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Review

Roles of channels and receptors in the growth cone during PNS axonal regeneration

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ABSTRACT

Neurons in the peripheral nervous system (PNS) are known to maintain a regenerative capacity and will normally regenerate their axons within a permissive growth environment. The success of regeneration in the PNS largely depends on maintenance of the supportive basal lamina membrane, efficient removal of axonal and myelin debris by macrophages and Schwann cells, expression of neurotrophic factors by Schwann cells, and up-regulation of the intrinsic growth program in PNS neurons. The PNS regenerative process is well characterized through initial Wallerian degeneration followed by axonal sprouting, formation of neuronal growth cones, active axonal growth to the target, and finally sensory and motor functional recovery. The initiation and maintenance of active growth cones during peripheral nerve regeneration recapitulate many aspects of early neural development and are achieved through the activation of complex signaling cascades, involving various receptors, channels, cytoplasmic signaling cascades, as well as transcriptional and translational programs. This review focuses on roles of cell surface ion channels and receptors in the growth cone during Wallerian degeneration and axon regeneration in the PNS.

Contents

Introduction

Axon regeneration is a complex, concerted process after axonal injury (Kim et al., 2006; Vargas and Barres, 2007). In the PNS, axon regeneration is rather successful compared to that in the central nervous system (CNS). Initial neuronal responses to axon injury in both PNS and CNS are similar in that Wallerian degeneration is initiated at the distal segment of severed axons, whereas axonal sprouting and growth cone formation occur in the proximal segment (Fig. 1). The extent and speed of these processes, however, are very different between the PNS and CNS. Axon and myelin debris are cleared by Schwann cells and macrophages promptly in the PNS, followed by sprouting of the proximal part of axons, resulting in active growth cones at the tips of axons. Neuronal growth cones are the machinery for detecting the environment for growth and guidance signals and also the major driving force for axonal elongation (Song and Poo, 1999; Zheng and Poo, 2007). Whether intracellular signaling mechanisms in the growth cones of regenerating axons resemble those in developing nervous system remains largely unknown. During PNS regeneration, Schwann cells secrete a variety of neurotrophic and neurotropic factors to support axonal regrowth and guidance. In concert with the expression of these factors, regenerating neuronal

