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Myelin-, Reactive Glia-, and Scar-Derived CNS Axon Growth Inhibitors: Expression, Receptor Signaling, and Correlation with Axon Regeneration

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KEY WORDS axon growth inhibitors; growth cone collapse; Rho-family GTPases; RhoA; Rac; Cdc42; protein kinase A; collapsin response mediator protein; astrocytes; oligodendrocytes; NG2-glia; meningeal fibroblasts; chondroitin sulfate proteoglycans; extracellular matrix molecules; Nogo; myelin-associated glycoprotein; oligodendrocyte myelin glycoprotein; Versican; Neurocan; Phosphacan; Brevican; Tenascin; NG2 chondroitin sulfate proteoglycans; semaphorins; neuropilin; $p75^{NTR}$; Nogo receptor; ephrin/Eph; axon regeneration; CNS scar

ABSTRACT Axon regeneration is arrested in the injured central nervous system (CNS) by axon growth-inhibitory ligands expressed in oligodendrocytes/myelin, NG2-glia, and reactive astrocytes in the lesion and degenerating tracts, and by fibroblasts in scar tissue. Growth cone receptors (Rc) bind inhibitory ligands, activating a Rho-family GTPase intracellular signaling pathway that disrupts the actin cytoskeleton inducing growth cone collapse/repulsion. The known inhibitory ligands include the chondroitin sulfate proteoglycans (CSPG) Neurocan, Brevican, Phosphacan, Tenascin, and NG2, as either membrane-bound or secreted molecules; Ephrins expressed on astrocyte/fibroblast membranes; the myelin/oligodendrocyte-derived growth inhibitors Nogo, MAG, and OMgp; and membrane-bound semaphorins (Sema) produced by meningeal fibroblasts invading the scar. No definitive CSPG Rc have been identified, although intracellular signaling through the Rho family of G-proteins is probably common to all the inhibitory ligands. Ephrins bind to signalling Ephs. The ligand-binding Rc for all the myelin inhibitors is NgR and requires $p75^{NTR}$ for transmembrane signaling. The neuropilin (NP)/plexin (Plex) Rc complex binds Sema. Strategies for promoting axon growth after CNS injury are thwarted by the plethora of inhibitory ligands and the ligand promiscuity of some of their Rc. There is also paradoxical reciprocal expression of many of the inhibitory ligands/Rc in normal and damaged neurons, and NgR expression is

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restricted to a limited number of neuronal populations. All these factors, together with an incomplete understanding of the normal functions of many of these molecules in the intact CNS, presently confound interpretive acumen in regenerative studies.

INTRODUCTION

During development, growth-inhibitory ligand/receptor (Rc) interactions regulate the guidance of axons toward their targets and mediate synapse selection (Flanagan and Vanderhaeghen, 1998; Holder and Klein, 1999; Raper, 2000; Zou et al., 2000; Cheng et al., 2001; Skutella and Nitsch, 2001; Yu and Bargmann, 2001; Goshima et al., 2002). In the early postnatal period, after all the major central nervous system (CNS) tracts are laid down, the mammalian CNS loses the ability both to regenerate axonal projections and to reestablish functional synaptic contacts. The causes for regenerative failure are complex and still largely unknown, but one possible explanation is that ontogenetic changes in inhibitory ligand/Rc expression transform the selectively axon growth-permissive immature CNS neuropil into a universally nonpermissive environment in the adult. This change may only partially occur in peripheral nerves (PN), since axons regenerate in adult PN after injury, although target reinnervation is often incomplete and inaccurate and, accordingly, functional recovery can be disappointing.

The results of the early experiments of Ramon y Cajal (1928) were the first to define the reaction of the adult CNS to injury and record that unlike PN, axons in the CNS are incapable of regrowing after transection in vivo. The strong correlation between the failure of CNS axon regeneration and the deposition of a dense collagen/glial cicatrix led Clemente (1964) and Windle (1956) to suggest that scarring was a major impediment to successful repair of CNS connections after injury. The scar is comprised of a fold of basal lamina surrounded by a dense meshwork of astrocyte processes that encloses a core of meningeal connective tissue embedded in an extracellular matrix (ECM) (Reier, 1986; Logan and Berry, 2001; Berry et al., 2002a). David and Aguayo (1981) demonstrated that the environment of a CNS lesion inhibited axon regrowth, whereas severed CNS axons did regenerate into and through PN grafts implanted into a wound. Berry (1982) suggested that central myelin proteins may act as major axon growth-inhibitory ligands and Schwab and Thoenen (1985) and Schwab and Caroni (1988) showed that the axons of dorsal root ganglion neurons (DRGN) failed to extend over oligodendrocytes and CNS myelin in culture. Several CNS myelin/oligodendrocyte-derived axon growth-inhibitory ligands have since been isolated, including Nogo (Prijha et al., 2000; Chen et al., 2001; GrandPré and Strittmatter, Chen et al., 2000), myelin-associated protein (MAG) (McKerracher et al., 1994; Mukhopadhyay et al., 1994; Filbin, 1995; Qiu et al., 2000), oligodendrocyte-myelin glycoprotein (OMgp) (Wang et al., 2002b), and myelin-associated chondroitin sulfate proteoglycans (CSPG). Astrocytes became implicated following the proposition that an astrocyte-derived physiological stop signal blocked DRG axon regeneration into the cord after dorsal root avulsion (Liuzzi and Lasek, 1987), probably mediated by CSPG (Mansour et al., 1990; Rudge and Silver, 1990; Snow et al., 1990; Lemons et al., 1999) and/or Tenascin (Letourneau et al., 1994; Becker et al., 2000) expressed on the plasmalemma of reactive astrocytes at the dorsal root entry zone (DREZ). Moreover, a population of glia expressing NG2 also undergoes reactive gliosis and upregulates the growth cone-repellent CSPG NG2 on their surface after injury (Levine et al., 2001). Reactive NG2-glia intermingle with those of reactive astrocytes in the CNS scar and at the DREZ (Zhang et al., 2001; Jones et al., 2002). Recently, a family of axon growth-inhibitory ligands called semaphorins (Sema) have been identified (Kolodkin, 1993, 1997), which are expressed by meningeal fibroblasts in CNS scars (Pasterkamp et al., 1998b). Moreover, ephrins/Ephs are differentially expressed on astrocytes and fibroblasts and regulate interactions between the two phenotypes (Bundesen et al., 2003). A list of abbreviations is included in the Appendix.

RHO-FAMILY GTPases AND GROWTH CONE COLLAPSE

Most axon growth-inhibitory ligands either repel or collapse growth cones via the Rho GTPase signaling pathway (Mueller, 1999; Tang, 2003) after binding to cognate surface Rc located on the axolemma. Axonal growth cones rely heavily on F-actin dynamics and microtubule assembly to drive growth and guidance. The Rho family of small GTPases regulates the actin cytoskeleton and most attention has been focused on the three most widely expressed family members, RhoA, Cdc42, and Rac1. Rho GTPases act as molecular switches, being active when bound to GTP and inactive when bound to GDP. Rho proteins bound to GTP interact with effectors, thereby triggering downstream signaling cascades. Three protein classes regulate the nucleotide-binding state of the Rho family of GTPases: guanine nucleotide exchange factors (GEF), GTPase-activating proteins (GAP), and guanine dissociation inhibitors (GDI). The Rho family of G-proteins are activated by GEF, which facilitate GDP/GTP exchange, whereas GAP inactivate them by enhancing their intrinsic GTPase activity. GDI participate in the regula-

tion of both the GDP/GTP cycle and the membrane association/dissociation cycle.

During development, repulsive ligand/Rc interactions regulate axon pathfinding. In the adult, similar inhibitory interactions probably mediate plasticity and stabilize established connections. In most cases, inhibitory ligand expression is upregulated in reactive glia/fibroblasts after CNS injury (Qiu et al., 2000), and interaction with Rc located on axon growth cones could cause growth cone collapse and account for the failure of damaged axons to regenerate (Fournier and Strittmatter, 2001; Pasterkamp and Verhaagen, 2001). Growth cones respond to some extracellular inhibitory molecular cues via a number of transmembrane Rc, most of which trigger signaling cascades that converge on RhoA, Cdc42, and Rac1. The regulatory proteins of the GTPase cycle, GEF and GAP, are also potential targets of upstream inhibitory molecules and may be used to change Rac1:RhoA equilibrium. Rac1 and RhoA probably play antagonistic roles in growth cone dynamics through their effector kinases, p21-activated kinase 1 (PAK1), a serine-threonine kinase, and Rho-associated protein kinase (ROCK), which stimulate growth cone mobility and collapse, respectively, by regulating the actin cytoskeleton of growth cones downstream of Rc activation. In the injured CNS, inhibitory molecules change the balance of Rac1, Cdc42, and Rho signaling, so that the activity of RhoA is elevated and that of Rac1/Cdc42 decreased, leading to paralysis of growth cone mobility and induction of growth cone collapse/repulsion. Coupling of neurite-inhibitory molecule Rc to the Rho family of G-proteins is a common thread shared by ephrins, Nogo, MAG, OMgp, and Sema to induce growth cone collapse, and it seems probable that this pathway may be involved in CSPG signaling, but this remains to be established. The role of other pivotal molecules, such as the G-protein regulating molecules like GEF, and the molecular links to F-actin dynamics are only partially defined.

ASTROCYTE-DERIVED AXON GROWTH INHIBITORS

CSPG

Molecular structure of ligand and Rc

CSPG are ECM molecules with a varied complex structural composition comprising transmembrane and secreted forms. Both types have a central core protein covalently attached to chondroitin sulfate (CS) and glycosaminoglycans (GAG) side chains. The structure of CSPG is diversified by variations in the core protein with the addition of N- and O-linked oligosaccharides; number, length, and sulfation patterns of CS GAG side chains; and proteolysis of translation products.

The hyalectan (lectican) CSPG family includes Versican, Neurocan, and Phosphacan (Friedlander et al., 1994; Milev et al., 1994; Yamada et al., 1997; Asher et al., 2000; Schmalfeldt et al., 2000; Tang et al., 2002). Lecticans all have an N-terminus containing a hyaluronic acid-binding region, a C-terminus with epidermal growth factor (EGF), lectin and complement regulatory protein (CRP) domains, and intervening regions to which CS side chains may attach. Neurocan is a secreted molecule and undergoes posttranslational modification in the CNS, resulting in a 150 kD C-terminus and 130 kD N-terminus fragment (Rauch et al., 1992; Matsui et al., 1994; Meyer-Puttlitz et al., 1995). Brevican (145 kD) is the smallest of the hyalectan family, with an 80 kD C-terminus core protein fragment (Yamaguchi, 1996). One spliced isoform is GPI-linked to cell surfaces and thus is not complexed to ECM (Seidenbecher et al., 1995). Phosphacan is expressed in the CNS as a secreted splice variant of the gene encoding the extracellular domain (ECD) of the transmembrane Rc-type tyrosine phosphatase (RPTPβ) (Maurel et al., 1994). Neither astrocytes nor microglia synthesize Versican (Asher et al., 2000). The GP Tenascin-C is a component of the ECM, constitutively expressed in astrocytes, and has a number of axon growth-inhibitory isoforms (Meiners et al., 1995). NG2 CSPG is expressed by NG2-glia (Berry et al., 2002b; Butt et al., 2002) and is also considered to be a major axon growth-inhibitory molecule in the CNS (Dou and Levine, 1994; Fidler et al., 1999; Chen et al., 2002).

No specific Rc for most of the CSPG has been identified, although some proteoglycans, such as Versican and NG2, are thought to bind potential CSPG Rc expressed on growth cones (Fawcett, 1997; Asher et al., 2002). Versican also interacts with ECM components and, through steric hindrance, blocks the efficacy of growth-promoting molecules. Neurocan interacts with a cell surface glycosyltransferase (Li et al., 2000), a GPI-linked protein that modulates important cell adhesion molecules such as β1-integrin, N-cadherin, L1, and N-CAM (Friedlander et al., 1994), all of which play critical roles in neurite outgrowth. Neurocan, for example, may inhibit neurite outgrowth in vivo by disrupting growth cone cell/substrate cell adhesion molecule interactions (Grumet et al., 1993).

Cellular localization

Astrocyte CSPG are either nonsecreted transmembrane GPI-linked molecules or, when secreted, complexed with the ECM.

Intracellular signaling pathway

Little is known about the intracellular signaling mechanisms by which CSPG/Tenascin-C inhibit neurite growth, although evidence is accumulating that interactions with cell surface adhesion molecules and direct growth cone signaling are important (Joester and Faissner, 2001), leading to activation of the Rho/

ROCK pathway (Monnier et al., 2002). Removal of the CS GAG side chains with chondroitinase ABC (ChABC) promotes neurite outgrowth on CSPG (Yick et al., 2000; Moon et al., 2001; Bradbury et al., 2002), suggesting that CS GAG side chains are the ligands that mediate growth cone collapse and retraction. However, the core proteins of CSPG also possess intrinsic inhibitory properties (Grumet et al., 1993; Dou and Levine, 1994; Balsamo et al., 1995; Lilien et al., 1999; Inatani et al., 2001).

Distribution in intact CNS

CSPG including Neurocan (Oohira et al., 1994; Meyer-Puttlitz et al., 1996; Asher et al., 2000), Brevican (Meyer-Puttlitz et al., 1996; Yamada et al., 1997), and Phosphacan (Canoll et al., 1996; Meyer-Puttlitz et al., 1996; McKeon et al., 1999) are produced by astrocytes in the intact CNS and expressed on the plasmalemma.

