], although the primary phenotype of the MAG mutant mice is a subtle defect in myelination [32,34]. Mice deficient for Nogo and OMgp have not yet been described
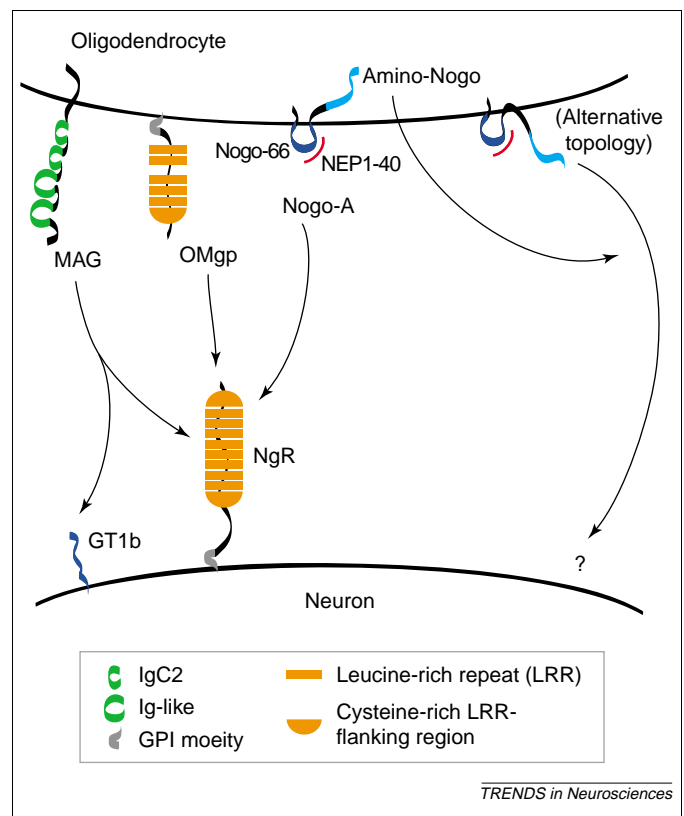
Fig. 1. Myelin-associated glycoprotein (MAG), oligodendrocyte-myelin glycoprotein (OMgp) and Nogo-66 are ligands for the Nogo-66 receptor (NgR). MAG, OMgp and Nogo-66 are all expressed by oligodendrocytes and bind to NgR. These ligands do not share any recognized protein domains. MAG contains IgC2 and Ig-like domains; OMgp has five leucine-rich repeats and an N-terminal flanking region. The C terminus is serine/threonine-rich (not shown). Domains have not been identified in Nogo-A. MAG binds to specific gangliosides, including GT1b, in addition to NgR. The Nogo-66 region (dark blue) binds to NgR. Amino-Nogo (light blue) is also inhibitory to neurite outgrowth and might be localized extracellularly in an alternative topology. The receptor for amino-Nogo has not been identified.

but the convergence of these disparate inhibitors on the NgR provides an opportunity to discriminate the relative contribution of these proteins and myelin-mediated inhibition to impeding axonal regeneration.

p75^NTR is a coreceptor for NgR

Extrapolating from recent observations that MAG-dependent inhibition of neurite outgrowth and activation of RhoA are impaired in neurons from p75^{NTR}-mutant mice [36], and that MAG is a ligand for NgR [24,25], two groups have examined the possibility that p75^{NTR} might be a coreceptor for NgR [37,38]. These studies demonstrated that at least a fraction of p75^{NTR} associates with NgR, as the two proteins can be co-immunoprecipitated from heterologous cells and cerebellar extracts. The decrease in average neurite length observed when neurons are cultured in the presence of myelin membranes, or with any of the three NgR ligands, is attenuated in cerebellar granule neurons transfected with a 'dominant-negative' p75^{NTR} construct that lacks the cytosolic domain of the receptor, and in neuronal cultures to which soluble p75^{NTR}-Fc fusion protein had been added, suggesting that p75^{NTR} function is required for inhibition [37]. A compelling result is that CGNs from p75^{NTR}-mutant mice are not responsive to GST–Nogo-66, Omgp–AP, MAG–Fc

