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Peripheral Regeneration

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Key Words

neurotrophic factors, extracellular matrix proteins, remyelination, Schwann cells, neurite outgrowth, conditioning lesion

Abstract

Whereas the central nervous system (CNS) usually cannot regenerate, peripheral nerves regenerate spontaneously after injury because of a permissive environment and activation of the intrinsic growth capacity of neurons. Functional regeneration requires axon regrowth and remyelination of the regenerated axons by Schwann cells. Multiple factors including neurotrophic factors, extracellular matrix (ECM) proteins, and hormones participate in Schwann cell dedifferentiation, proliferation, and remyelination. We describe the current understanding of peripheral axon regeneration and focus on the molecules and potential mechanisms involved in remyelination.

Contents

INTRODUCTION

Wallerian degeneration: series of cellular responses leading to degeneration of the axon distal to the injured site

PNS: peripheral nervous system

ECM: extracellular matrix

Bünger bands: tubular cellular aggregates formed by proliferating Schwann cells after nerve injury

After nerve crush injury or axotomy, the distal stump of the peripheral nerve undergoes Wallerian degeneration. This process leads to the removal and recycling of axonal- and myelin-derived fragments and generates a permissive environment for axonal regeneration. Macrophages are recruited to the injury sites, and along with Schwann cells, contribute to debris clearance. While the distal stump undergoes degeneration, the proximal stump begins regeneration. The signals initiating the regeneration program have not yet been definitively clarified (Makwana & Raivich 2005), although injury-induced disruption of the retrograde flow of signals, calcium influx, and exposure of the injured axon end to the degenerating and inflammatory environment may synergistically activate axon regeneration in the proximal stump of the nerve (for a review, see Makwana & Raivich 2005). Peripheral axon injury activates intrinsic growth capacity within the affected neurons, which can promote axonal regeneration in both the peripheral nervous system (PNS) and CNS (Richardson & Issa 1984) and can overcome the effect of myelin-associated inhibition of regeneration (Neumann & Woolf 1999, Neumann et al. 2002, Qiu et al. 2002a). In the PNS, the activated intrinsic growth capacity in the neuronal cell body coupled with local permissive environment and axon guidance cues such as extracellular matrix (ECM) proteins and cell adhesion molecules lead to successful regeneration.

Regeneration requires remyelination of the regenerated axons. Intact axons nwith aberrant myelination are functionally impaired and are the underlying pathology of many human peripheral neuropathies (Höorste et al. 2006) and analogous animal models (Chen & Strickland 2003, Feltri et al. 2002, Yu et al. 2005). After injury, Schwann cells undergo dedifferentiation and proliferation. They form Bünger bands at injury sites resulting in a permissive environment for axon regeneration and ensuing remyelination (Fawcett & Keynes 1990). Once Schwann cells contact the regrowing axons, they start remyelination about eight days after nerve injury (Akassoglou et al. 2002, Fawcett & Keynes 1990). Peripheral nerve remyelination by Schwann cells recapitulates development in many ways (Kioussi et al. 1995, Scherer et al. 1994, Zorick et al. 1996). However, the proliferation of Schwann cells during regeneration is different from development in terms of molecular programs used (Atanasoski et al. 2001, Atanasoski et al. 2006, Kim et al. 2000).

Because considerable progress has been made in understanding the molecular mechanism of peripheral axon regeneration after injury (for review see Makwana & Raivich 2005, Snider et al. 2002), we focus on recent studies of signaling pathways involved in axon regrowth. We also discuss current understanding of molecular mechanisms and molecules involved in the proliferation and remyelination of Schwann cells during regeneration.

AXON REGENERATION

Activation of Neuronal Intrinsic Growth Capacity in Peripheral Axon Regeneration

One important feature of axon regeneration is the activation of the intrinsic growth capacity by peripheral nerve injury. This is best studied in the dorsal root ganglion (DRG) primary sensory neurons. The DRG neurons are pseudobipolar neurons and have only one axon stemming from the cell body. However, the axon branches out to two axons: The peripheral branch innervates the sensory organs in the peripheral tissues, and the central branch enters the spinal cord and ascends the dorsal column terminating in the brain. DRG neurons do not possess dendrites in vivo even though they may grow multiple processes in vitro. The two axonal branches from the same cell body are fundamentally different in their responses to injury. The peripheral branch regenerates spontaneously after injury, resulting in functional recovery, but the central branch does not. This difference in regenerative potential is largely due to their environments. However, when central branch injury occurs after peripheral branch lesion, the former can regenerate into and beyond the injury site in the inhibitory environment of the spinal cord, a phenomenon known as conditioning peripheral lesion (Neumann & Woolf 1999, Richardson & Issa 1984).