Distribution after CNS injury

CSPG expression is upregulated in reactive astrocytes (Snow et al., 1990; Smith-Thomas et al., 1994) in lesions of, for example, the spinal cord (Fitch and Silver, 1997; Tang et al., 2002), fornix (Lips et al., 1995), and DREZ (Pindzola et al., 1993; Tang et al., 2002), where NG2 (Fidler et al., 1999; Hirsch and Bähr, 1999), Neurocan, Brevican, and Phosphacan (Maurel et al., 1994; Snyder et al., 1996; Mckeon et al., 1999) are all produced. In spinal cord wounds, Versican, Brevican, and Neurocan are upregulated in astrocytes and meningeal cells up to 6 months after injury (Jones et al., 2002; Tang et al., 2002). All lecticans interact with ECM and cell-bound Tenascin-R (Aspberg et al., 1995, 1997). A membrane-bound CSPG, injured membrane proteoglycan (IMP) (Bovolenta et al., 1993), and Tenascin-C are expressed after CNS injury and upregulated in reactive astrocytes (Fawcett, 1997; Tang et al., 2002).

Regeneration correlates

Except in the optic nerve, regenerating axons do not usually penetrate areas of CNS neuropil containing reactive astrocytes in vivo (Fawcett et al., 1989; Bähr et al., 1995). The regeneration of DRGN axons, after atraumatic DRGN transplantation into the CNS, is inhibited when growth cones confront CSPG-rich astrocytes in a CNS lesion (Davies et al., 1997, 1999). In vitro, neurites will not grow over astrocytes expressing CSPG (Grierson et al., 1990; Meiners et al., 1995; Canning et al., 1996), of which Neurocan (Friedlander et al., 1994; Katoh-Semba et al., 1995, 1998; McKeon et al., 1995, 1999; Haas et al., 1999; Asher et al., 2000), Brevican (Yamada et al., 1997), and Phosphacan (Grumet et al., 1993; Milev et al., 1994; Katoh-Semba et al., 1998; Garwood et al., 1999) have all been shown to be inhibitory. IMP also inhibits neurite outgrowth in vitro (Bovolenta et al., 1997). After repeated contact with CSPG in culture, the filopodia of growth cones do not collapse and there is no growth arrest; instead, growth cones are repelled and change direction, avoiding the inhibitory substrate (Snow et al., 2001; Monnier et al., 2002). Conversely, after treatment with ChABC (McKeon et al., 1995), the repellant characteristics of CSPG are blocked in glial scars supported in a nitrocellulose scaffold explanted in culture (Rudge and Silver, 1990; McKeon et al., 1991; Smith-Thomas et al., 1994) and in cryosections of normal CNS (Zuo et al., 1998). Moreover, chABC treatment in vivo improves CNS regeneration into PN grafts implanted into the spinal cord (Yick et al., 2000). Serial ChABC injections degrade keratin/CS PG (Moon et al., 2002) in the wound and block the inhibition of dopaminergic fibers in the lesioned nigro-striatal tract (Moon et al., 2001) and dorsal funicular fibers in the transected spinal cord (Bradbury et al., 2002), promoting functional recovery.

Neurocan inhibits neurite outgrowth on L1 and N-CAM substrates (Asher et al., 2000), possibly through direct binding to either L1 or N-CAM, disrupting/blocking substrate interactions with cell adhesion molecules (Grumet et al., 1993; Friedlander et al., 1994; Katoh-Semba et al., 1995, 1998). CS side chains probably mediate both L1 and N-CAM binding (Friedlander et al., 1994; Oleszewski et al., 2000). Transforming growth factor β (TGFβ) and EGF upregulate Neurocan expression in CNS lesions (McKeon et al., 1995, 1999) and in cultured astrocytes (Asher et al., 2000). Messenger RNA of the secreted isoform of Brevican is upregulated in reactive astrocytes after injury (Jaworski et al., 1999). Axon growth inhibition by Brevican (Yamada et al., 1997) is abolished after ChABC treatment, indicating a function for the CS GAG side chains (Moon et al., 2001). Phosphacan inhibits neurite extension by direct binding to the surface of the growth cone and interacting with L1/NgCAM/laminin (Lam) substrates (Grumet et al., 1993; Milev et al., 1994; Garwood et al., 1999). Disinhibition does not occur after ChABC treatment, indicating that the core protein, and not the CS GAG side chains, mediates the growth-inhibitory activity. In conclusion, data demonstrating a role of astrocyte-derived CSPG in growth cone collapse are descriptive; little is known about the mechanisms of their inhibition of axon growth.

ECM Molecules

The ECM of a CNS scar is formed by both glia and meningeal fibroblasts and composed of secreted CSPG, Tenascins (Faissner, 1997; Pesheva and Probstmeier, 2000; Tang et al., 2002), hyaluronic acid (Asher et al., 1991; Rauch et al., 1991; LeBaron et al., 1992; Perides et al., 1992; Retzler et al., 1996), Sema 3A (Pasterkamp and Verhaagen, 2001), Lam, fibronectin (FN), and col-

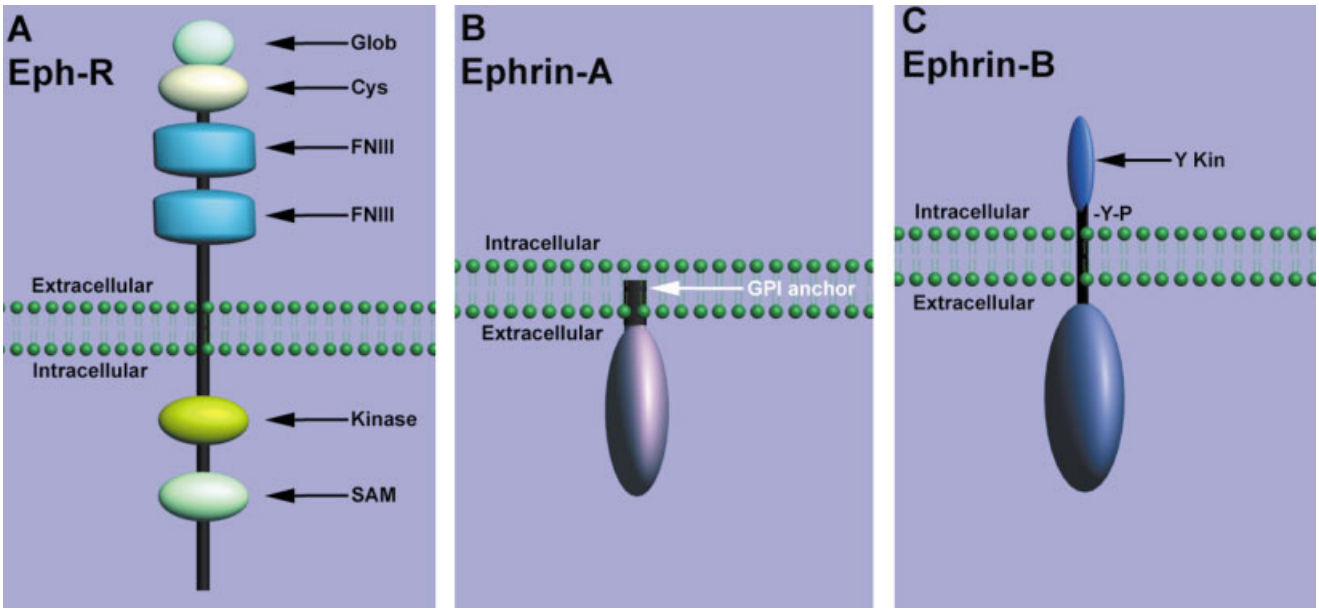

Fig. 1. Schematic representation of the structure of (**A**) Eph Rc, (**B**) ephrin-A, and (**C**) ephrin-B, illustrating known bioactive domains. Cys, cysteine-rich; FN III, fibronectin type III repeats; Glob, globular; GPI, glycosylphospatidylinositol anchor; Kinase, tyrosine kinase; SAM, sterile alpha motif; Y-Kin, tyrosine kinase; Y-P, tyrosine phosphatase.

lagens (Logan and Berry, 1999, 2001). These molecules bind by homophilic and heterophilic interactions to form a potential axon growth-inhibitory ECM (Yamagata et al., 1986). Degradation of ECM in CNS lesions promotes fiber growth across the wound (Stichel et al., 1999a, 1999b). ECM deposition is regulated by both TGFα and TGFβ (Lindholm et al., 1992; Rabchevsky et al., 1998; Logan and Berry, 2001) and connective tissue growth factor (CTGF) (Grotendorst, 1997; Kothapalli et al., 1998; Brigstoch, 1999; Logan and Berry, 1999; Moussad and Brigstock, 2000), all of which become upregulated in neurons, astrocytes, microglia, and hematogenous cells after injury. The expression of TGFβ2, not TGFβ1, is correlated with scar deposition (Lagord et al., 2002). Reducing titers of TGFβ in CNS lesions using either neutralizing antibodies or decorin attenuates ECM deposition (Logan and Berry, 1999; Logan et al., 1999a, 1999b) but does not enhance axon growth. The roles of ECM CSPG in neural/glial adhesion, axon growth/guidance, and neuronal survival have been reviewed by Margolis and Margolis (1997) and Dow and Wang (1998).

Ephrins

Molecular structure of ligand (ephrin) and Rc (eph)

Ephrins are categorized into two classes, cell surface-bound GPI-linked ephrin-A, and the transmembrane ephrin-B proteins (Fig. 1B and C, respectively). Eph constitute the largest family of Rc tyrosine kinases (RTK) and are classified into Eph-A and Eph-B subfamilies, reflecting their binding preference for either GPI-anchored ephrin-A or transmembrane ephrin-B ligands (Pandey et al., 1995; Ephrin Nomenclature Committee, 1997; Orioli et al., 1997; Holder and Klein, 1999). However, Eph-A4 binds members of both class A and class B ephrins (Gale et al., 1996). Generally, all Eph contain an extracellular domain (ECD) with a globular ligand-binding domain on the N-terminus adjacent to a cysteine-rich domain (CRD) and two FN-III domains, which contain a dimerization motif (Fig. 1A). The transmembrane domain (TMD) is a sequence of hydrophobic amino acids next to a intracellular domain (ICD) C-terminus containing kinase and sterile alpha motif (SAM) domains. SAM domains homo- and hetero-oligomerize to mediate specific protein-protein interactions. A highly conserved subclass of SAM domains is present at the intracellular C-terminus of more than 40 Eph tyrosine kinases that are involved in the control of axonal pathfinding upon ephrin-induced oligomerization and participate in downstream signaling events via interactions with cytosolic proteins.

Cellular localization

Ephrin and Eph are expressed on both adult neurons and astrocytes (Winslow et al., 1995; Janis et al., 1999; Miranda et al., 1999; Kromer et al., 2002; Bundesen et al., 2003; Willson et al., 2002).

Intracellular signaling pathway and functions

Ephrin function both as Rc and ligands and are therefore able to initiate bidirectional signaling in association with Eph. The prototypic function of astrocytic ephrins is to induce either growth cone repulsion or collapse but under some circumstances the pattern of ligand/Rc expression induces growth cone attraction/adhesion (Knöll and Drescher, 2002). Ephrin-A and ephrin-B interact with the N-terminus globular domain of Eph and induce Rc dimerization through the FN and SAM domains and tyrosine phosphorylation of the ICD of ephrin-B by an unknown tyrosine kinase (Y-Kin). Binding of ephrin induces Eph autophosphorylation in the juxtamembrane region, providing docking sites on two conserved tyrosine residues for Nck, the SH2/SH3-domain adaptor proteins, Src family kinases (whose principle substrate is p190 RhoGAP), and RAS GTPase-activating protein (RasGAP) with its associated phosphopeptide, p62. RasGAP associates and inhibits a negative regulator of RhoA, a tyrosine phosphorylated form of p190 RhoGAP, a small GTPase implicated in the regulation of the cellular actin cytoskeleton (Brambilla and Klein, 1995; Chant and Stowers, 1995; Stein et al., 1996; Orioli and Klein, 1997; Bruckner and Klein, 1998).

It seems that, in common with other neurite-inhibitory ligands, ephrins induce growth cone collapse through activation of RhoA and its downstream effector ROCK (key control elements of the assembly and disassembly of the actin cytoskeleton) via the Rho-activating GEF, in this instance, a protein termed "Ephexin," and by simultaneous downregulation of Cdc42 and Rac1 and their downstream effector PAK1 (Fig. 2) (Wahl et al., 2000).

There are a number of other potential pathways that may contribute to ephrin-induced growth cone repulsion/collapse. For example, on ligand activation, the SH2/SH3 domain adaptor protein Grb4 binds to a conserved tyrosine embedded in the SAM domain of the ICD of Eph through a phosphotyrosine-dependent mechanism (Knöll and Drescher, 2002); and ephrin-A1 activates Eph-A2 converting integrins into an inactive conformation that leads to growth cone retraction by reductions in cell adhesion, spreading, and migration (Miao et al., 2000; Knöll and Drescher, 2002). Binding of active phosporylated focal adhesion kinase (FAK) plays a crucial role in inactivation of Eph-A. Following ephrin-A binding to Eph-A2, FAK is inactivated by dephosphorylation and dissociates from Rc. Since FAK is the principal tyrosine kinase for integrin signaling, it could provide a means for ephrin-A regulation of integrin function (Knöll and Drescher, 2002). Activation of Eph-A also leads to an inactivation of the MAP kinase pathway and modulation of growth cone migration through MAP kinase-driven regulation of myosin light chain (MLC) protein, a key player in actin-myosin cytoskeletal contractions (Dickson, 2001). Furthermore, cleavage of ephrins by the metalloprotease, kuzbanian (Kuz), induces Eph binding to growth cones (Holmberg and Frisen, 2002).