Box 1. Molecular characterization of ligand–receptor interactions

The Nogo-66 receptor (NgR) is a leucine-rich repeat (LRR) protein. It contains eight LRRs flanked by cysteine-rich regions (Fig. I). A unique sequence precedes the C-terminal consensus sequence for the glycosylphosphatidylinositol (GPI) anchor. LRRs are present in a variety of proteins with diverse cellular functions but are believed to mediate protein interactions in most cases [57,58]. LRRs are not generally considered to be dimerization domains but evidence suggests that NgR can multimerize with unclear functional consequences [22]. The flanking regions and all eight LRRs are required for binding Nogo-66 [22]. This finding is not unexpected, as regions flanking LRR regions are often an integral part of these domains [58]. The interaction between Nogo-66 and NgR is antagonized by a peptide containing a fragment of the Nogo-66 sequence, NEP1–40 [17]. Deletion studies indicate that myelin-associated glycoprotein (MAG) and oligodendrocyte-myelin glycoprotein (OMgp) also bind to the region containing the cysteine-rich flanking regions and LRRs. Whether or not NEP1–40 blocks the binding of these ligands to NgR has not been determined. OMgp contains a smaller group of LRRs and a serine/threonine-rich region proximal to the GPI moiety. Similarly, p75^{NTR} is a coreceptor for both the trk family of receptors and NgR. Both the trks and NgR contain LRRs but the binding sites of p75^{NTR} to the trks and NgR have not been identified.
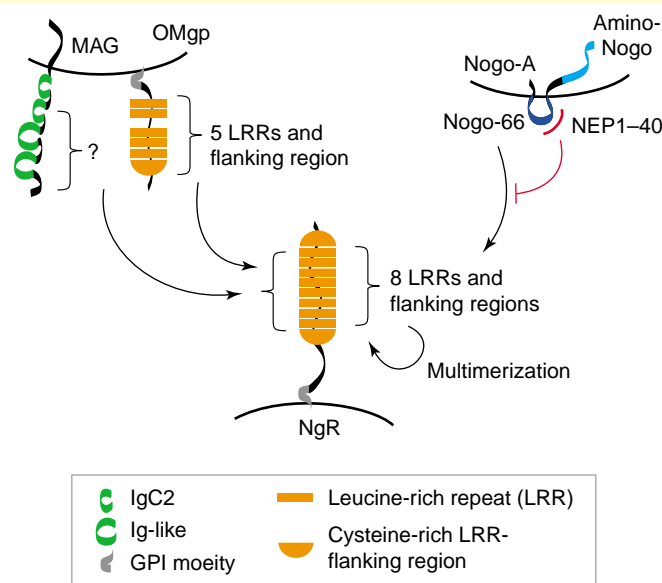
Fig. I. Nogo ligand–receptor interactions. Abbreviations: GPI, glycosylphosphatidylinositol; Ig, immunoglobulin; MAG, myelin-associated glycoprotein; NEP1–40, Nogo extracellular peptide; NgR, Nogo-66 receptor; OMgp, oligodendrocyte-myelin glycoprotein.

or CNS myelin membranes. It has not yet been determined whether transfection of a full-length p75^{NTR} construct rescues the inhibitory response of neurons from p75^{NTR}-mutant mice to these ligands. Whether p75^{NTR} is expressed in all injured adult CNS neurons that are inhibited by myelin is not well defined; additional NgR coreceptors might be expressed in some neurons. It will be of great interest to examine the role of p75^{NTR} in limiting axon regeneration and functional recovery after CNS injury *in vivo*. If p75^{NTR} is the only coreceptor of NgR, then the result will be as dramatic as anti-Nogo-antibody and NgR-antagonist studies.