In vitro, DRG neurite outgrowth is inhibited by myelin-associated glycoprotein (MAG) and myelin. However, when the peripheral branch is lesioned prior to culture, DRG neurons can grow neurites on MAG or myelin (Neumann et al. 2002, Qiu et al. 2002a). Both in vitro and in vivo experiments indicate that lesion of DRG peripheral axons activates the intrinsic growth capacity sufficiently to overcome the inhibitory effects of myelin-associated inhibitory molecules.

How do peripheral axon lesions activate the intrinsic growth capacity? Two groups have found that intracellular cyclic adenosine monophosphate (cAMP) is increased after peripheral nerve lesion. Injection of a cAMP analog, dibutyryl-cAMP (db-cAMP) into the DRG without prior peripheral nerve lesion is sufficient to initiate the neuronal intrinsic growth capacity and promote the central branch of DRG neurons to regenerate after injury (Neumann et al. 2002, Qiu et al. 2002a,b). Prior injection of db-cAMP in vivo also promotes neurite growth of subsequently cultured DRG neurons on MAG (Neumann et al. 2002, Qiu et al. 2002a,b). However, why only peripheral nerve lesions elevate intracellular cAMP and trigger the intrinsic growth capacity while axonal lesions in the CNS do not is not clear.

The action of cAMP proceeds through protein kinase A (PKA); blocking PKA activity abolishes conditioning lesion-induced neurite growth of sensory neurons grown on MAG or myelin (Neumann et al. 2002, Qiu et al. 2002a). PKA may regulate cytoskeleton organization by inactivating Rho and promoting axonal elongation (Snider et al. 2002). The effects of cAMP and PKA on regeneration are transcription dependent (Cai et al. 2002, Gao et al. 2004). This transcriptional regulation seems to go through cAMP response element binding protein (CREB); activated CREB is sufficient to overcome myelin-derived inhibition of neurite growth and promote spinal axon regeneration in vivo (Gao et al. 2004) (**Figure 1**). c-Jun is induced by peripheral nerve injury, and conditional knockout of c-Jun gene expression in neurons reduces nerve regeneration (Raivich et al. 2004).

Several genes are transcriptionally regulated by peripheral nerve injury. Arginase I, an enzyme involved in polyamine synthesis, is upregulated by cAMP and PKA after peripheral lesion (Cai et al. 2002). Overexpression of Arginase I overcomes the neurite growth inhibition effect of MAG and myelin. Blocking polyamine synthesis abolishes the cAMP effect of neurite growth on MAG and myelin. Polyamines may further induce expression of other genes necessary for axonal regeneration or directly affect cytoskeleton

DRG: dorsal root ganglion

MAG: myelin-associated glycoprotein

cAMP: cyclic adenosine monophosphate

CREB: cAMP response element binding (protein)