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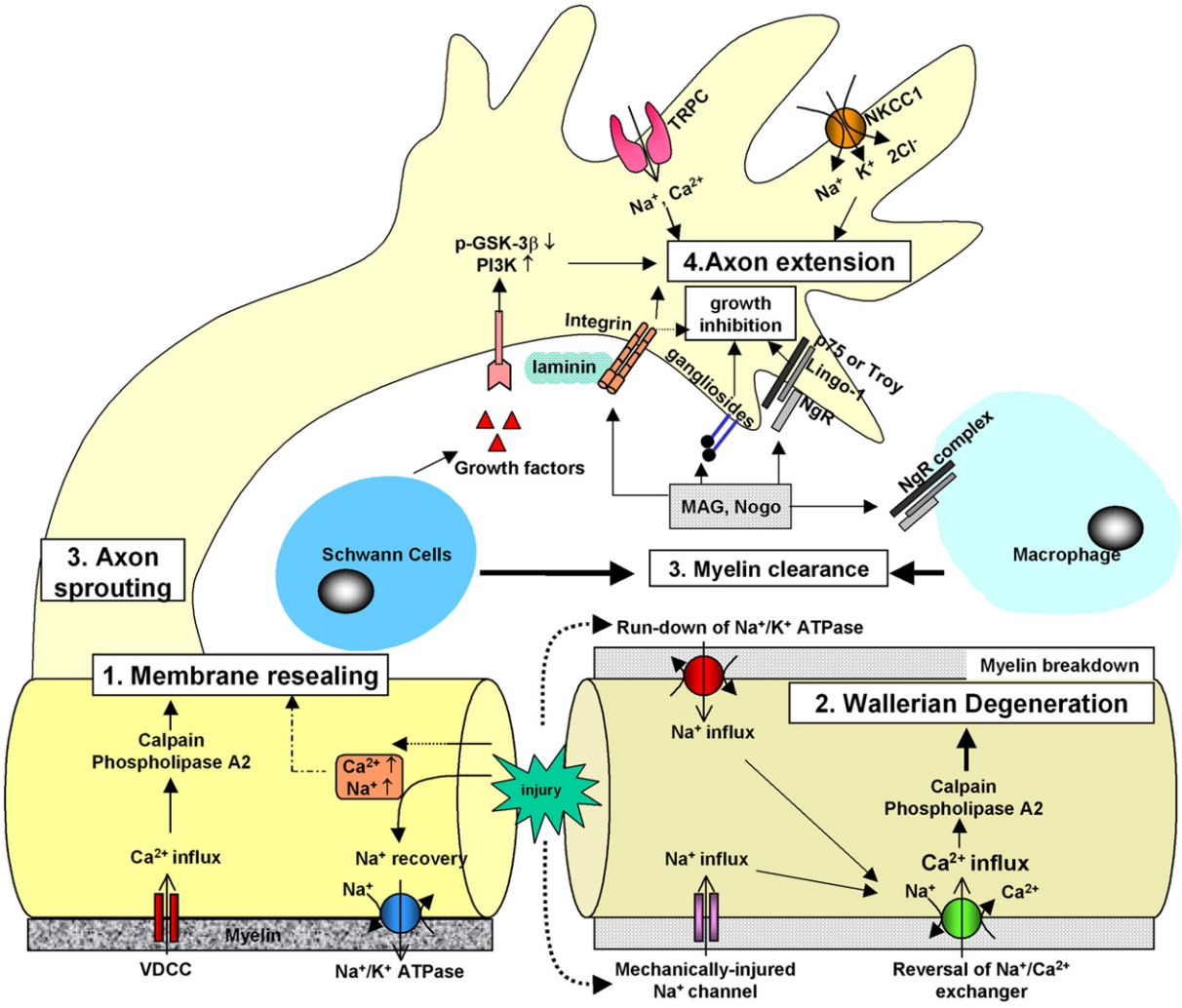

Fig. 1. Role of ion channels and receptors in PNS axonal regeneration. Axon injury in the PNS leads to sequential events that involve the following: (1) Membrane resealing: Intra-axon Ca^{2+} rises through VDCC mediate membrane resealing after nerve injury via calpain and phosphatase A2 activation, whereas Na^+ influx from the cut end diffuses along the transected axon and returns to resting values with the help of Na^+–K^+ ATPase. (2) Wallerian degeneration of distal stump: is triggered by intra-axonal Ca^{2+} elevation. A prolonged Na^+ leak into the axon due to the reduced Na^+–K^+ ATPase activity and mechanically injured Na^+ channel in lesioned axons promotes reversed operation of the Na^+–Ca^{2+} exchanger and subsequent Ca^{2+} influx. (3) Myelin clearance and axonal sprouting: Wallerian degeneration activates Schwann cells to produce growth factors and to clear the myelin debris together with macrophages. MAG–NgR signaling also mediates elimination of macrophage after myelin clearance. (4) Axonal regeneration: Growth factor signaling, laminin/integrin signaling, NKCC1, and TRPC promote outgrowth of regenerating axon, while myelin-associated inhibitors, such as MAG and Nogo-A signaling through their receptors NgR complex, integrins, and gangliosides, inhibit axon growth and sprouting.

growth cones have been shown to express many correspondent receptors to resume outgrowth and steering to their targets. It is well known that activation of ion channels in neuronal growth cones plays an important role in adjusting the homeostasis of ions and membrane potentials, which sets the stage for subsequent growth cone responses to growth factors and guidance cues (Zheng and Poo 2007). Similar to cell membrane receptors, the expression of many ion channels is dynamically regulated during PNS axon regeneration. Understanding how these channels and the cell surface receptors are differentially regulated in response to injury and how signals converge to produce cytoskeletal changes in regenerating growth cones may lead to strategies to enhance PNS regeneration and promote CNS regeneration.