p75^{NTR} is known to interact with a broad variety of ligands and intracellular proteins but, foremost, it is a coreceptor for neurotrophins with the trk family of receptor tyrosine kinases [39,40]. Pretreatment of cultured dorsal root ganglia and cerebellar granule neurons with specific neurotrophins abolishes the MAG-dependent inhibition of neurite outgrowth from these neurons [8] (Fig. 2). At first glance, it might seem paradoxical that p75^{NTR} is required for the inhibition of outgrowth by myelin-associated factors (as a coreceptor with NgR) but contributes to repressing this inhibition (as a coreceptor with trkB or trkC). An improved understanding of the molecular basis for the interaction of p75^{NTR} with these proteins might help to resolve this issue (Box 1). As an NgR coreceptor, p75^{NTR} is expressed *in cis* with NgR in neurons and *in trans* with myelin proteins. The well-documented roles of p75^{NTR} in myelin-forming Schwann cells and oligodendrocytes [40–42] indicate that interactions *in cis* with myelin components and *in trans* with neuronal NgR must also be considered.

Rho-based signaling

Downstream of the NgR complex, the small G protein Rho appears to provide a major link to cytoskeletal regulation [43]. Data indicate that MAG activates RhoA by increasing the proportion of the protein bound to GTP [36]; Nogo-66 and myelin utilize this same signaling pathway [44]. The p75^{NTR} could provide a direct link to RhoA [45], or there might be additional, as yet unidentified, Rho-specific guanine-nucleotide exchange factors (GEFs) or GTPase-activating proteins (GAPs) involved in signal transduction. Pharmacological studies *in vitro* and *in vivo* indicate that downstream of RhoA, the
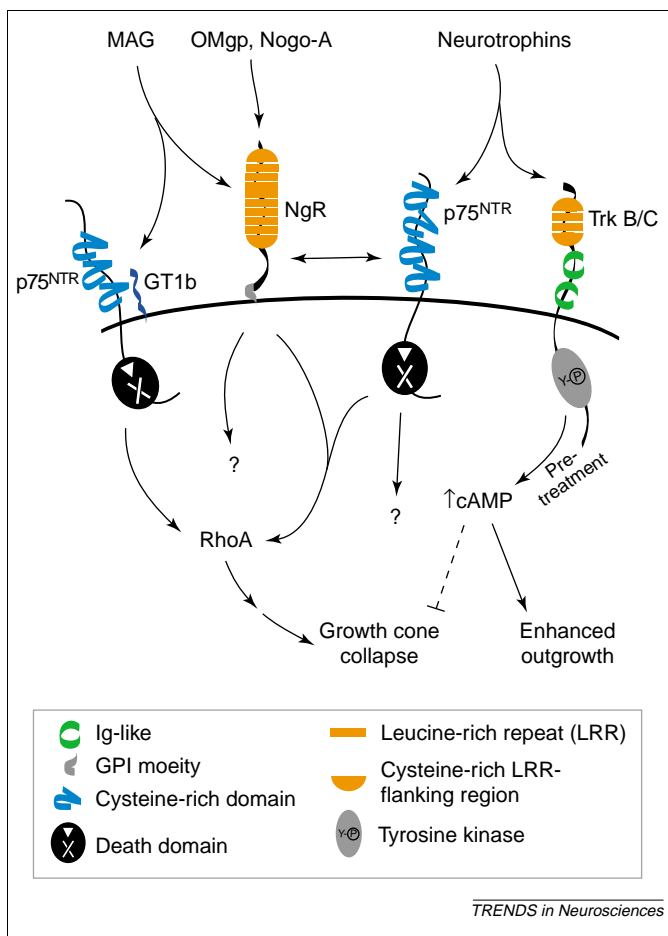
Fig. 2. Signal transduction by the Nogo-66 receptor (NgR) complex. The p75[NTR] low-affinity neurotrophin receptor interacts with the ganglioside GT1b and NgR, in addition to the trk neurotrophin receptors. p75[NTR] could mediate inhibitory signaling of myelin-associated ligands via NgR and GT1b (for the myelin-associated glycoprotein, MAG) by activating RhoA. Pretreatment of neurons with neurotrophins increases intracellular cAMP concentrations, which both suppresses inhibition by myelin and increases neurite outgrowth on permissive substrates. NgR and p75[NTR] might also have additional signaling activities, independent of their association.

Rho-associated kinase ROK plays a prime role in mediating myelin-induced inhibition via NgR [44,46].