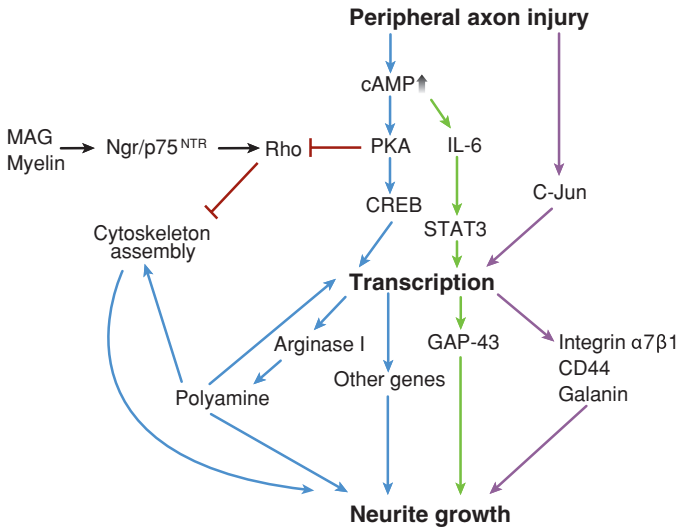

Figure 1

Activation of intrinsic growth capacity by peripheral nerve injury. Peripheral nerve injury elevates intracellular cAMP levels, which activates PKA. PKA triggers gene expression through CREB, resulting in transcriptional upregulation of regeneration-related genes such as Arginase I. Arginase I promotes the synthesis of polyamines, which may directly regulate cytoskeleton assembly or further induce gene expression necessary for regeneration. Activation of PKA also inhibits Rho antagonizing MAG or myelin-induced Rho activation and inhibition of neurite growth. Elevated cAMP levels also upregulate IL-6, which, through STAT3, induces regeneration-related genes such as GAP-43. Peripheral injury additionally induces c-Jun transcription factor–dependent regeneration-related gene expression such as integrin α7β1 CD44 and galanin. Activation of the intrinsic growth capacity is regulated mainly at transcriptional level.

organization to promote axonal elongation (Cai et al. 2002). In addition, in c-Jun knockout mice, induction of integrin α7β1, CD44, and galanin, molecules involved in regeneration, is significantly impaired (Raivich et al. 2004) (**Figure 1**).

Intrinsic growth capacity activation enables neurons to overcome the inhibitory effects of myelin-associated molecules on neurite outgrowth in vitro and axon regeneration in vivo, possibly by antagonizing signaling mediators of myelin-associated inhibitory molecules. Binding of the Nogo receptor (Ngr)-p75 neurotrophic receptor ($p75^{NTR}$) complex by either MAG or myelin activates Rho, which, through activation of Rho-associated kinase (ROCK) and other downstream effectors, inhibits cytoskeleton assembly. Peripheral nerve injury–induced cAMP elevation can inhibit Rho and antagonize Rho activation by myelin-associated inhibitory molecules (**Figure 1**). Finally, interaction of neurons with myelin-associated inhibitory molecules may also activate G_i protein, inhibiting adenylate cyclase and decreasing intracellular cAMP (for review see Filbin 2003). Peripheral nerve–conditioning lesions elevate intracellular cAMP levels thereby antagonizing MAG or myelin-induced cAMP decrease.

Owing to the unique structure of the DRG sensory neuron, stimulation of the intrinsic growth capacity in the whole cell will increase the growth capacity of both peripheral and central axons. Whether an increase in the cAMP levels in neurons in the CNS will activate their intrinsic growth capacity is not clear. A recent study showed that altering cAMP levels in retinal ganglion neurons does not put them into a growth state (Goldberg et al. 2002). However, in zebrafish, injection of cAMP into spinal neurons postlesion, which would not normally regenerate, induced functional regeneration (Bhatt et al. 2004). It would be interesting to test whether injection of db-cAMP into corticospinal tract neurons in the cerebral cortex that project to the motor neurons in the spinal cord (corticospinal tract) can activate the intrinsic growth capacity and promote axonal regeneration in the spinal cord after injury.

Activation of the intrinsic growth capacity will increase regenerative ability, but functionally successful regeneration depends on a permissive environment and axon guidance cues leading the axons to regrow toward the correct targets. The latter aspect may depend on ECM proteins and neuronal adhesion molecules expressed in the peripheral nerves. In zebrafish, the CNS is permissive for regeneration, where some neurons are able to regrow but others are not, reflecting their intrinsic growth capacity (Becker et al. 1997,

Becker et al. 1998, Zottoli et al. 1994). Increasing the cAMP levels in neurons that are intrinsically incapable of regeneration leads to functional axon regrowth (Bhatt et al. 2004), suggesting that both intrinsic growth capacity and permissive environment are important for functional regeneration. Even though activation of the intrinsic growth capacity by peripheral nerve conditioning lesions can promote axon regeneration in the CNS, the effect of blocking peripheral nerve injury–induced activation of intrinsic growth capacity on peripheral nerve regeneration is not clear.