Role of ion channels in PNS axon degeneration and regeneration

Nerve injury in myelinated nerve fiber disrupts the structural integrity of the axonal plasma membrane and electrical properties of injured nerves. The perturbations in ion channel composition and homeostasis of intracellular ions, including Ca^{2+}, Na^+, and K^+, have been closely associated with axonal degeneration and regeneration processes (Fig. 1).

Voltage-dependent calcium channels

Neurons are electrically excitable due to the expression of many neuronal specific ionic channels. Ion channels and transporters generate ionic currents that segregate charges, which in turn produce voltage gradients across the cell membrane important for excitability and the propagation of electric signals. One of the earliest regenerative responses of neurons to axonal injury is the resealing of damaged axons prior to the sprouting and formation of new growth cones at the tip of proximal axons. Disruption of the membrane integrity from injury transiently opens the axoplasma membrane and causes rapid entry of extracellular ions with higher external concentrations, such as Ca^{2+} and Na^+, which results in depolarization of axons. Appropriate control of intracellular Ca^{2+} and Na^+ seems to be essential for the closure of the lesion sites in the PNS (David et al., 1997; Nehrt et al., 2007) (Fig. 1). Na^+ influx from the lesion site diffuses along the transected axon but returns to normal resting values with the action of

Na^+–K^+ ATPase. Thus, the spatial–temporal gradients of Na^+ along the transected axon appear to define the resealing site (David et al., 1997). In addition to passive entry of ions through the injury site, an active involvement of voltage-dependent Ca^{2+} channels (VDCC) has also been implicated. Blocking the activity of VDCC significantly suppresses membrane resealing, whereas moderate enhancement of VDCC activity accelerates the process (Nehrt et al., 2007). The VDCC-dependent resealing may involve Ca^{2+}-dependent exocytosis of intracellular vesicles, such as lysosomes and enlargesomes, to the site of membrane disruption to support membrane repair (Rodriguez et al., 1997; Reddy et al., 2001). Moreover, the L-type calcium channel is shown to play a significant role in mediating Ca^{2+} entry and membrane resealing (Nehrt et al., 2007). In an *in vitro* sympathetic neuron neuritotomy model, inhibition of L-type calcium channels at the time of injury facilitates the initiation of regeneration in an temporally dependent manner (Kulbatski et al., 2004). Protease calpain and phospholipase A2 activated by Ca^{2+} may serve as major intracellular mediators for membrane resealing by enhancing the disassembly of the cytoskeletal components and the mobility and accessibility of membrane components (Yawo and Kuno, 1983, 1985; Xie and Barrett, 1991; Howard et al., 1999). Interestingly, the resealing of injured CNS axons is significantly delayed compared with those in the PNS, which may contribute to the failure of CNS neurons to effectively regenerate following injury (Ahmed et al., 2001).

Subsequent growth cone formation following membrane resealing is another critical step for the initiation of regeneration and this process also appears to be Ca^{2+}-dependent. Transient and localized Ca^{2+} elevation and subsequent local activation of calpain shortly after injury have been shown to be crucial for the induction of growth cone formation in cultured *Aplysia* neurons (Gitler and Spira, 1998, 2002; Spira et al., 2003). Phospholipase A2 and PKC, two Ca^{2+}-dependent enzymes, are also implicated in the formation of regenerative growth cones (Geddis and Rehder, 2003a,b). Thus, Ca^{2+} signaling plays dual roles for both membrane resealing and growth cone formation, two crucial steps for the initiation of axonal regeneration that involve multiple downstream players that regulate protein phosphorylation states. The identity of these proteins remains elusive. In addition to the modulation of existing proteins, local synthesis of new proteins and proteasome-mediated protein degradation have been shown to be essential for new growth cone formation after axotomy. Axotomy induces a large increase in new protein synthesis in axons and cell bodies of dorsal root ganglion (DRG) neurons, but a significant decrease in protein translation machineries in retinal ganglion cells (RGC) (Verma et al., 2005; Park et al., 2008). It is hypothesized that the differential axonal regenerative capability between PNS and CNS may thus be attributable, at least in part, to different axonal levels of protein synthesis machinery. The molecular players and mechanisms underlying the differential intrinsic capacity of membrane resealing and new growth cone formation between PNS and CNS remain largely unknown. Further understanding of the exact action of the involved channels and their downstream effectors may lead to the identification of potential therapeutic targets and the development of new strategies to enhance regeneration in the initial phase after an axonal lesion.