Normal distribution

Eph-B (Miranda et al., 1999), Eph-A7, and Eph-A (Willson et al., 2002) are expressed in normal astrocytes. In the cord, Eph-B2 is expressed by a subpopulation of small- and medium-sized DRGN and meningeal fibroblasts, and ephrin-B2 ligand is produced exclusively by astrocytes, including their end-feet about blood vessels and at the glia limitans externa (Kromer et al., 2002, Bundesen et al., 2003). Ephrin-B/Eph-B in adult DRGN and spinal cord regulate sensory connectivity and modulate pain processing (Battaglia et al., 2003). During development, they regulate CNS axon growth and pathfinding in ontogeny (Flanagan and Vanderhaeghen, 1998; Holder et al., 1998; McLaughlin and O'Leary, 1999).

Distribution after injury

In the injured adult rat spinal cord, ephrin-A3, -A4, and -A7 mRNA are upregulated, and Eph-A3, -A4, -A6, and -A8 immunoreactivity is increased in the ventrolateral funiculi at the lesion epicenter (Willson et al., 2002). Ephrin-B2 (Bundesen et al., 2003), ephrin-B3 (Miranda et al., 1999), and Eph-A (Willson et al., 2002) are upregulated in reactive astrocytes, and Eph-B2 expression is also upregulated in meningeal fibroblasts about the lesion (Bundesen et al., 2003). At the boundary where ephrin-B2-positive astrocytes and Eph-B2-positive meningeal cells emigrating into the wound ultimately meet, a basal lamina is formed. Astrocyte ephrin/fibroblast/Eph interactions at this interface may control basal lamina deposition (Bundesen et al., 2003). In the adult mouse superior colliculus, the patterns of expression of ephrin-A/B are similar to those seen during the development of the visual projections (McLaughlin and O'Leary, 1999; Knöll et al., 2001) and are retained after deafferentation, although titers of Ephrin-A are reduced. This is the first report suggesting that topographical guidance cues may be preserved in denervated CNS targets after CNS lesions, holding a promise that functional reconnection may be possible after regeneration of the retinotectal projection.

OLIGODENDROCYTE/MYELIN-DERIVED AXON GROWTH INHIBITORS

Nogo

Molecular structure of ligand and Rc

Nogo-A (1,162 amino acids), -B (373 amino acids), and -C (199 amino acids; Fig. 3A) are all members of the reticulon family and inhibit axon growth (Chen et al., 2000; GrandPré et al., 2000; Prinjha et al., 2000).

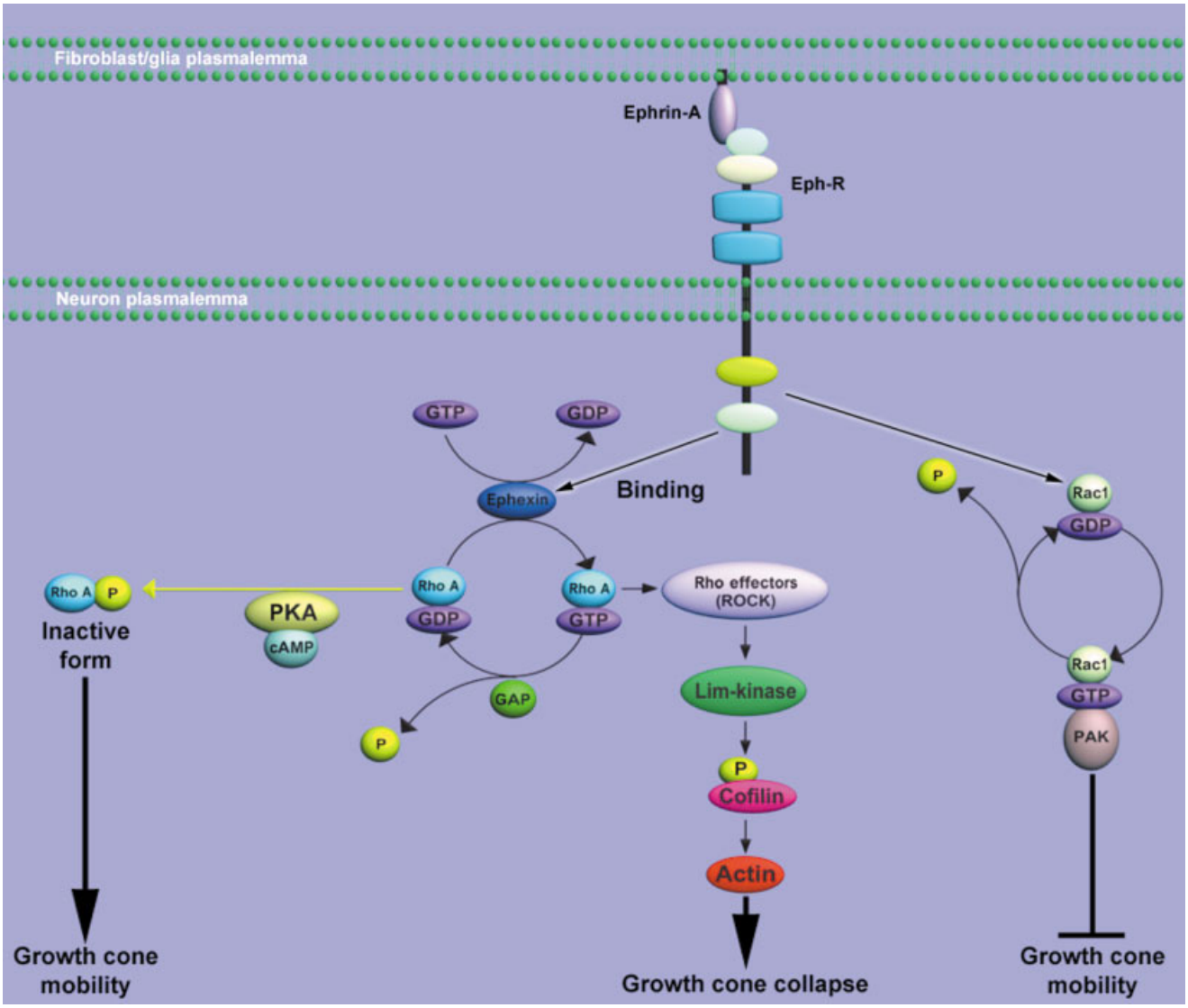

Fig. 2. The signaling pathway used by ephrins/Ephs to induce growth cone collapse. When Eph is expressed in excess of the ligand on the growth cone, the SAM domain of Eph interacts with Ephexin (a guanine nucleotide exchange factor, GEF, for RhoA) after ephrin activation. Activation of RhoA by Ephexin engages its downstream effector Rho kinase (ROCK), which in turn activates LIM kinase, thereby modulating actin dynamics via phosphorylation of cofilin. Other antagonistic GTPases mediating growth cone mobility signals, such as Rac1 and Cdc42, are probably simultaneously downregulated. GTP, guanosine triphosaphate; GDP, guanosine diphosphate; LIM, the three gene products Lin-11, Is-1, and Mec-3; GAP, GTPase-activating protein; PKA, protein kinase A; PAK, P_{21}-activated protein kinase; SAM, sterile alpha subunit.

Nogo-A, -B, and -C have a common carboxy terminus of 188 amino acids and share a 172 amino acid N-terminus. Alternative transcription of one common gene results in the three different splice variants. All three Nogo isoforms have two hydrophobic domains close to the C-terminus of 35 and 36 amino acids, and both Nogo-A and -B have additional short stretches of hydrophobic amino acids. The hydrophobic domains indicate that Nogo isoforms are integrated membrane proteins. There is inhibitory activity in both the amino terminus of Nogo-A and a common 66 amino acid inhibiting domain (Nogo-66) lying between the two hydrophobic motifs in the ECD (GrandPré et al., 2000; Prinjha et al., 2000; Fournier et al., 2001). Nogo-A also has seven N-glycosylation and several O-glycosylation sites. Nogo isoforms have no sequence homology with any known cell adhesion molecules, ECM proteins, or axon chemoattractive/repulsive molecules. A double lysine endoplasmic reticulum (ER) retention signal is found at the C-termini of all three Nogo isoforms, a property common to several myelin membrane proteins including PMP-22 (Welcher et al., 1991).

The Nogo Rc (NgR; Fig. 3D) binds Nogo-66 (Fournier et al., 2001) and is a 473 amino acid protein with a signaling sequence, a leucine-rich repeat-type N-terminus flanking domain, and a 140 amino acid linker domain connecting a GPI region on the C-terminus (Wang et al., 2002c), suggesting that NgR associates in

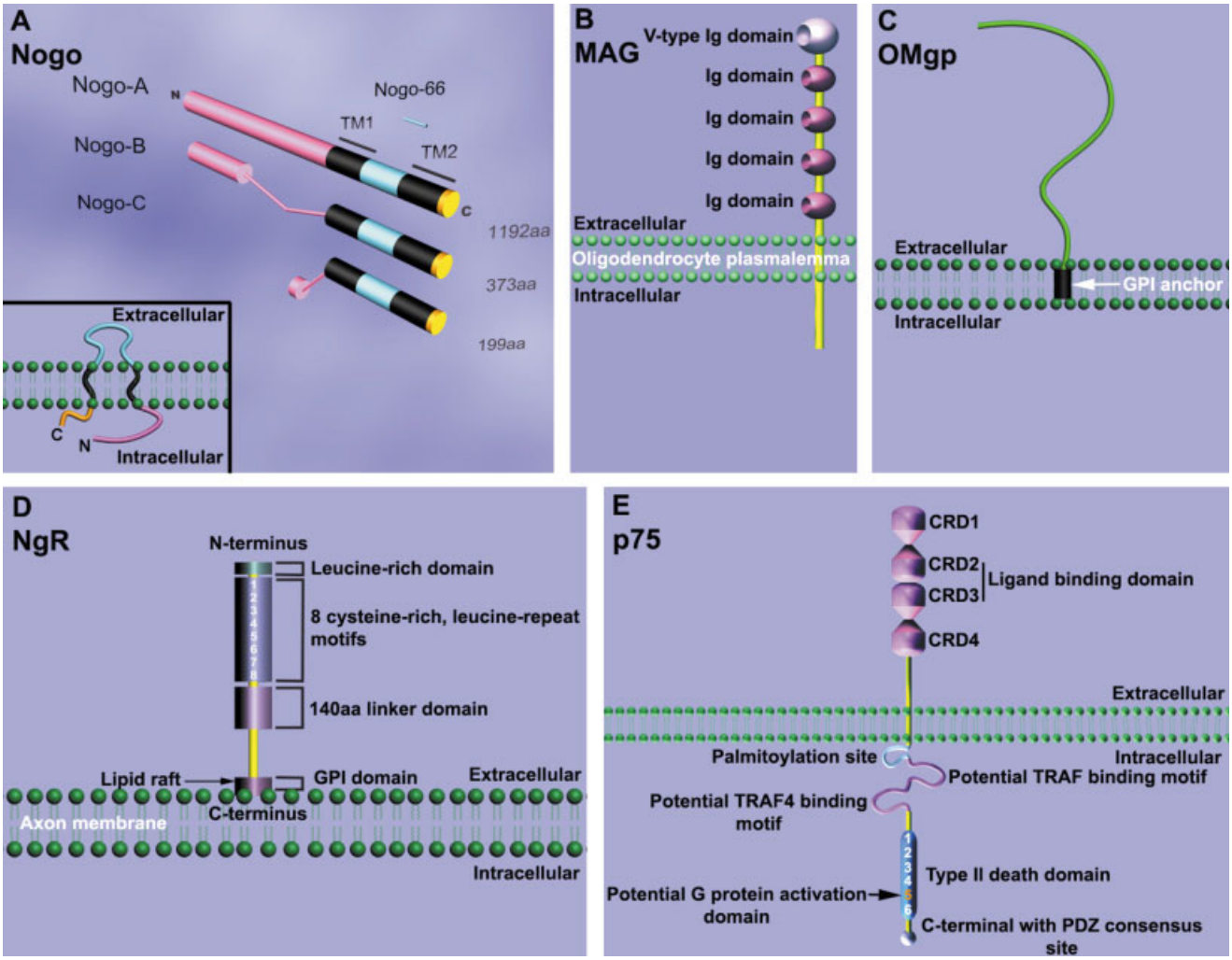

Fig. 3. Schematic representation of the structure of (**A**) Nogo protein sequences and their interrelationships, (**B**) MAG, (**C**) OMgp, (**D**) NgR, and (**E**) $p75^{NTR}$ (p75), illustrating known bioactive domains. TM, transmembrane; Ig, immunoglobulin; GPI, glycosylphospatidylinositol anchor; CRD, cyteine-rich domains; TRAF, TNFR-associated factor-binding sites; PDZ, PSD-95/Dlg/ZO-1-binding motif.

lipid rafts with another transmembrane signal-transducing polypeptide (Brittis and Flanagan, 2001), now known to be $p75^{NTR}$. The transmembrane Rc $p75^{NTR}$ (Fig. 3E) is a member of the tumor necrosis factor Rc (TNFR) superfamily with four extracellular CRD and multiple O- and N-linked glycosylation sites (Roux and Barker, 2002). The ICD contains a palmitoylation site at cysteine 279, two potential TNFR-associated factor (TRAF)-binding sites, and a type II death domain that contains a potential GTPase-activating domain for interaction with RhoA. At the C-terminal tail is a PSD-95/Dlg/ZO-1 (PDZ)-binding motif that may bind tyrosine phosphatase, and recently PDZ-Rho-GEF have been identified, which may be of relevance to the Rho signaling pathway (Kuner et al., 2002).