Enviromental Factors in Peripheral Axon Regeneration

The PNS is structurally different from the CNS. In peripheral nerves, Schwann cells are the primary glial cells. They both ensheath and myelinate peripheral axons and also form a continuous basal lamina. In the CNS, oligodendrocytes ensheath and myelinate axons, but they do not produce a continuous basal lamina in association with axons. The major obstacles for axon regeneration in the CNS are myelin-associated inhibitory molecules and glial scars induced by injury. Astrocytes, which form glial scars in the CNS after injury are absent in the PNS. Myelin-associated inhibitory molecules in the CNS such as MAG, oligodendrocyte myelin glycoprotein (OMG), and receptors of these proteins, Ngr and $p75^{NTR}$, are expressed in the PNS (for review see Filbin 2003). However, in contrast with the CNS, after injury, Schwann cells and macrophages in the PNS rapidly remove myelin debris (Schafer et al. 1996), and Schwann cells also dedifferentiate and downregulate myelin proteins. This different local reaction after injury is an important factor that contributes to the ability of the PNS to regenerate. Another myelin-associated inhibitor of regeneration, Nogo-A, is normally not expressed in the PNS, which may contribute to successful regeneration, as transgenic mice expressing Nogo-A in their Schwann cells show impaired axonal regeneration after peripheral nerve injury (Pot et al. 2002).

In the PNS, laminin, an ECM protein, is expressed in large amounts in intact and injured nerves. Substantial evidence demonstrates that laminin plays an important role in neurite outgrowth in vitro (for review see Luckenbill-Edds 1997). In addition, laminin $\gamma 1$ is required for regeneration of severed axons in the rat hippocampus (Grimpe et al. 2002). Laminin may play an important role in successful PNS regeneration. Of the 15 known laminin isoforms, laminin 2 ($\alpha 2\beta 1\gamma 1$) and laminin 8 ($\alpha 4\beta 1\gamma 1$) are expressed in the endoneurium of peripheral nerves (Patton et al. 1997). After peripheral nerve injury, these laminins are upregulated (Doyu et al. 1993, Kuecherer-Ehret et al. 1990, Wallquist et al. 2002), indicating a role for laminin in peripheral axonal regeneration. In an in vitro assay, Agius & Cochard (1998) showed that an antibody specific for an $\alpha 2$-laminin chain reduced neurite outgrowth on denervated nerve sections Agius & Cochard 1998. When Schwann cell production of the laminin $\gamma 1$ chain is ablated by conditional gene knockout, expression of most if not all the laminin subunits is abolished, and axon regeneration after sciatic nerve crush injury (See Sciatic Nerve Injury Model) is severely impaired (Chen & Strickland 2003). Because laminin can directly promote neurite extension (Menager et al. 2004) and because Schwann cells are dramatically affected in the knockout mice, this result suggests that laminin may play an important role in successful axonal regeneration by either directly serving as a substrate for axon regeneration or indirectly supporting the proper behavior of Schwann cells or a combination of both.

Laminin receptors expressed in the peripheral nerve include integrins and dystroglycan. Consistent with the notion of laminin participating in peripheral axonal regeneration, integrin receptors for laminin are induced in both the cell bodies and the regenerating axons of motor neurons after

Endoneurium: the connective tissue surrounding each individual axon-Schwann cell unit and the myelin sheath

SCIATIC NERVE INJURY MODEL

Experimental sciatic nerve injury is a common approach for the study of peripheral nerve regeneration. The most popular methods for sciatic nerve injury are complete nerve transection (CNT, similar to neurotmesis), crush injury (CI, similar to axonotmesis) (Bridge et al. 1994), and chronic constrictive injury (CCI, similar to neuropraxia).

CNT without surgical or mechanical repair results in slow regeneration, aberrant reinnervation, and poor functional recovery. CNT with repair (reanastomosis by epineurial suture, nerve graft, and entubulation) improves and accelerates the recovery rate. CI and CCI allow rapid axonal regeneration into the distal stump with fully functional recovery.

CNT and CI are acute injuries leading to prompt infiltration of macrophages with rapid debris removal. CCI is a chronic injury model, whereas partial injury is introduced by the tying of four loose ligatures around the nerve (Bennett & Xie 1988). Sciatic nerve CCI results in transient loss of hindpaw motor function without the loss of paw withdrawal responses to various sensory stimuli (heat, cold, or pinch). In contrast, the sciatic nerve CI usually results in transient loss of both functions. CCI also causes exacerbated pain (hyperalgesia, allodynia, and dysesthesia) and is often used in chronic neuropathic pain study.