Voltage-dependent sodium and potassium channels

Voltage-dependent ion channels, including both Na^+ and K^+ channels, are critical for the generation and propagation of electrical signals along myelinated axons (Mert, 2007). Among these, voltage-dependent Na channels (Na_v) are densely expressed at nodes of Ranvier of both PNS and CNS neurons and are important for the generation of propagating action potentials (Mert, 2007). One specific type of voltage-dependent K (K_v) channel, KCNQ is found to be co-localized with Na_v channels at nodes of Ranvier of all PNS axons and contributes to the maintenance of the resting membrane potential. Other voltage-dependent K^+ channels, such as $K_v1.1$ and $K_v1.2$, cluster mainly at juxtaparanodes (Mert, 2007). Nerve injury in myelinated nerve fiber alters not only the distribution of these voltage-dependent ion channels but also the expression of these channels and related family members. For example, following peripheral nerve injury, the expression of $Na_v1.3$ in primary sensory neurons is up-regulated, whereas $Na_v1.1$, $Na_v1.2$, and $Na_v1.6$–1.9 are down-regulated (Navarro et al. 2007). Similarly, the expressions of $K_v1.2$ and $K_v2.1$ are significantly decreased following axotomy (Ishikawa et al., 1999). The resulting different profiles of Na_v and K_v channels in the neuronal membrane are thought to contribute to the hyperexcitability of injured neurons. Interestingly, during the early stage of PNS regeneration, K_v1 channels are first detected at the node and are subsequently distributed throughout the axolemma at higher levels, rather than only at juxtaparanodes as in uninjured neurons (Vabnick et al., 1999; Rasband et al., 2001). Whether these Na_v and K_v channels are also redistributed into the regenerating growth cones and contribute to axonal outgrowth and targeting remain to be determined. During early neural development, activities involving these Na_v and K_v have been shown to regulate axonal outgrowth, growth cone targeting, arborization, and synapse formation (Wada, 2006), thus it is conceivable that the dispersed distribution of these channels during the early regeneration phase may play a functional role within the growth cones during PNS axon regeneration.

Transient receptor potential channels (TRPs)

TRP channels are a large family of voltage-independent cation channels functioning as cellular sensors essential for detecting environmental changes, including temperature, pain, taste, osmolarity, stretch, touch, and positional cues for navigation (Clapham, 2003; Talavera et al., 2008). The canonical TRP channels (TRPCs), a subfamily of TRP channels, are Ca^{2+}-permeable cation channels. A number of studies have shown their involvement in neural development and synaptic plasticity. For example, TRPC1 and TRPC3 are highly expressed in the neuronal growth cones and mediate growth cone turning responses to brain-derived neurotrophic factor (BDNF) and netrin-1, two well-characterized guidance molecules (Li et al., 2005; Shim et al., 2005; Wang and Poo, 2005). Emerging evidence also supports roles of TRPCs in axon regeneration. TRPC1 mediates growth cone responses to myelin-associated glycoprotein (MAG), a component of myelin sheath that is released during axonal injury and negatively influences axonal regeneration (Shim et al., 2005). TRPC4 expression is up-regulated in the adult DRG after sciatic nerve transection, and knockdown of TRPC4 significantly reduced the length of neurites of cultured dorsal root ganglion (DRG) neurons (Wu et al., 2008).

In addition to its role in neuronal growth cones for axon guidance and outgrowth, TRPCs may also participate in neuron–glia interaction during regeneration (Davies et al., 2004). Together, these studies point to an important role of non-voltage-gated channels in regulating growth cone responses to environmental cues during regeneration. Future applications of drugs targeted to these channels may enhance the regenerative capacity of both PNS and CNS neurons.