Cellular localization

The membrane topology of Nogo is still controversial but it seems that a major portion of the molecule is cytoplasmically orientated since the ER retention motif in the C-terminus is located within oligodendrocyte and neuronal intracellular membranes (GrandPré et al., 2000; Liu et al., 2002a). Nogo-A is identical to the Reticulon 4-A protein, a member of the Reticulon family with no known functions (van de Velde et al., 1994) that is expressed on the luminal surface of the ER (GrandPré et al., 2000). GPI anchor Nogo-A to the ER and only small amounts of Nogo-66 are detectable on the plasmalemmal surface of oligodendrocytes in culture (GrandPré et al., 2000), and thus the molecule may normally function intracellularly (Chen et al., 2000; GrandPré et al., 2000; Prinjha et al., 2000). Nogo-A also has the potential to bind within mitochondria to a Nogo-interacting mitochondrial protein (NIMP), comprising the UQCRC1/2 components of complex III of the mitochondrial respiratory chain (Hu et al., 2002). This interaction may metabolically compromise CNS neurons at critical periods during their abortive postinjury growth response. NgR is localized

to the axolemma and found in both discrete classes of CNS neurons and in astrocytes, but not in oligodendrocytes or microglia (Hunt et al., 2002a, 2002b).

Intracellular signaling pathway and functions

NgR has no intracellular component (Fournier et al., 2001). Intracellular signal transduction is mediated by $p75^{NTR}$, which acts as co-Rc for NgR (Wang et al., 2002a; Wong et al., 2002). Appropriately, $p75^{NTR}$ is enriched in CNS axons and axon terminals (Roux and Barker, 2002) and acts as a bidirectional switch controlling growth cone dynamics in response to external stimuli, regulated by cAMP and/or intracytoplasmic downstream adapter proteins (Fig. 4) (Skaper et al., 2001; Dechant and Barde, 2002; Watkins and Barres, 2002; Wong et al., 2002; Tang, 2003).

Upon Nogo binding, the extracellular leucine-rich repeat-type N-terminus domain, the eight cysteine-rich leucine-rich repeat-type C-terminus flanking domain, and the C-terminus of NgR all bind with the CRD2-3 domains in the ECD of $p75^{NTR}$ within lipid rafts in the membrane, initiating intracellular signaling of inhibition via the ICD of $p75^{NTR}$ (Wang et al., 2002a). The precise mechanism of NGR/$p75^{NTR}$-mediated RhoA activation remains to be determined, but may involve interaction with Rho GDI (Yamashita and Tohyama, 2003); GEF; the fifth helix of the death domain (Roux and Barker, 2002); and/or Rac1/Cdc42 causing Rho/ROCK downregulation (Fig. 4) (Niederöst et al., 2002).

Distribution in intact CNS

Nogo-A is strongly expressed in the cytoplasm of oligodendrocytes and the inner and outer loops of their myelin sheaths, colocalized with MOG, OMgp, and MAG (Chen et al., 2000; Huber et al., 2002; Liu et al., 2002a; Wang et al., 2002c). Paradoxically, Nogo-A is expressed in selected neurons, e.g., some DRGN, retinal ganglion cells (RGC), PC, ventral/dorsal horn spinal, and cranial nerve nuclei. NgR is similarly restricted to the above selected postnatal neurons and also to cerebral cortical pyramidal, hippocampal, amygdaloid, dorsal thalamic, deep cerebellar nuclear, cerebellar granule, and pontine neurons, but absent from all glia (Fournier et al., 2001; Hu et al., 2002; Hunt et al., 2002a, 2002b; Liu et al., 2002a; Wang et al., 2002). There is also restricted expression of $p75^{NTR}$ in adult neurons (Harvey, 1994), and notably RGC appear not to express $p75^{NTR}$ (Hu et al., 1999), although the use of $p75^{NTR}$ antibodies on tissues is fraught with technical problems (Lee et al., 1998). Presumably, the regeneration of only NgR/$p75^{NTR}$-bearing neurons is inhibited by oligodendrocyte/CNS myelin-derived Nogo/OMgp/Mag.

Distribution after CNS injury

After injury, although there is upregulation of $p75^{NTR}$ in some mature neurons (Rende et al., 1993; Roux et al., 1999), Nogo-A and NgR expression is unchanged (Huber et al., 2002; Hunt et al., 2002a, 2002b; Wang et al., 2002b).

Regeneration correlates

The growth cones of axons collapse when they contact oligodendrocytes/CNS myelin in vitro (Caroni and Schwab, 1988; Brandtlow et al., 1990, 1993; Schnell and Schwab, 1990; Vanselow et al., 1990). Treatment with an antibody Fab fragment (IN-1), which neutralizes the axon growth-inhibitory effects of Nogo-A, promotes spontaneous sprouting of, for example, PC axons (Buffo et al., 2000), and the regeneration of lesioned descending spinal axons (Brösamle et al., 2000; Fouad et al., 2001) with increased locomotor recovery (Bregman et al., 1995; Merkler et al., 2001; Raineteau et al., 2001); has no affect on ascending sensory spinal projections (Oudega et al., 2000); and increases pontine collateral innervation after medullary pyramidal tract transection (Blöchlinger et al., 2001). Vaccination with either myelin (Huang et al., 1999) or a Nogo-A-derived peptide (Hauben et al., 2001) improves recovery from partial spinal lesions (Filbin, 2000). Axon regeneration is impaired after sciatic nerve crush in transgenic mice with inducible Nogo-A expression in Schwann cells, demonstrating that Nogo-A overrides the permissiveness of the PN environment (Pot et al., 2002).

Cleavage of NgR from the axolemma renders growth cones insensitive to the collapsing properties of the extracellular Nogo-66 domain (GrandPré et al., 2000; Fournier et al., 2001; GrandPré and Strittmatter, 2001). A NgR antagonist peptide promotes DRGN neurite regeneration in vitro, although blockage of myelin inhibition is incomplete, perhaps explained by either the weak expression of NgR by DRGN in vivo (Hunt et al., 2002a, 2002b), or the combined additional suppression of the N-termini of Nogo-A, MAG, and OMgp in vivo (GrandPré et al., 2002). A soluble truncated NgR reverses outgrowth inhibition of E13 chick RGC neurites on both myelin and Nogo substrates (Fournier et al., 2002). Interfering with NgR/$p75^{NTR}$ downstream signaling also modulates the inhibition of axon growth. For example, neurons are not responsive to NgR ligands in $p75^{NTR}$ null transgenetic mice; after antibody neutralization of the ectodomain of $p75^{NTR}$; and after inhibiting interaction between Rho-GDI and $p75^{NTR}$ using a peptide that binds to the fifth α-helix of $p75^{NTR}$. Inhibition is attenuated after overexpression of the truncated $p75^{NTR}$ protein lacking the ICD (Wang et al., 2002a; Wong et al., 2002; Yamashita and Tohyama, 2003). Intrathecal administration of a $p75^{NTR}$ blocking peptide, after mid thoracic dorsal spinal hemisection, stimulates ectopic sprouting of corticospinal and raphe axons rostral to the lesion, improving motor recovery.

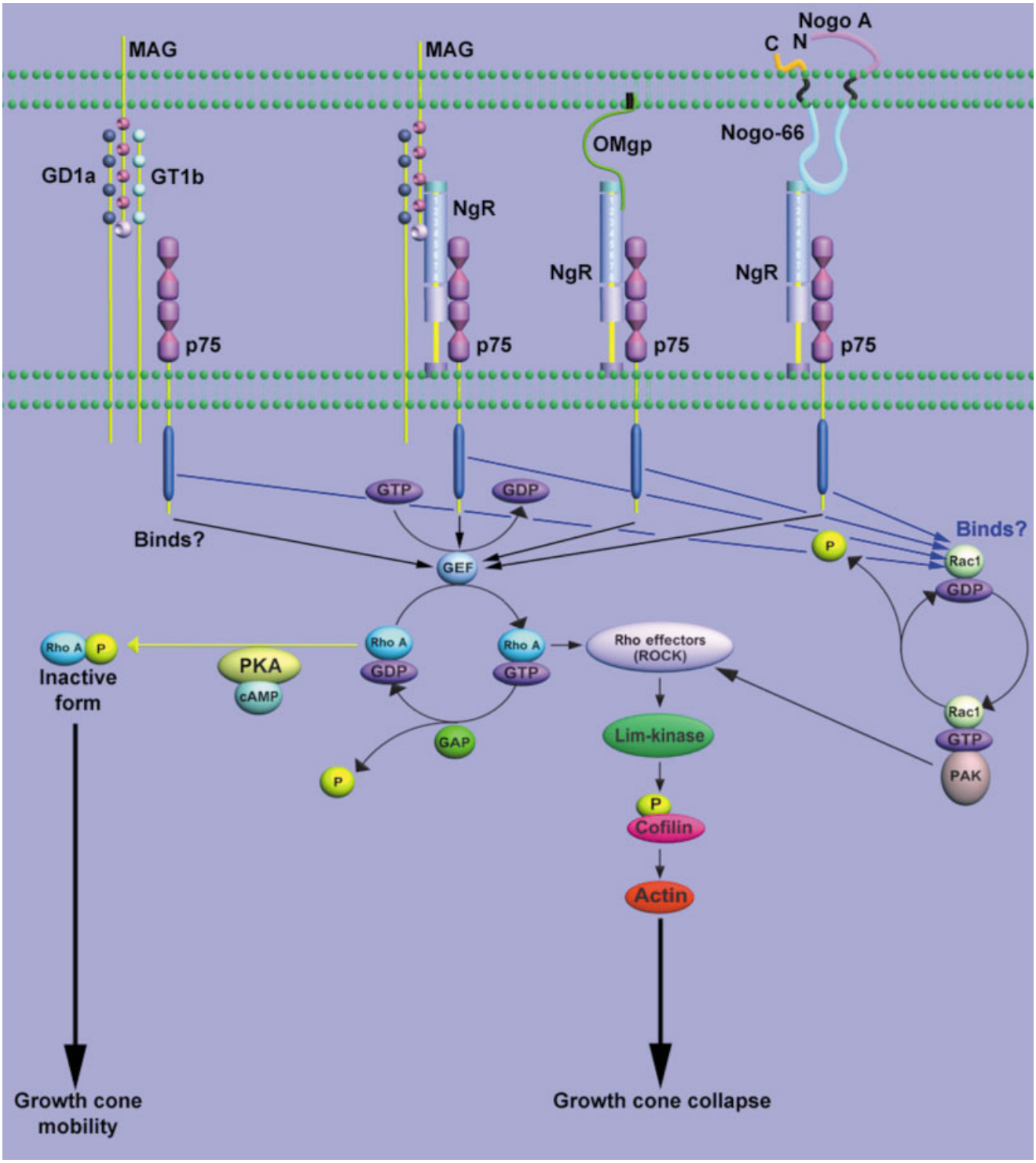

Fig. 4. Model of NgR/p75^{NTR} (p75)-mediated signaling. Three growth-inhibitory molecules, MAG, OMgp, and Nogo, are produced by oligodendrocytes. They all bind NgR that interacts directly with p75^{NTR}, which is responsible for NgR-mediated inhibitory signaling via GEF-induced RhoA activation and simultaneous Rac1/Cdc42 inactivation. Activation of PKA leads to inactivation of RhoA and prevents growth cone collapse. GEF, guanine nuclear exchange factors; GAP, GTPase-activating proteins; PKA, protein kinase A; PAK, P_{21}-activated kinase; ROCK, Rho-associated protein kinase.

Thus, the titer of Nogo displayed on the surface of oligodendrocyte/CNS myelin membranes appears sufficient to mediate growth cone collapse.

There are no simple unifying models to explain how Nogo-A functions (Goldberg and Barres, 2000; Tessier-Lavigne and Goodman, 2000; Brittis and Flanagan,

2001). Moreover, the role of NIMP in the mediation of axon growth inhibition by Nogo-A is confused, since Nogo-A is not colocalized with NIMP in mitochondria, although Nogo-A/NIMP interaction is demonstrable in isolated CNS extracts in vitro. However, no detectable change in Nogo-A/NgR expression occurs after CNS injury, but it is possible that Rc/inhibitory ligand binding occurs after trauma when sequestration of both molecules is broken down after cellular damage (Hunt et al., 2002a, 2002b). The N-terminus of the ICD (Chen et al., 2000; Prinjha et al., 2000) and the ER luminal Nogo-66 linker (GrandPré et al., 2000) are both inhibitory domains of Nogo-A and may only be active in vivo when released from intracytoplasmic stores after cellular disruption/lysis following CNS injury. Thus, in intact CNS, much of the Nogo-A may be sequestered from NgR, possibly explaining why adult neurons, atraumatically transplanted into CNS white matter, exhibit florid regeneration (Davies et al., 1997, 1999). The colocalization of Nogo-A and NgR in both neurons and glia will make interpretation of antibody neutralizing and future dominant/negative transgenic studies difficult in vivo. CNS neural NgR expression is not correlated with the efficacy of axon regeneration into PN grafts in which Nogo-66 is strongly upregulated (Hunt et al., 2002a, 2002b). Moreover, Nogo/OMgp/MAG-mediated inhibition is only relevant to selected subpopulations of neurons that express NgR (Hunt et al., 2002a, 2002b). The promiscuity of NgR for all CNS myelin-derived inhibitors probably explains why suppression of one ligand alone is ineffective in promoting CNS axon regeneration (Zheng et al., 2003). $P75^{NTR}$ is also injury-responsive, being variously up- and down-regulated, or unchanged after CNS damage (Harvey, 1994; Hu et al., 1999; King et al., 2000). NgR/$p75^{NTR}$-inhibitory ligand interactions at nerve terminals are far removed from the site of RhoA production in neuronal somata and it is not understood how Rc signal inhibition over such long distances. Moreover, ephrins/Ephs are differentially expressed on astrocytes and fibroblasts and regulate interactions between the two phenotypes (Bundesen et al., 2003). A list of abbreviations is included in the Appendix.