PI3K: phosphoinositide 3-kinase

GSK-3β: gylcogen synthase kinase-3β

peripheral axon injury (Hammarberg et al. 2000). In integrin α7 knockout mice (α7β1 is a receptor for laminin), the rate of motor axonal outgrowth is reduced (Werner et al. 2000). In vitro, postnatal days 2–3, rat DRG neurons show robust neurite outgrowth when cultured on low levels of either laminin or fibronectin substratum, but DRG neurons from adult animals exhibited little neurite outgrowth in the same condition. When integrin expression in adult DRG neurons was increased to levels comparable to those seen in newborn neurons by adenovirus-mediated gene transfer, neurite outgrowth was similar to that of early postnatal neurons (Condic 2001). Moreover, overexpression of integrin α1 in adult DRG neurons is sufficient to promote axon growth on substrata containing inhibitory chondroitin sulfate proteoglycans (CSPGs), a main inhibitor associated with glial scars in the CNS and low levels of laminin (Condic 2001). Therefore, when integrin expression is elevated and a complementary ligand is provided, adult neurons can overcome inhibitory factors such as CSPGs (Condic et al. 1999).

Besides functions in promoting axonal regeneration, laminin and other ECM proteins may also have roles in axonal guidance. In the PNS, axons regenerate within basal lamina tubes and are likely guided to the correct targets by the tubes. It will be interesting to see whether axons can regenerate to the correct target in the absence of the basal lamina tubes, a situation seen in laminin γ1 conditional knockout mice.

Although laminin can promote neurite outgrowth, axon regeneration, and guidance, the mechanisms for these actions are not yet clearly defined. Laminin plays a critical role in axon establishment in vitro. When embryonic rat hippocampal neurons are cultured on coverslips patterned with alternating stripes of laminin and Poly-D-lysine (PDL), the neurite that first encounters laminin becomes the axon (Esch et al. 1999). Also, the PI (phosphoinositide) 3-kinase/AKT/GSK-3β signaling pathway is crucial in axon formation in vitro (Jiang et al. 2005, Shi et al. 2003, Yoshimura et al. 2005) because laminin induces PI 3-kinase activation followed by rapid neurite elongation sufficient for axon specification. Using the pleckstrin homology domain of AKT tagged with green fluorescent protein (AKT-PH-GFP), Menager and coworkers (2004) showed that PI 3-kinase is activated locally when neurites reach laminin. AKT-PH-GFP-expressing neurons cultured in the presence of laminin-coated beads rapidly translocated AKT-PH-GFP to the site of neurite-laminin contact, leading the neurite in contact with the laminin bead to elongate at a rate greater than 30-fold faster. When a second neurite from the same neuron contacts the laminin-coated beads, this neurite rapidly elongates, whereas the first

laminin-contacted neurite stops elongation (Menager et al. 2004). The addition of PI 3-kinase inhibitors blocked laminin-induced AKT-PH-GFP accumulation and neurite elongation (Menager et al. 2004), suggesting that localized activation of PI 3-kinase signaling mediates laminin-induced neurite elongation and axon specification.

Laminin binding to integrins triggers integrin receptor–induced phosphorylation and activation of PI 3-kinase, which activates AKT. Active AKT then phosphorylates and inhibits GSK-3β activity and triggers cytoskeleton-binding proteins to organize cytoskeleton elongation (**Figure 2**). Integrin function–blocking antibodies inhibit laminin-induced neurite outgrowth (Bates & Meyer 1997), verifying that the effect of laminin on neurite elongation is likely to be mediated by integrin receptors in association with PI 3-kinase/AKT signaling. This pathway also regulates laminin-induced neuronal polarization. Thus it appears that laminin-induced axon growth is mediated by a conserved cell polarity signaling pathway (Menager et al. 2004, Zhou et al. 2006).