Cell surface ion transporters

Wallerian degeneration refers to the breakdown and clearance of myelin and axons distal to the site of an injury. This active process is known to be a prerequisite to ensure normal regeneration following nerve injury. Faster and more extensive Wallerian degeneration in the PNS may account for the relatively successful regeneration compared to that observed in the CNS (Vargas and Barres, 2007). Wallerian degeneration seems to be attributable to a delayed but steady Na^+-dependent extracellular Ca^{2+} entry, where Na^+–K^+ ATPases and Na^+–Ca^{2+} exchangers play important roles (LoPachin and Lehning, 1997; Coleman, 2005). A prolonged Na^+ leak into the

axon due to ATP deficiency and reduced Na^+–K^+ ATPase activity in lesioned axons triggers a reversal in the operation of the Na^+–Ca^{2+} exchanger (LoPachin and Lehning, 1997; Kapoor et al., 2003; Coleman, 2005), leading to an increase in the intra-axonal Ca^{2+} level (Fig. 1). Mechanically injured Na^+ channels and proteolytic degradation of the Na^+ channel α-subunit may also exacerbate the effect of sustained influx of Na^+ and Ca^{2+} through a deleterious feed-forward process (Iwata et al., 2004) (Fig. 1).

The cytoplasmic chloride (Cl^-) concentration is developmentally regulated through the sequential expression of Cl^- transporters, with expression of NKCC1 transporters (Na:K:Cl cotransporter that imports Cl^-) in immature neurons followed by a switch to KCC2 (K:Cl cotransporter that exports Cl^-) during neuronal maturation (Ge et al., 2007). Neurotransmitters GABA and glycine are known to play trophic roles in immature neurons due to the high intracellular Cl^- state and resultant neuronal depolarization. Although similar regulatory mechanisms exist for both PNS and CNS neurons during development, DRG neurons, but not CNS neurons, maintain a high intracellular Cl^- state throughout adulthood (Stein and Nicoll, 2003), suggesting an intrinsic advantage in regeneration capacity. DRG neurons express both $GABA_A$ and $GABA_B$ receptors and the tonic modulation of $GABA_A$ receptor has been shown to be responsible for the chronic pain after sciatic nerve injury (Naik et al., 2008). Furthermore, peripheral nerve injury induces elevated NKCC1 activity through phosphorylation and subsequent intracellular Cl^- accumulation in DRGs. A decrease in the intracellular Cl^-, either by application of a potent inhibitor of NKCC1 bumetanide or by genetic down-regulation of NKCC1 leads to decreased velocity of regenerative neurite growth in a preconditioning peripheral nerve injury model *in vivo* (Pieraut et al., 2007). The exact mechanisms underlying NKCC1 phosphorylation after nerve injury and signal cascades leading to accelerated neurite extension remain to be determined but likely involve GABA signaling. It appears that injured peripheral neurons can revert to a state similar to immature neurons, with both higher intrinsic and inducible levels of NKCC1 activity, thus shifting the action of GABA to become significantly more excitatory (Ge et al., 2006, 2007). In addition, Toyoda et al. (2003) reported a decrease of KCC2 expression in axotomized neurons in a facial nerve transection model. Together, these studies suggest that Cl^- homeostasis and GABA-induced depolarization may provide an important mechanism to activate the highly coordinated regeneration program in the PNS.