Myelin-associated inhibitors in cortical plasticity

Myelin-associated outgrowth inhibitors collapse growth cones and impede neurite outgrowth *in vitro* but the physiological functions of these proteins are likely to involve more than hindering neuronal regeneration following injury. MAG regulates aspects of myelination [32,34] and recent studies indicate that p75[NTR] also promotes myelin formation [42]. Expression of NgR and Nogo-A by oligodendrocytes increases in the developmental time-frame subsequent to axon pathfinding, concomitant with synaptogenesis for many projection neurons [15]. In the CNS, perhaps these inhibitors serve to consolidate neuronal function by suppressing sprouting and synapse formation after neurons have established 'appropriate' connectivity. Indeed, NgR is found both along mature axons and at synaptic sites [15]. Myelination increases through the end of the developmental critical period in both visual cortex and somatosensory cortex, and neurite-growth-inhibiting factors have been proposed to

contribute to the termination of the critical period in visual cortex [47]. Recent studies indicate that enzymatic digestion of chondroitin sulfate proteoglycans (CSPGs), which are axonal sprouting inhibitors, promotes both a reactivation of plasticity in ocular dominance columns in visual cortex of adult rats [48] and functional regeneration in the spinal cord [49]. There is evidence to suggest that application of an antibody directed against Nogo enhances functional recovery and neuroanatomical plasticity in an artery-occlusion model of stroke [50]. It will be interesting to determine whether MAG, OMgp and NgR also regulate cortical plasticity or whether they influence the reorganization of cortical structure and function following other kinds of debilitating injuries, such as strokes and seizures.

Concluding remarks

NgR binds to three characterized proteins that promote axonal growth cone collapse: Nogo, OMgp and MAG. The convergence of these three disparate myelin-associated components onto one receptor suggests that NgR could be a crucial regulator of neurite outgrowth. NgR is attached to the plasma membrane by a GPI moiety, indicating that a transmembrane coreceptor translates signals to the cytoskeleton. p75[NTR] appears to be a coreceptor with NgR in at least some circumstances: it binds NgR and is required for myelin-mediated inhibition *in vitro*. Downstream of NgR and its ligands, the GTPase RhoA promotes growth cone collapse and inhibits neurite extension. The hypothesis that myelin plays a role in regulating axonal sprouting and plasticity in the adult brain can now be tested with these defined signal-transduction components.

The recent identification of this pathway, from myelin to axonal NgR to intracellular second messengers, provides an opportunity to develop rational interventions to promote CNS axon regeneration after injury. Evidence suggests that targeting the myelin-derived Nogo ligand with a blocking antibody is effective [51,52] but this approach might be limited by the presence of the three independent inhibitors within myelin. The NgR provides an attractive therapeutic target because of its essential role, high-affinity interactions and neural specificity. A peptide antagonist is effective in promoting functional recovery [17] but a small-molecule antagonist of NgR or a broad-spectrum antagonist blocking Nogo, MAG and OMgp might be more effective. p75[NTR] might be a less attractive target, owing to its numerous functions. There is also interest and demonstrated efficacy for blockade of Rho or Rho Kinase [46,53] but, as these signaling molecules are present in all cell types of the body, specificity is a concern. The multiple potential points of attack in this pathway increase the likelihood that it will be targeted by clinically effective axon-regeneration agents.

However, myelin is not the only source of axon outgrowth inhibition. CSPGs and other components of the glial scar [3] inhibit neurite outgrowth, and the regenerative capacity of projection neurons is relatively feeble. Chondroitinase ABC digests CSPGs; when infused into the CNS it promotes axon elongation and improves functional recovery following injury [49], as do neurotrophins [54] and cyclic nucleotide analogs [55,56]. These beneficial effects might be additive with methods for

repression of myelin-linked inhibition. Understanding of how signals from extracellular factors associated with myelin and the injury site are integrated with neuro-trophins and outgrowth promoting signals to regulate axon elongation should further facilitate the development of interventions to ameliorate the effects of spinal cord injury, head trauma, stroke and multiple sclerosis.

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