MAG

Molecular structure of ligand and Rc

MAG is a sialic-dependent immunoglobulin-like family member lectin (SIGLEC) protein with an affinity for GDIa and GTIb gangliosides. MAG has an ECD consisting of a terminal V-like domain and four C2-type Ig domains, a TMD, and a short ICD (Fig. 3B) (Filbin, 1995). MAG binds to NgR on the axolemma with high affinity, but requires $p75^{NTR}$ as a co-Rc for signaling MAG-mediated inhibition of axon growth and intracellular Ca^{2+} elevation (Domeniconi et al., 2002; Liu et al., 2002a; Wong et al., 2002). MAG and Nogo bind to the same ECD of NgR containing all eight leucine-rich repeat domains, but not to the GPI linker domain (Liu et al., 2000a). Rc/ligand binding is insensitive to sialation of both MAG and NgR. Domeniconi et al. (2002) suggest that MAG and Nogo-66 compete for binding to the same NgR site, but Liu et al. (2002a) propose that, since one ligand does not block binding of the other, there are two separate NgR-binding sites each for Nogo-66 and MAG.

Cellular localization

MAG is exclusively found in the myelin sheaths of both oligodendrocytes and Schwann cells (Filbin, 1995). The sialic acid-bearing glycosphingolipid gangliosides GD1a and GT1b are enriched in the plasmalemma of all neurons. They act as low Rc affinity-binding sites for MAG, facilitating NgR binding. The distribution of the MAG cognate Rc, NgR/$p75^{NTR}$, is discussed above.

Intracellular signaling pathway

MAG binds to GD1a and GT1b and then to NgR in lipid rafts on the axolemma in a manner reminiscent of Nogo/NgR binding. Within rafts, each can associate with $p75^{NTR}$ either independently or together to form an MAG/NgR/$p75^{NTR}$ complex that transmits an inhibitory signal via $p75^{NTR}$-induced modulation of RhoA, as described earlier (Fig. 3) (Vinson et al., 2001; Vyas et al., 2002; Wong et al., 2002; Yamashita et al., 2002). The concomitant inactivation of Rac1/Cdc42 has recently been confirmed (Niederöst et al., 2002). Phosphatidyl-inositol-specific phospholipase C (PI-PLC) treatment, which removes the ectodomain of the GPI-anchored NgR, prevents MAG binding to NgR (Domeniconi et al., 2002; Liu et al., 2002a), and a dominant negative form of NgR abolishes MAG-induced inhibition of neurite growth, an effect that is reversed by addition of NgR-Ecto protein (Liu et al., 2002a).

Both chemoattraction and chemorepulsion of neurites may be regulated by dynamic alterations in the intracellular concentrations of cyclic nucleotides (Ming et al., 1997; Song et al., 1997, 1998). MAG-dependent inhibition of axonal regeneration is blocked with neurotrophins possibly by activation of the cAMP-PKA pathway (Cai et al., 1999). Neurotrophic priming may overcome MAG-induced effects on G-proteins that inhibit neurotrophin-induced stimulation of the cAMP-PKA pathway. It is possible that cAMP and other signaling pathways such as cGMP utilize a common downstream intracellular target to control the growth of neurites and the Rho family of small GTPases may be a target candidate. Furthermore, since PKA phosphorylates and inactivates RhoA (Laudanna et al., 1997; Fournier et al., 2001), growth is promoted when RhoA is inhibited by C3 transferase-mediated ADP ribosylation (Jin and Strittmatter, 1997), and MAG-

induced axon inhibition can be overcome by C3 transferase treatment (Lehmann et al., 1999).

Distribution in intact CNS

MAG-positive myelin sheaths are found in all CNS tracts and all PN. The distribution of NgR and $p75^{NTR}$ is given above.

Distribution after CNS injury

After CNS damage, the disruption of myelin sheaths and degeneration of distal myelinated tracts probably results in the release of a soluble proteolytic fragment of MAG, termed dMAG (Tang et al., 1997), which blocks regrowth during the abortive phase of CNS axon regeneration, possibly by binding NgR/$p75^{NTR}$ on axonal growth cones. dMAG released from damaged white matter is suggested to account for the majority of inhibitory activity after CNS injury (Tang et al., 2001).

Regeneration correlates

MAG has long been recognized as a bifunctional molecule promoting neurite outgrowth of young neurons (Johnson et al., 1989; Filbin, 1996), but inhibiting neurite extension from older neurons (McKerracher et al., 1994; Mukhopadhyay et al., 1994; Tang et al., 1997). Changes in endogenous levels of neuronal cAMP may account for the switch (Song et al., 1998; Cai et al., 1999, 2001), although there is a positive correlation between NgR expression developmentally and the sensitivity of neurons to MAG inhibition. For example, the growth of neurites of NgR-expressing adult DRGN is inhibited by MAG, whereas that of embryonic DRGN neurites lacking NgR is not (Liu et al., 2002b). Notwithstanding the presence of MAG in PN myelin sheaths, the regeneration of PN is probably explained by rapid clearance myelin debris by macrophages, the downregulation of myelin protein production by dedifferentiating Schwann cells (Fawcett and Keynes, 1990; Brown et al., 1991; Bedi et al., 1992; Filbin, 1995), the lack of NgR expression (Hunt et al., 2002a) and the down regulation of p75NTR mRNA in DRGN after axotomy (Allchorne et al., 2003). NgR interacts with MAG, Nogo-A, and OMgp additively. Thus, reduction in any one of these ligands is unlikely to promote extensive CNS regeneration, an observation that could account for the absence of CNS axon regeneration in the lesioned optic nerve and corticospinal tracts in MAG dominant negative transgenic mice (Bartsch et al., 1995).

Other Oligodendrocyte/CNS Myelin-Derived Inhibitors

OMgp

GPI-anchored OMgp (Fig. 3C) (Mikol and Stefansson, 1988; Mikol et al., 1990) is an inhibitor of neurite outgrowth in cultured neurons (Wang et al., 2002b), binding to NgR with high affinity similar to that of Nogo-66 and MAG. Like other inhibitory molecules, OMgp mediates neurite growth inhibition by NgR binding and $p75^{NTR}$ signaling through Rho GTPases, competing for the active binding sites on NgR with Nogo-66 and MAG (Fig. 4) (Domeniconi et al., 2002; Wang et al., 2002b). Unlike intracellular Nogo-A, OMgp and MAG are expressed on oligodendrocyte plasmalemma, and thus both might more readily act as a physiological ligand for NgR (Wang et al., 2002b). Like Nogo, OMgp is also expressed in neurons (Habib et al., 1998), where its function is unknown.

Versican $V_{2/3}$

O2A progenitor cells (Asher et al., 1999), CNS myelin, and oligodendrocytes appear rich in the CSPG, brain-specific Versican V_2/V_3 splice variants (LeBaron, 1996; Nierderöst et al., 1999; Schmalfeldt et al., 2000). Versican V_2 is an inhibitor of neurite growth (Schmalfeldt et al., 2000), the potency of which is reduced after treatment with chABC, but not abolished (Schmalfeldt et al., 2000), possibly because the core protein retains inhibitory properties. The differential formation of mRNA splice transcripts of Versican accounts for the structural diversity of its core protein. Four distinct splice forms have been reported, of which Versican V_2 is dominant in the CNS (Ito et al., 1995; Asher et al., 1999). The extensive glycosylation of Versican V_2 may block substrate/growth cone interactions by steric hindrance either directly or by preventing interaction with growth-promoting substrate molecules. Antibodies raised against Versican $V_{2/3}$ promote the growth of cerebellar granule cell neurites cocultured with axon growth-inhibitory fractions of CNS myelin.

Brevican

Brevican is an axon growth-inhibitory CSPG (Yamada et al., 1997) isolated from CNS myelin (Niederöst et al., 1999), and a surface-bound GPI-linked isoform is expressed in oligodendrocytes (Seidenbecher et al., 1995, 1998).

Tenascin-R

Tenascin-R GP are expressed as 160 and 180 kD isoforms by oligodendrocytes and their precursors, secreted into the extracellular ECM, and upregulated at

lesion sites after injury (Pesheva et al., 1989; Fuss et al., 1993; Wintergerst et al., 1993; Angelov et al., 1998; Probstmeier et al., 2000a). Expression is regulated by cytokines and growth factors including TNFα and platelet-derived growth factor (PDGF) (Jung et al., 1993; Probstmeier et al., 1999). Like MAG, Tenascin-R is a bifunctional molecule promoting both neurite adhesion and antiadhesion, thereby enhancing and inhibiting axon growth, respectively (Pesheva et al., 1989, 1991, 1993; Goodman, 1996; Song and Poo, 1999). Neurite growth is inhibited after binding of the neuronal GPI-anchored Rc protein F3/F11 to the EGF-like domain (rat), and the second–third FN III-like domains (chicken) of Tenascin-R (Brümmendorf et al., 1993; Pesheva et al., 1993; Nörenberg et al., 1995; Xiao et al., 1996, 1997, 1998). Substrate inhibition is mediated through the heparin/PG/integrin-binding fragments of FN by steric hindrance/conformational change in Tenascin-R cell-binding sites (Peshevar et al., 1994; Pesheva and Probstmeier, 2000). Removal of the Tenascin-R 160-linked CS GAG side chains with chABC neutralizes binding to the heparin-binding FN fragment and promotes cell adhesion (Probstmeier et al., 2000b). Tenascin-R blocks FN-mediated neurite adhesion and outgrowth by inhibition of integrin/RGD-dependent adhesion to FN (Probstmeier et al., 2000b). Astrocytes and oligodendrocytes adhere to Tenascin-R through surface membrane-associated sulfatides (Pesheva et al., 1997). Tenascin-R isoforms interact with both lecticans through their C-type lectin domains (Aspberg et al., 1995, 1997) and heterophilically to FN and collagen 1, but not to either collagen IV or Lam (Faissner et al., 1990; Pesheva et al., 1994).

NG2-GLIAL-DERIVED AXON GROWTH INHIBITORS

In the past, all cells expressing NG2 in the CNS have been considered adult OPC on the basis of their antigenic phenotype (Dawson et al., 2000; Levine et al., 2001). However, the vast majority of NG2-expressing glia in the adult CNS are postmitotic with a complex stellate morphology (Fig. 5) and intricate heterologous contacts, indicating that they are a novel type of mature specialized NG2-glia (Butt et al., 1999, 2003; Nishiyama et al., 1999, 2003; Berry et al., 2002a,b, 2003). NG2-glia are distinct from OPC that give rise to oligodendrocytes during development (Mallon et al., 2002; Greenwood and Butt, 2003; Matthias et al.). Adult NG2-glia respond rapidly to CNS disruption by morphogenic changes (Fig. 5), proliferation, and migration (Nishiyama et al., 1997; Levine et al., 2001). The response of NG2-glia to a range of insults is stereotypic, for example, to trauma and ischemia (Levine, 1994; McTigue et al., 2001; Jones et al., 2002; Tang et al., 2002), excitotoxicity (Ong and Levine, 1999; Bu et al., 2001), viral infection (Levine et al., 1998), and demyelination (Nishiyama et al., 1997; Keirstead et al., 1998; Di Bello et al., 1999; Levine and Reynolds, 1999; Chari and Blakemore, 2002).