Role of cell surface receptors in growth cones during PNS axon regeneration

Growth factor receptors

Unlike oligodendrocytes in the CNS, Schwann cells in the PNS play a pivotal role in enhancing regeneration of damaged axons. These glial cells clear myelin debris through intrinsic processes and also by attracting scavenger macrophages (Vargas and Barres, 2007). More importantly, denervated Schwann cells produce many growth factors to support survival, stimulate axonal growth, and provide guidance for successful PNS regeneration, including BDNF, nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), insulin-like growth factor (Stefansson et al., 2002), and fibroblast growth factor (FGF) (Liu and Snider, 2001; Chen et al., 2007; Vargas and Barres, 2007). Accordingly, regenerating growth cones of injured PNS axons also modulate the expression of receptors for these factors, thus potentially maintaining optimal responsiveness to the plethora of trophic stimuli (Ebadi et al., 1997). For instance, after sciatic nerve crush, the mRNA levels of GDNF and its receptor GFRα-1 and Ret are rapidly increased in the distal segment of the injured PNS axons (Naveilhan et al., 1997; Boyd and Gordon, 2003). Similarly, the TrkB receptor and p75 neurotrophic receptor, CNTFR and LIFR, have been shown to be up-regulated in various PNS injury models (Boyd and Gordon, 2003). Activation of these receptors induces a tightly regulated and localized activation of PI3K at growth cones, which in turn phosphorylates and inactivates GSK-3β to promote axonal growth (Chen et al., 2007) (Fig. 1). Intriguingly, a direct comparison study of optic nerve (CNS model) and sciatic nerve injury (PNS model) showed that CNTF and CNTFRs are differentially regulated in the CNS and PNS, suggesting a potential mechanism underlying the different regenerative capacity in the CNS and PNS (Kirsch et al., 1998). The exact mechanisms by which the expression of these receptors is regulated in the newly formed growth cones are still waiting for further investigation. Many other important questions remain. Given the difference in the environment between injured and normal conditions, does the signaling downstream of these receptors also differ from that in developing growth cones? At which level does receptor signaling during axon regeneration converge and diverge from developmental mechanisms?

Guidance cue receptors and axon regeneration

Regenerative growth cones are reminiscent of developing growth cones that function to detect environmental signals for their growth and guidance. Many developmental guidance cues and associated receptors are shown to be altered after axonal injury, including netrins, slits, semaphorins, Ephrins, and bone morphogenic proteins (BMPs) (Tessier-Lavigne, 2002; Koeberle and Bahr, 2004; Bolsover et al., 2008). Netrin is a bifunctional chemotrophic factor that functions to attract or repel growth cones of both developing CNS and PNS neurons through the activation of receptors or receptor complexes involving DCC and UNC-5 family members (Leonardo et al., 1997; Ren et al., 2004). Netrin and its receptors are continuously expressed in the adult nervous system (Ellezam et al., 2001; Manitt et al., 2004; Osborne et al., 2005; Wehrle et al., 2005) and have been shown to be down-regulated after spinal cord injury and optic nerve transection (Ellezam et al., 2001; Manitt et al., 2006; Low et al., 2008). Adult DRG neurons abundantly express the netrin receptor UNC5H. Netrin treatment leads to the inhibition of outgrowth of adult DRG neurons in explant and dissociated cultures (Park et al., 2007), whereas neutralization of netrin increases neurite outgrowth from spinal motor neurons *in vitro* (Low et al., 2008), suggesting that netrin/UNC5H signaling may function as a negative regulator of axonal regeneration in the adult PNS and CNS. Recent work also identified other functional receptors for netrins, including DSCAM (Ly et al., 2008), integrins (Nikolopoulos and Giancotti, 2005), and adenosine A2bR (Corset et al., 2000). Whether these receptors also operate in regenerative growth cones is unknown. Semaphorins are mainly developmental repulsive guidance cues and their signaling is mediated by neuropilin (NPN) and Plexin receptor complexes (Huber et al., 2003). mRNA expressions of Plexin-A1, -A3, and -A4 but not Plexin-A2 are up-regulated in facial motoneurons following injury (Spinelli et al., 2007). NPN-1 and NPN-2 are also up-regulated in DRG neurons in a sciatic nerve crush model and have been proposed to guide the regenerating growth cones (Scarlato et al., 2003). The downstream signaling of these receptors is complex and not completely understood. Application of netrin induces a rapid increase of Ca^{2+} signaling within the growth cone that is required for guidance responses to netrins through the activation of TRPC channels (Hong et al., 2000; Shim et al., 2005; Wang and Poo, 2005). The exact mechanisms underlying netrin receptor modulation of TRPC channels are not clear but may involve PLC signaling (Li et al., 2005). TRPC activation also leads to Na^+ influx and membrane depolarization, thus providing a potential mechanism for the activation of voltage-gated channels, such as L-type Ca^{2+} channels (Nishiyama et al., 2003), in growth cones during pathfinding. Future studies should elucidate roles of these channels in regenerating axons, and novel therapeutic approaches may be designed to target these channels.