Other Factors Involved in Peripheral Axon Regeneration

Neurotrophic factors. Neurotrophic factors play critical roles in neuronal survival after nerve injury (Koliatsos et al. 1993, Miyata et al. 1986, Wiese et al. 1999, Yan et al. 1992). Protecting neurons from death after injury will increase the potential for axon regeneration. Recent studies show that neurotrophic factors such as nerve growth factor (NGF), neurotrophin 3 (NT-3), and brain-derived neurotrophic factor (BDNF) induce axon growth through a conserved cell polarity signaling pathway in vitro (Yoshimura et al. 2005, Zhou et al. 2004, Zhou et al. 2006). These trophic factors induce a tightly regulated and localized activation of PI3K at the growth cone. Locally activated PI 3-kinase phosphorylates and inactivates GSK-3β promoting axonal growth through regulation of cytoskeleton protein–binding proteins (Yoshimura et al. 2005, Zhou et al. 2004). Neurotrophic factors induce axonal growth via a similar intracellular signaling pathway as does laminin (Arimura & Kaibuchi 2005, Menager et al. 2004, Zhang & Guth 1997), questioning whether they may have coordinated interactions. Indeed, NGF enhances axon growth of DRG neurons induced by laminin, whereas neurotrophins or laminin alone induce limited neurite growth from either CNS or PNS neurons during development (Lentz et al. 1999, Liu et al. 2002).

Neurotrophins such as NGF and BDNF are upregulated after peripheral nerve injury, but their role in peripheral axon regeneration is not clear (Makwana & Raivich 2005, Markus et al. 2002, Snider et al. 2002). Application of a low dose of BDNF to the injury site only promoted axon regeneration in chronic axotomy-induced lesion, whereas it had no effect on acute nerve injury; however, high doses of BDNF inhibited regeneration in both injury models (Boyd & Gordon 2002). Because ECM proteins and neurotrophins promote axon elongation via similar intracellular signaling pathways, the peripheral nerve after injury may be optimized for regeneration by balancing the effects of ECM proteins and neurotrophic factors. Addition of exogenous neurotrophic factors may disturb this equilibrium. Similarly, the effects of lacking one neurotrophic factor in regeneration may be compensated by other neurotrophic factors or ECM proteins. Therefore, knocking out one neurotrophin gene may not significantly affect peripheral axon regeneration.

Cytokines. One cytokine involved in peripheral nerve regeneration is interleukin-6 (IL-6). After motor neuron axotomy IL-6 mRNA is induced in non-neuronal cells surrounding the motor fibers of the facial nucleus (Kiefer et al. 1993). Additionally, IL-6 mRNA