NG2 Proteoglycan

Molecular structure of ligand and Rc

NG2 is a transmembrane CSPG (Fig. 6) and is also secreted into the ECM after proteolytic cleavage from its TMD (Nishiyama et al., 1995). The complete cDNA and primary amino acid sequences for NG2 have been cloned (Nishiyama et al., 1991). The molecule is divided into a short 76 amino acid ICD, a single 25-residue TMD, and a large 2,224-residue of the ECD. The C-terminus of the ICD contains a PDZ-binding motif, which interacts with the cytoplasmic scaffolding protein MUPP1 (Barritt et al., 2000) and provides a potential cytoplasmic signaling pathway for the interactions of NG2 with the actin cytoskeleton for potentiation of cell motility and process extension (Lin et al., 1996a, 1996b; Burg et al., 1997, 1998; Eisenmann et al., 1999; Fang et al., 1999). The ECD has three subdomains, comprising an N-terminus globular domain 1 and a juxtamembrane globular domain 3, connected by a central domain 2 that contains binding sites for collagens and CS GAG side chains (Burg et al., 1997; Tillet et al., 1997). The current evidence is that domain 2 contains only a single CS GAG side chain, which does not modulate the binding properties of NG2, but does play a role in the targeting of NG2 to specific subcellular microdomains (Stallcup and Dahlin-Huppe, 2001). Domain 3 contains sites for proteolytic processing of NG2 for release from the cell surface (Nishiyama et al., 1995). The ECD of NG2 interacts with a number of ligands, including PDGF-AA and FGF-2, metalloproteases (MMP), palsminogen, collagen II/V/VI, Lam, Tenascins (Sallcup et al., 1990; Nishiyama and Stallcup, 1993; Grako and Stallcup, 1995; Ieda et al., 1995, 2001; Burg et al., 1996, 1997; Tillet et al., 1997, 2002; Goretzki et al., 1999, 2000; Grako et al., 1999). In most cases, NG2 modulates the ligand-dependant activation of the primary signaling Rc. For example, by selectively binding PDGF-AA and FGF-2, NG2 acts as an auxiliary cell surface Rc, potentiating activation of respective Rc tyrosine kinases (Goretzki et al., 1999; Grako et al., 1999). NG2 may also act as a primary signaling molecule by binding to collagen and mediating cell migration, proliferation, and survival (Burg et al., 1997, 1998).

The axon growth-inhibitory potential of NG2 has been established in vitro (Dou and Levine, 1994; Fidler et al., 1999; Chen et al., 2002; Ughrin et al., 2003), but the relative contribution of the core protein and the CS GAG side chains is controversial. Removal of CS GAG side chains with ChABC abolishes the inhibitory properties of NG2 in an astrocytic cell line (Fidler et al., 1999). In contrast, it has been shown that ChABC does not affect the axon growth-inhibitory properties of ei-

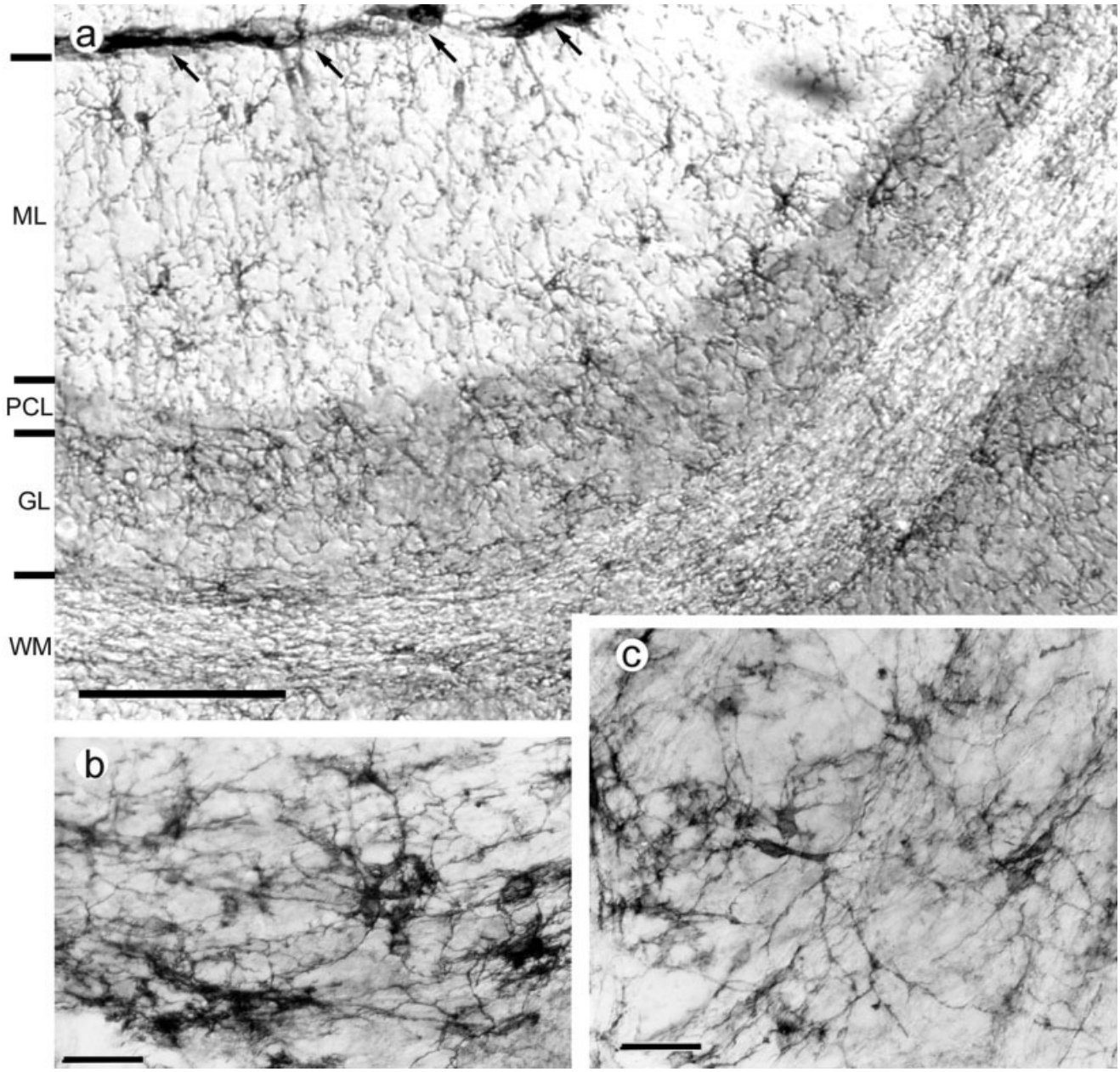

Fig. 5. NG2-glia in a normal adult rat cerebellar folium (**a**), showing their distribution in white mater (WM), granule cell layer (GL), Purkinje cell layer (PCL), and molecular layer (ML). Arrows mark the pial surface. Examples of reactive NG2-glia (**b** and **c**) in fascicles of axons 5 days after transection in the adult rat anterior medullary velum demonstrated by immunohistochemistry, using an anti-NG2 antibody. Note the changed morphology compared with normal NG2-glia shown in a. Bars, 80 μm in a; 20 μm in b and c.

ther purified NG2 or membranes from embryonic OPC and OPC lines, and domains 1 and 3, which do not bind CS GAG side chains, are each sufficient to inhibit neurite growth (Dou and Levine, 1994; Chen et al., 2002; Ughrin et al., 2003). Domain 2 does inhibit neurite outgrowth in vitro when expressed as a fusion protein carrying one or more CS GAG side chains (Ughrin et al., 2003). However, domains 1 and 3 are responsible for the inhibitory properties of the whole NG2 molecule and the CS GAG side chain is likely to make only a minor contribution (Chen et al., 2002; Ughrin et al., 2003). The N-terminus domain 1 is exposed when NG2 is an integral membrane protein, whereas juxtamembrane domain 3 is only exposed when NG2 is secreted (Ughrin et al., 2003). Thus, the axon growth-inhibitory properties of the NG2 molecule expressed by NG2-glia are likely to be mediated through domain 1. However, the CS GAG side chain plays an important role in targeting the expression of NG2 (Stallcup and Dahlin-Huppe, 2001), which could affect subcellular sites at which NG2 interacts with neurites and ECM components.

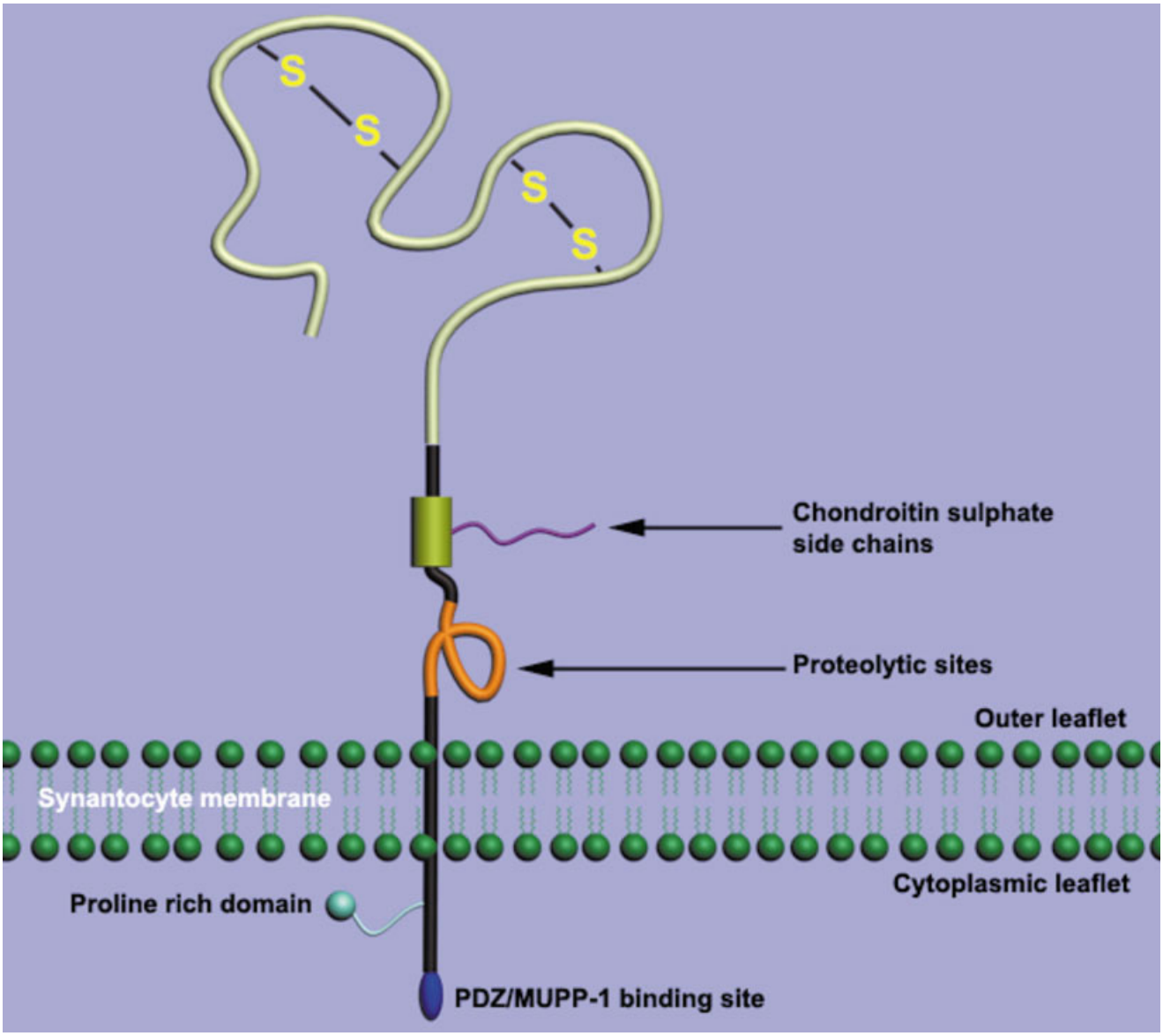

Fig. 6. Schematic representation of the structure of NG2, illustrating known bioactive domains. (Synantocytes are NG2 glia-see Berry et al. (2002b) and Butt et al. (2002) for new nomenclature.)

To date, no Rc for the NG2 ligand has been identified, but the presence of neuronal Rc has been inferred from binding studies using radiolabeled NG2 and by partially reversing NG2-mediated inhibition with agents that raise cAMP and intracellular Ca^{+} levels (Dou and Levine, 1997).

Cellular localization

NG2 is expressed on the surface of the somata and processes of NG2-glia and OPC (Butt et al., 1999; Ong and Levine, 1999), as well as macrophages, and possibly fibroblasts at the injury site, but it is not known whether they also secrete the molecule (Nishiyama et al., 1991; Levine and Nishiyama, 1996; Zhang et al., 2001; Jones et al., 2002).

Intracellular signaling pathway

The mechanisms by which NG2 inhibit neurite outgrowth still remain largely unknown. Several possibilities exist, including binding to growth promoting substrates such as L1 and Lam; disrupting interactions between cell adhesion molecules on the growth cone membrane and interacting substrates; interaction via an Rc with activation of an intracellular signaling cascade involving a pertussis toxin-sensitive G-protein mechanism (Dou and Levine, 1997); and interaction

with ECM molecules such as collagen IV and Tenascin, augmenting the inhibitory ECM environment (Yamagata et al., 1986).

Distribution in intact CNS

The presence of NG2 on cell membranes (Butt et al., 1999) is consistent with the molecule being an integral membrane CSPG (Nishiyama et al., 1991). The processes of NG2-glia extend along CNS axons and their myelin sheaths and often form a perineuronal lattice in gray matter (Butt et al., 1999; Ong and Levine, 1999; Bergles et al., 2000). In the spinal cord, NG2-glia are also localized to the DREZ and contribute to the formation of the glia limitans at the CNS-PNS interface (Zhang et al., 2001). In addition to NG2, embryonic/adult OPC express NG2 and other axon-repellents, including Neurocan (Asher et al., 2000; Chen et al., 2002), or one element of the intracellular signaling cascade Versican V_2 (Asher et al., 1999), Brevican (Seidenbacher et al., 1995, 1998; Yamada et al., 1997), and Phosphacan (Canoll et al., 1996; Chen et al., 2002). The properties of the NG2 molecule suggest that NG2-glia may have special functions in cell-cell and cell-ECM interactions, the functional consequences of which are cell adhesion, migration, proliferation, process outgrowth, and the stabilization of the ECM, all of which are important for normal physiology and for the formation of the glial scar (Butt et al., 2003).