Myelin-associated inhibitory factors and their receptors in axon regeneration

The PNS is considered to be a relatively hospitable environment for axon regeneration with rapid removal of myelin debris by macrophages and Schwann cells. Several myelin-associated inhibitory factors are present in the PNS after the axonal injury, including MAG and oligodendrocyte myelin glycoprotein (OMgp) (Filbin 2003). MAG is a well-characterized component of myelin that is a potent inhibitor of axonal regeneration in both CNS (McKerracher et al., 1994; Mukhopadhyay et al., 1994; Guntinas-Lichius et al., 2002; Filbin, 2003; Venkatesh et al., 2005; Quarles, 2009) and in the PNS (Bedi et al., 1992; Shen et al., 1998; Yin et al., 1998; Gupta et al., 2006). Recently, MAG also has been suggested to promote axonal stability in the PNS (Nguyen et al., 2009). Local down-regulation of MAG by proliferating Schwann cells in chronic nerve compression (CNC) injury has been suggested to provide a critical signal to permit axonal sprouting (Gupta et al., 2006). Furthermore, expression of exogenous MAG results in reduced axonal sprouting following CNC injury *in vivo* as well as in DRG cultures *in vitro* (Shen et al., 1998; Gupta et al., 2006).

Nogo-A is another CNS myelin-associated inhibitory factor that inhibits axonal outgrowth and regeneration in the adult CNS and restricts functional recovery after injury (GrandPre et al., 2000; Filbin, 2003; McGee and Strittmatter, 2003; He and Koprivica, 2004; Schwab, 2004). While Nogo-A is not detectable in peripheral nerve myelin under normal conditions, transgenic expression of Nogo-A in peripheral nerve Schwann cells results in impaired axonal regeneration and functional recovery after a sciatic nerve injury, suggesting that Nogo-A can be a potent inhibitor of peripheral axonal regeneration that can override regenerating-promoting environments of lesioned peripheral nerves (Pot et al., 2002).

All three myelin-associated inhibitors, MAG, Nogo-A, and OMgp, bind to the same receptor complex consisting of Nogo receptor 1 (NgR1) (Fournier et al., 2001; Domeniconi et al., 2002; Liu et al., 2002; He and Koprivica, 2004; Schwab, 2004; Venkatesh et al., 2005), the leucine-rich repeat transmembrane protein LINGO-1 (Mi et al., 2004) and either the neurotrophin receptor $p75^{NTR}$ (Wang et al., 2002; Wong et al., 2002) or the orphan TNF receptor TAJ/TROY (Park et al., 2005; Shao et al., 2005). NgR2 binds selectively to MAG but not Nogo-A and OMgp (Venkatesh et al., 2005) (Fig. 1). NgR1 and NgR2 are expressed in neurons in the developing and adult CNS and PNS (Lauren et al., 2003; Venkatesh et al., 2005). Interestingly, a recent study identified paired immunoglobulin-like receptor B (pirB) as another functional receptor for these three myelin inhibitors, blocking PirB and NgR simultaneously leads to near-complete release from myelin inhibition (Atwal et al., 2008). Although myelin inhibition in regeneration is not as severe as in the CNS due to the rapid clearance of myelin debris by phagocytic macrophages, timely termination of inflammatory responses is also critical for successful nerve repair (Fenrich and Gordon, 2004). A recent study provides evidence for a role of MAG/NgRs signaling in the elimination of hematogenous macrophages and the resolution of inflammation after peripheral nerve injury (Fry et al., 2007). NgR1, NgR2, and TROY expressions were markedly up-regulated on the surface of macrophages infiltrated into the distal nerve stump, and the interaction between the NgR complex on macrophages and newly remyelinated myelin inhibitors, such as MAG, in Schwann cell membranes is required for the timely elimination of macrophages from the lesioned nerve at the end of the period of Wallerian degeneration (Fry et al., 2007).