Distribution after CNS injury

NG2 is upregulated in cells around CNS lesions in white and gray matter (Levine, 1994; Ong and Levine, 1999; Levine et al., 2001; Jones et al., 2002; Tang et al., 2002). After injury to the CNS, NG2-glia undergo a rapid and localized injury response at the lesion edge characterized by an increase in the number of processes that form a dense fibrous mat of $NG2^+$ material among the processes of reactive astrocytes (Jones et al., 2002; Tang et al., 2002). Following spinal cord injury, NG2-glia are specifically activated at the lesion site, upregulate NG2 within 24 h, attaining high levels within 3 days, peaking at 7 days. Thereafter, NG2 expression remains stable at markedly elevated levels over the long term (Jones et al., 2002). Reactive NG-2 glia about the lesion margins also upregulate and colocalize Tenascin-C and Neurocan 8 expression (Tang et al., 2002). NG2 is also expressed by hematogenous macrophages, endothelial cells, and meningeal cells migrating into the wound (Levine and Nishiyama, 1996; Zhang et al., 2001; Jones et al., 2002). Macrophages are probably the main cell type contributing to the secretion and deposition of NG2 into the lesion core (Jones et al., 2002).

Regeneration correlates

NG2 inhibition of neurite growth in culture is blocked by anti-NG2 antibodies (Dou and Levine, 1994; Chen et al., 2002; Ughrin et al., 2003) and, in the spinal cord, NG2 is in the right place at the right time to inhibit regeneration (Zhang et al., 2001; Jones et al., 2002). Significantly, removal of the CS GAG side chain by ChABC treatment reduces the inhibitory properties of NG2-expressing cell lines and embryonic OPC in vitro (Fidler et al., 1999; Asher et al., 2002) and promotes regeneration and functional recovery in vivo (Moon et al., 2001; Bradbury et al., 2002). ChABC does not affect the inhibitory properties of the whole NG2 molecule and domains 1 and 3 of the NG2 core protein alone are sufficient to inhibit neurite outgrowth in vitro (Dou and Levine, 1994; Chen et al., 2002; Ughrin et al., 2003). Thus, CS GAG side chains may contribute to the inhibitory properties of the glial scar, but not to those of NG2-glia. NG2-glia augment their inhibitory properties by producing Versican and Neurocan in vivo (Tang et al., 2002). However, in spinal cord injury, Versican is only moderately upregulated and Neurocan is only weakly expressed compared to NG2 (Jones et al., 2002). NG2-glia form a potential interactive zone at the interface between astrocytes at the lesion edge and the hematogenous material in the core of the wound, suggesting that NG2 CS GAG side chains may organize the ECM and stabilize the glial scar, although recent evidence suggests that ephrin/Eph interactions organize the deposition of the basal lamina of the glia limitans accessoria (Kromer et al., 2002; Bundesen et al., 2003).

FIBROBLAST/MENINGEAL CELL-DERIVED GROWTH INHIBITORS

Sema

Molecular structure of ligand and Rc

Sema family members are classified as either transmembrane, GPI-linked, or secreted and are currently designated into eight subclasses expressed in both vertebrates and invertebrates (Semaphorin Nomenclature Committee, 1999; Raper, 2000). A $\sim$ 500 amino acid ECD characterizes the Sema family members. Sema 3A, a secreted axon-repellent molecule, consists of an N-terminal signal peptide followed by the Sema domain and an IgG domain of $\sim$ 70 amino acids (Luo et al., 1993, 1995; Püschel et al., 1995; Püschel, 1996). A basic domain is present at the carboxyl end of the molecule, which is unique to Sema 3A (Fig. 7).

Class 3 Sema bind to NP/PlexR complexes. NP-1/2 bind several Sema family members (He and Tessier-Lavigne, 1997; Kitsukawa et al., 1997; Kolodkin et al., 1997; Nakamura et al., 1998; Renzi et al., 1999; Raper, 2000). NP-1/2 comprise an ECD of two CUB motifs, a1 and a2, next to two domains with homology to coagulation factors V and VIII, b1 and b2, an MAM domain,

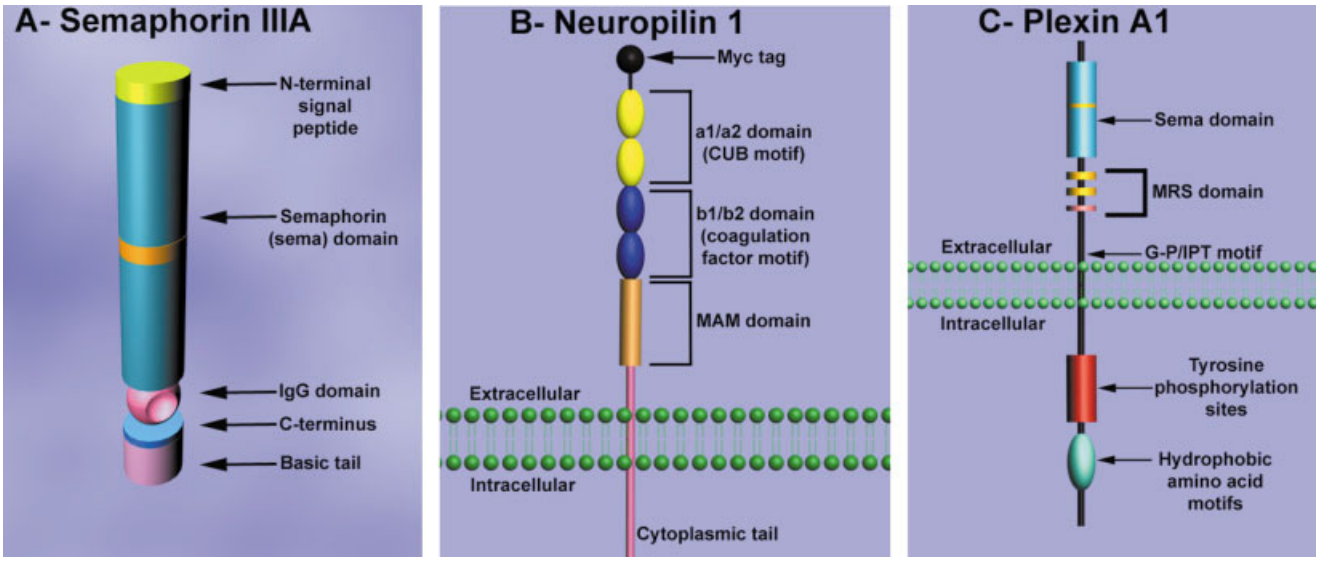

Fig. 7. Schematic representation of the structure of (**A**) Sema IIIA, (**B**) NP-1, and (**C**) Plex A1, illustrating known bioactive domains. Sema, sema domain; CUB, complement binding domain; MAM, mephrin A5 domain; MRS, Met-related sequences.

a single TMD, and a short ICD of 39 amino acids lacking any known signaling motifs (Fig. 7).

Plex are NP signaling co-Rc (Takahashi et al., 1999; Raper, 2000). Nine variants of Plex are expressed in vertebrates, divided into four subfamilies (A–D) based on structural homology (Tamagnone et al., 1999; Cheng et al., 2001). Plex are large transmembrane proteins with an ECD homologous to scatter factor Rc encoded by the MET oncogene family (Tamagnone and Comoglio, 1997; Tamagnone et al., 1999). They also contain a ~ 500 amino acid sequence with homology to the Sema domain (Kolodkin et al., 1993; Winberg et al., 1998). Plex-1 signaling is autoinhibited by its Sema domain, and Sema 3A/NP-1 binding restores signaling (Takashi and Strittmatter, 2001). The ECD of Plex B1 and B2 contains furin-like protease cleavage sites (Tamagnone et al., 1999) and cysteine-rich MRS motifs. The Plex ICD of ~ 600 amino acids is highly conserved, containing several hydrophobic amino acid motifs that may have a role in internalization and downregulation of transmembrane Rc (Fig. 5c) (Sandoval and Blakke, 1994). In addition, α-helices on the ICD are potential tyrosine phosphorylation sites signaling via a tyrosine kinase and believed to be important in protein-protein interactions (Tamagnone et al., 1999).

Cellular localization

Sema 3A is secreted by fibroblasts and neurons and binds to a membrane-bound nonsignaling co-Rc, NP-1 (He and Tessier-Lavigne, 1997; Kolodkin et al., 1997). Functional Sema 3A Rc are formed when the Sema 3A/NP-1 complex on the neuronal membrane binds to the signaling transmembrane Rc Plex 1 (Takahashi et al., 1999; Tamagnone et al., 1999).

Intracellular signaling pathway

When Sema bind with NP/Plex co-Rc complexes on cell membranes, a intracellular signaling cascade is activated, which changes actin dynamics, cell adhesion, cytokinesis, trafficking, and gene expression (Ramakers, 2002). Plex probably signal growth cone collapse using the collapsin response mediator protein (CRMP) and Rho (Fig. 8) (Winberg et al., 2001). Sema signaling of growth cone collapse requires both activated Rac1 and RhoA. Sema binding to growth cones may induce ligand-mediated clustering of Plex B Rc (Hu et al., 2001). Sema binding increases Plex B affinity for the GTP form of Rac, sequestering Rac1 from PAK, and leading to inhibition of growth cone lamellipodial extension. Additionally, in PAK overexpression studies, the Plex B gain-of-function phenotype is suppressed, suggesting that PAK is also negatively regulated by Plex B activation. Plex B-mediated signaling may be facilitated by blocking recruitment of PAK to specific sites on the growth cone membrane by the adaptor protein Dock, preventing the activation by the GTP-bound forms of Rac and Cdc42 (Hing et al., 1999; Newsome et al., 2000; Hu et al., 2001). Sema 3A binding activates LIM kinase downstream of Rac1, which in turn may induce phosphorylation of cofilin, an actin-binding protein that modulates F-actin turnover via actin depolymerization (Aizawa et al., 2001). Plex B also binds directly to RhoA through a sequence moiety of its ICD, which leads to increased output of RhoA and the previously described induction of ROCK-mediated growth cone collapse, probably also mediated through activation of LIM kinase (Hu et al., 2001). However, it seems that RhoA is downstream of Rac1 in the cascade from Plex-1 Rc activation. Interestingly, Plex B may interact with RhoA in both the GDP- and GTP-bound forms.

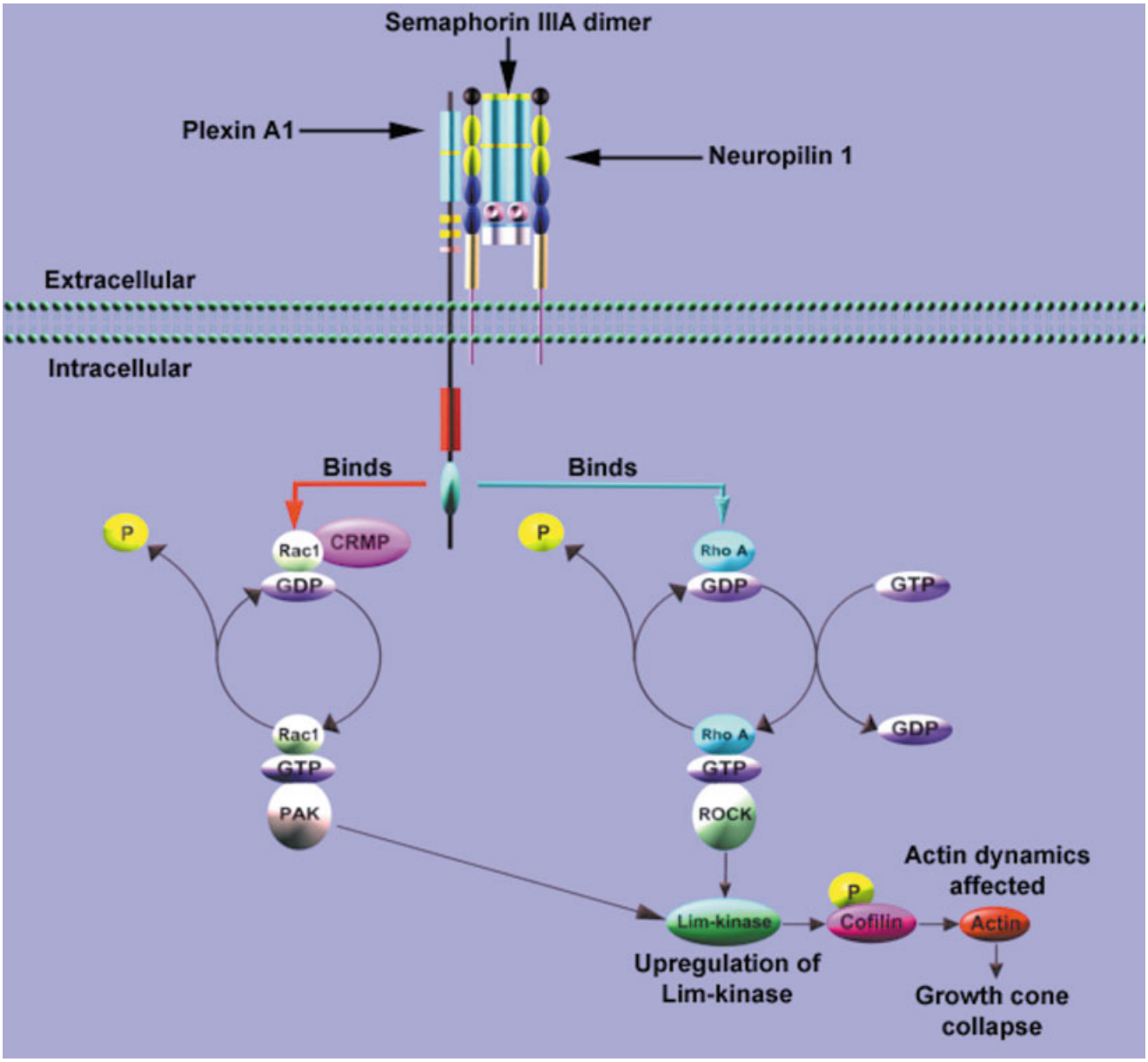

Fig. 8. Model of Sema-induced signaling of growth cone collapse. Sema activation of the NP/Plex Rc complex leads to alterations of RhoA and Rac1 activity in a CRMP-dependent process that modulates actin filament assembly via alterations in their downstream effectors, LIM kinase and cofilin.