In addition to the NgR complex, some gangliosides, which are sialic acid-containing glycosphingolipids, including GD1a and GT1b, have also been shown to be MAG receptors and to inhibit axonal regeneration (Vinson et al., 2001; Vyas et al., 2002). Several reports demonstrated direct interactions between $p75^{NTR}$ and NgR (Wang et al., 2002; Wong et al., 2002), GT1b-$p75^{NTR}$ (Fujitani et al., 2005), and GT1b-NgR1 (Williams et al., 2008). MAG-binding gangliosides are localized on the axolemmal surface of myelinated axons and Schwann cells (Sheikh et al., 1999). Interestingly, perturbation of lipid rafts and gangliosides in neuronal growth cones disrupts their responses to guidance cues (Guirland et al., 2004), suggesting a role of MAG/gangliosides signaling at neuronal growth cones, and possibly at regenerating growth cones as well. Consistent with this notion, interference of MAG function with a MAG–antibody enhances target reinnervation of regenerating axons and enhanced functional recovery (Mears et al., 2003). In contrast, another study showed that application of MAG significantly reduced the axonal branching of injured peripheral axons, *in vitro* and *in vivo*, via activation of RhoA, a key signal for the inhibitory effect on axonal regrowth (Lehmann et al., 1999). Excessive collateral sprouting and formation of multiple growth cones may increase the probability of appropriate target contacts (Nguyen et al., 2002), yet reduces the accuracy of target reinnervation (Guntinas-Lichius et al., 2002). Therefore, MAG may play a dual role to regulate growth cone responses and control specificity of target reinnervation during PNS regeneration.

Successful peripheral axonal regeneration also depends on the interaction of growth cones of regenerating axons that express integrins with components in the extracellular matrix, such as laminin. Rapid down-regulation and re-expression of integrins and associated ligands, including laminin, during nerve degeneration and regeneration have been correlated with successful regeneration of peripheral nerves (Previtali et al., 2001; Chen et al., 2007; Lemons and Condic, 2008; Tucker and Mearow, 2008). Effects of laminin/integrin signaling on peripheral nerve regeneration may involve either the regulation of growth cone outgrowth, or Schwann cell differentiation, myelination, and survival (Previtali et al., 2001; Chen et al., 2007; Tucker and Mearow, 2008). Recently, integrins have been identified as a novel mediator for myelin-associated inhibitor proteins, MAG and Amino-Nogo. β_1-Integrin directly interacts with MAG and mediates MAG-dependent repulsive growth cone responses independent of the NgR receptor complex (Goh et al., 2008). The α_5 and α_v integrins also physically interact with Amino-Nogo and mediate cell adhesion and axon outgrowth by Amino-Nogo (Hu and Strittmatter, 2008). These results raise the possibility that myelin-mediated inhibition and laminin-mediated stimulation may compete with one another and converge on the integrin signaling to regulate timely axonal degeneration or regeneration (Fig. 1).

Conclusion

While axon regeneration in the PNS can be considered successful in comparison to that in the CNS, PNS regeneration capacity is reduced over time, especially in the case of long-distance repair. Much research is still needed in order to understand how to optimize the environment for maximum regeneration potential in both PNS and in CNS. Clearly, ion channels, transporters, and cell membrane receptors play essential roles most likely in every step of the regeneration process including, but not limited to, Wallerian degeneration, membrane resealing at the injury site, growth cone formation, extension and guidance. How ion channels regulate ion homeostasis, how surface receptors are regulated, how cytoskeletal changes are directed, and how they lead to differential intrinsic regenerative capacities of the PNS and CNS are critical questions that remain to be answered. A better understanding of signaling mechanisms underlying PNS responses after injury not only will lead to strategies to further enhance PNS regeneration but also will shed light on potential strategies to overcome the poor regeneration in the mature mammalian CNS.

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