Distribution in intact CNS

There is constitutive expression of Sema 3A in meningeal fibroblast (Pasterkamp et al., 1998a, 1998b, 1999), mature cerebellar cells (Rabacchi et al., 1999), second-order olfactory bulb neurons (Pasterkamp et al., 1998c), and spinal motoneurons (Pasterkamp et al., 1998a, 1998b, 1999).

NP-1 mRNA is expressed in DRGN (Reza et al., 1999; Gavazzi et al., 2000), and NP-1 and CRMP-2 in primary olfactory neurons (Satoda et al., 1995; Kawakami et al., 1996; Pasterkamp et al., 1998a, 1998b, 1999). However, the site of functional interaction between putative responsive elements bearing NP-1/Plex 1 complexes and soluble Sema 3A has not been defined in the adult CNS.

Distribution after CNS injury

There is upregulation of Sema 3A mRNA in wound fibroblasts, which secrete the molecule into the ECM where it binds to CSPG (Pasterkamp et al., 1999). The ECM-bound Sema 3A is thought to interact with NP-1/Plex A1 expressed on growth cones of axotomized neurons invading the developing scar, arresting regen-

eration (Pasterkamp et al., 1999, 2001; Pasterkamp and Verhaagen, 2001).

Regeneration correlates

Activation of the Plex A1 ICD by GTPases Rnd1 and RhoD triggers growth cone collapse through CRMP (Vastrik et al., 1999; Arimura et al., 2000; Goshima et al., 2000; Gu and Ihara, 2000; Nakamura et al., 2000; Rohm et al., 2000; Driessens et al., 2001; Liu and Strittmatter, 2001). L1 is a component of the Sema 3A Rc complex specifically binding to NP-1 (Castellani et al., 2000), either modulating Plex 1 signaling and/or stabilizing the NP-1/Plex A1 complex (He, 2000). Sema 3A is a chemorepellent for the growing axons of several classes of neurons in vitro (Luo et al., 1993; Messersmith et al., 1995; Püschel et al., 1995; Shepherd et al., 1996, 1997; Kobayashi et al., 1997; Valera-Eschavarría et al., 1997; Bagnard et al., 1998; Chédotal et al., 1998; Polleux et al., 1998; Rochlin and Farbman, 1998; Reza et al., 1999). Sema 3A/Np-1/Plex A1 interactions are also implicated in CNS regenerative failure in vivo (Goshima et al., 2000; Gavazzi, 2001). Meningeal fibroblasts migrate into CNS wounds (Li and David, 1996) and form the core of the scar becoming surrounded by a basal lamina partly secreted by reactive astrocyte foot processes (Logan and Berry, 2001; Kromer et al., 2003; Bundesen et al., 2003). Regeneration occurs in the lesioned olfactory tract where Sema 3A is not expressed, but not after bulbectomy when a Sema 3A-rich scar persists (Pasterkamp et al., 1999). However, the arrest of axon regeneration in dorsal funicular lesions, in which Sema 3A is expressed (Pasterkamp et al., 2001), may not correlate with the upregulation of NP-1 mRNA by DRGN (Gavazzi et al., 2000). Sema 3A genes delivered to organotypic spinal cord explants inhibit NGF-dependent sensory afferent growth (Pasterkamp et al., 2000). Sema III is expressed in cord lesions and NP-1 is expressed in the red nucleus and layer V of the cerebral neocortex (de Winter et al., 2001), a correlation that could explain the failure of regeneration in these systems. Moreover, interactions with Sema 3A may regulate cell motility and angiogenesis during scar formation (Pasterkamp and Verhaagen, 2001).

Other Fibroblast-Derived Inhibitors

As mentioned above, CSPG and Eph are also secreted/expressed by fibroblasts. In particular, interactions at the interface between ephrin and Eph-expressing reactive astrocytes and meningeal fibroblasts, respectively, within a CNS wound may determine the site of deposition of the basal lamina of the glia limitans externa enveloping the scar (Bundesen et al., 2003). Other CSPG family members, including NG2 and Phosphacan, and the PG, Tenscin-C, are also upregulated in meningeal fibroblasts invading the wound (Levine and Nishiyama, 1996; Tang et al., 2002).

CONCLUSIONS

In vitro, axon growth-inhibitory ligand/Rc binding mediates the arrest of axon growth. The multiple ligands present in vivo, and their partial sequestration, probably account for the unconvincing regeneration reported across lesions after blocking individual inhibitory ligands. For example, the IN-1 antibody neutralizes the inhibitory action of Nogo-A in CNS wounds (Schnell and Schwab, 1990), and the moderate regeneration seen is probably explained by the precocious binding of myelin/oligodendrocyte-derived axon-repellent ligands other than Nogo-66, including MAG and OMgp to the NgR/p75^{NTR} Rc complex. This convergence onto a single signal transduction pathway might provide a focus for more effective therapies designed to promote CNS axon regeneration, although not a panacea since NgR/p75^{NTR} are not expressed in all CNS neurons (Hunt et al., 2002b).

The small regulatory tyrosin kineases of the Rho family (Rac, Rho, and Cdc42) regulate cell motility and axon growth by modulation of the cytoskeleton (Hall, 1998). In neurons, RhoA mediates growth cone collapse (Mueller, 1999), and RhoA activity is reduced after both neurotrophin-induced axon growth, mediated by p75^{NTR} (Yamashita et al., 1999), and phosphorylation by cAMP-activated PKA (Schoenwaelder and Burridge, 1999). Inactivation of Rho isoforms by ADP-ribosylation, using the *Clostridium botulinum* C3 enzyme (Rubin et al., 1988), blocks ephrin-induced growth cone collapse of chick RGC (Wahl et al., 2000); promotes neurite growth on CNS myelin (Jin and Strittmatter, 1997; Lehmann et al., 1999); and promotes regeneration in the optic nerve (Lehmann et al., 1999) and spinal cord (Dergham et al., 2002). However, at present, there is little understanding of how somal production of these proteins, their transport, and ultimate cytoskeletal disruption in growth cones through Rc/inhibitory ligand signaling are integrated.

The reexpression and/or retention in adult CNS targets of ontogenetic axon-repellent/attractive ligands, which regulate axonal guidance and the topology of synaptogenesis during embryogenesis, is an encouraging observation, boding well for accurate reinnervation and functional recovery, if regeneration were possible. It has already been demonstrated that fetal/neonatal hippocampal grafts implanted into the denervated adult dentate gyrus accurately reinnervate vacated postsynaptic sites (Zhou et al., 1985). At present, there is evidence for ephrin expression in denervated targets similar to that seen during development. It is not known if other developmental axon guiding ligands, e.g., Slit, Robo, and Nestin, are similarly expressed in deafferented adult targets.

Strategies for promoting axon regrowth after CNS injury center on immunoneutralizating oligodendrocyte/CNS myelin-derived inhibitors; modulating the scar by neutralizing/downregulating the inhibitory ligands; inactivating the Rho signaling pathway; blocking/downregulating Rc of growth-inhibitory ligands

and/or modulating $p75^{NTR}$ signaling, which probably occur ontogenetically, as the CNS neuropil is switched from a growth-promoting to a growth-inhibitory state; developing dominant/negative inhibitory ligand/Rc transgenic animals; and using antisense and siRNA technologies. Interestingly, since Nogo/OMpg/NgR are expressed in both neurons and oligodendrocytes (which, paradoxically, are effector and target cells, respectively), such strategies are unlikely to shed light on the role of these molecules in the injured animal until the functions of these molecules are understood in the intact CNS.

In the adult rat visual system, good regeneration of the optic nerve is achieved after either PN transplantation into the vitreous body (Berry et al., 1996, 1999) or lens injury (Fischer et al., 2000, 2001; Leon et al., 2000; Lorber et al., 2002; Yin et al., 2003), without neutralization of growth-inhibitory ligands. Optic axons regenerate through the optic nerve scar, degenerating myelin/reactive astrocytes and NG2-glia in the distal optic nerve segment and, in the chiasm, preferentially grow through the homologous degenerating trajectories, they previously occupied, rather than heterologous intact tracts where myelin-inhibitory ligands are largely sequestered. Surprisingly, no scar tissue is deposited in the lesions of regenerating rat optic nerves (Berry et al., 1996, 1999). One explanation for these findings is that PN grafting/lens injury releases a neurotrophic stimulus that not only promotes axon growth, but also downregulates axon growth-inhibitory Rc on growth cones and/or modulates $p75^{NTR}$ signaling; stimulates intracellular cAMP that blocks ligand-induced G-protein-mediated axon growth inhibition (Cai et al., 1999); and stimulates MMP/plasminogen activator secretion by growth cones, thereby dispersing the scar and degrading, for example, inhibitory ligands such as CSPG bound to ECM. This hypothesis highlights a maxim that mobilization of growth by neurotrophins is redundant unless these molecules also block inhibitory ligand signaling and/or downregulate Rc as well as promote enzyme release to neutralize all inhibitory signals the axons may confront, and abrogate scar development. The observation that the $p75^{NTR}$ switch controls downstream growth promoting, growth arresting, and apoptotic signaling after activation by multiple neurotrophic and growth cone-repellent ligand-binding co-Rc is likely to prove significant as the field unfolds.

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APPENDIX

The following abbreviations are used in this article: ADP, adenosine diphosphate; CAMP, cyclic adenosine monophosphate; CGMP, cyclic guanosine monophosphate; ChABC, chondroitinase ABC; CRD, cysteine-rich domains; CRMP, collapsin response mediator protein; CRP, complement regulatory protein; CS, chondroitin sulfate; CSPG, chondroitin sulfate proteoglycans; CTGF, connective tissue growth factor; CUB motif, comprising complement components C1r/C1s, the sea urchin protein Uegf, and BMP-1; DREZ, dorsal root entry zone; DRG, dorsal root ganlion/ganglia; DRGN, dorsal root ganglion neuron(s); ECD, extracellular domain; ECM, extracellular matrix; EGF, epidermal growth factor; Eph A, ephrin A; Eph B, ephrin B; Eph Rc, ephrin receptor (Eph); ER, endoplasmic reticulum; FAK, focal adhesion kinase; FGF-2, fibroblast growth factor 2; FN, fibronectin; GAG, glycosaminoglycans; GAP, GTPase-activating proteins; GDI, guanine dissociation inhibitors; GDIa/GTIb, sialic acid-bearing glycosphingolipid gangliosides; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factors; Glob, globular ligand-binding domain; GPI, glycosylphosphatidylinositol; GTP, guanosine triphosphate; GTPase, guanosine triphosphatase; ICD, intracellular domain; Ig, immunoglobulin; IMP, injured membrane proteoglycan; Lam, laminin; LIM, acronym for three gene products Lin-11, Isl-1, and Mec-3; MAG, myelin-associated glycoprotein; MAM, mitochondria-associated membrane domain; MAP kinase, mitogen-activated protein kinase; MET, gene family encoding scatter factor receptors; MLC, myosin light chain protein; MMP, metalloproteases; MRS, Met-related sequences; N-CAM, neuronal cell adhesion molecule; Nck, a mammalian SH3/SH2 adaptor protein homologous to dreadlocks (Dock) in *Drosophila*; NgR, NOGO receptor; NIMP, Nogo-interacting mitochondrial protein; NP-1/2, neuropilin-1/2; OMgp, oligodendrocyte myelin glycoprotein; OPC, oligodendrocyte precursor cell; $p75^{NTR}$, 75 kDa low-affinity Trk receptor; PAK, p21-activated protein kinase; PDGF, platelet-derived growth factor; PDZ, PSD-95/Dlg/ZO-1-binding motif; PI-PLC, phosphatidyl-inositol-specific phospholipase C; PKA, protein kinase A; Plex, plexins; PLP, proteolipid protein; PN, peripheral nerve; PNS, peripheral nervous system; RasGAP, RAS GTPase-activating protein; Rc, receptor; RGC, retinal ganglion cell(s); ROCK, Rho-associated protein kinase; RPTP, receptor type; RTK, receptor tyrosine kinases; SAM, sterile alpha motif domains; Sema, semaphorin; SH2/SH3, domain adaptor proteins; SIGLEC, sialic-dependent immunoglobulin-like family member lectin; Src, family kinases; TGFβ, transforming growth factor β; TMD, transmembrane domain; TNFα, tumor necrosis factor α; TNFR, tumor necrosis factor receptor; TRAF, TNFR-associated factor; Y-kin, tyrosine kinase; Y-P, tyrosine phosphatase.