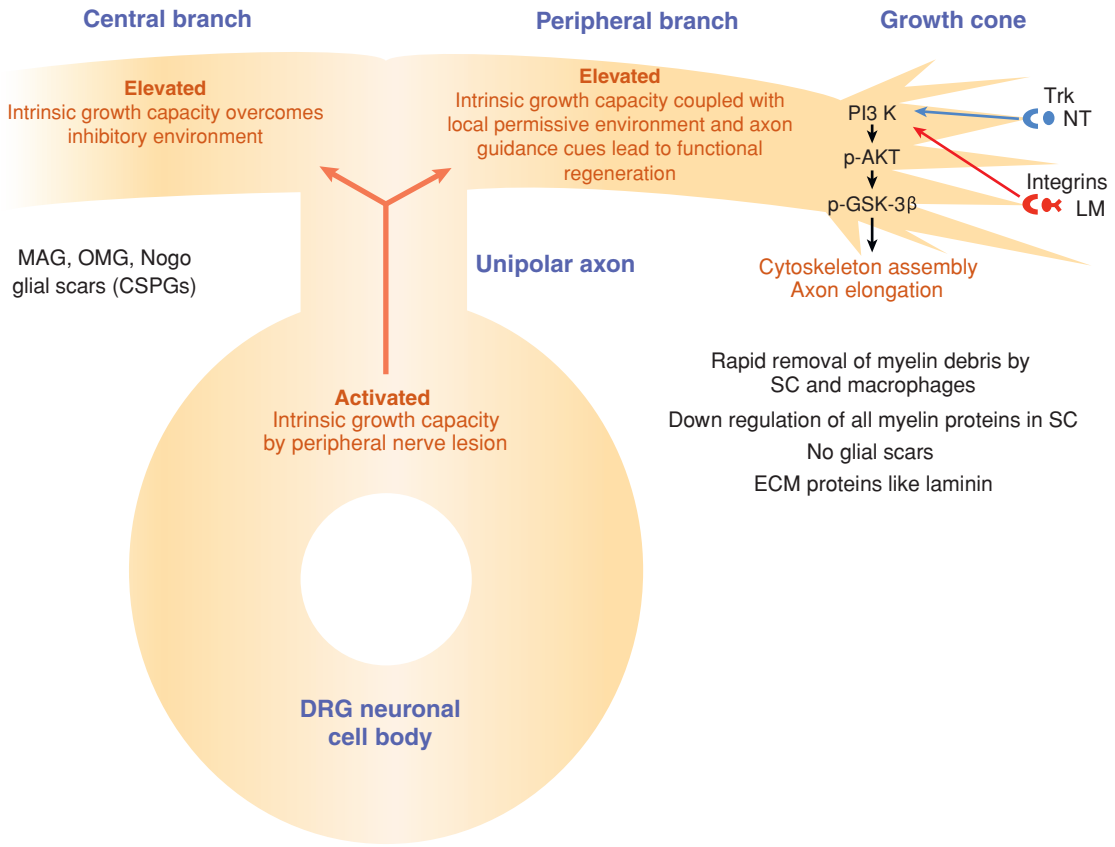

Figure 2

Axon regeneration in peripheral nerves. After peripheral nerve injury, myelin debris is rapidly removed by Schwann cells and macrophages. Schwann cells dedifferentiate and downregulate all myelin proteins generating a permissive environment. ECM proteins such as laminin (LM) bind integrin receptors at the growth cone and activate PI3K locally resulting in accumulation of active Akt at the axon/laminin contact sites. Activated Akt phosphorylates and inactivates GSK-3β. Inactivation of GSK-3β regulates cytoskeleton-binding proteins, promoting cytoskeleton assembly. Peripheral nerve injury also increases the neuronal intrinsic growth capacity. Locally facilitated machinery for cytoskeleton assembly coupled with activated intrinsic growth capacity in the whole cell leads to rapid axon growth along the basal lamina tubes (can serve as guidance cue). Neurotrophins (NT) may also participate in promoting axon regeneration through tropomyosine kinase receptors (Trk) via a similar intracellular signaling pathway to laminin. Activated intrinsic growth capacity promotes axon regeneration in the CNS by antagonizing the signal mediators of myelin-associated inhibitory molecules.

IL-6: interleukin-6

is induced in the DRG sensory neurons after injury (Murphy et al. 1995), at degeneration sites during Wallerian degeneration after sciatic nerve injury (Bolin et al. 1995, Bourde et al. 1996, Kurek et al. 1996, Reichert et al. 1996, Zhong & Heumann 1995). A beneficial function of IL-6 in peripheral nerve regeneration is demonstrated using the IL-6 knockout mice with the adult knockout mouse showing sensory defects and delayed regeneration of sensory axons after crush injury (Zhong et al. 1999).

IL-6 is upregulated in DRG neurons after a conditioning lesion and by treatment with db-cAMP (Cao et al. 2006). Moreover, delivery of IL-6 into DRG neurons mimics both peripheral conditioning lesion and cAMP effects seen in vitro and in vivo. The effect of

IL-6 is transcription dependent but cAMP independent (Cao et al. 2006). Therefore, IL-6 is one of the genes induced by either cAMP or conditioning lesion. Because blocking IL-6 signaling had no effect on cAMP's ability to overcome myelin inhibitors and IL-6 knockout mice respond to a conditioning lesion similar to wild-type mice, IL-6 is likely one of the signaling pathways downstream of cAMP, and other signaling pathways parallel IL-6. These signaling pathways can compensate for one another (Cao et al. 2006).

Another cytokine induced after sciatic nerve injury is leukemia inhibitory factor (LIF), which is closely related to IL-6 and acts via overlapping receptor mechanisms as IL-6 (Banner & Patterson 1994, Curtis et al. 1994, Dowsing et al. 1999). LIF can be retrogradely transported to the sensory neurons in the DRG and induce gene expression that contributes to regeneration (Thompson et al. 1997). LIF knockout mice show impaired peripheral nerve regeneration after injury (Cafferty et al. 2001).

Transcription factors. Signal transducer and activator of transcription 3 (STAT3) is a transcription factor involved in the signal transduction of IL-6 and LIF in peripheral nerve regeneration. Nerve injury induces IL-6 and LIF in injury sites. IL-6 and LIF bind to their respective receptors and activate Janus kinase (JAK), which phosphorylates STAT3 (Aaronson & Horvath 2002, Qiu et al. 2005, Shuai & Liu 2003). Phosphorylated STAT3 (pSTAT3) is retrogradely transported from the injury sites to the cell body and translocated into the nucleus (Schweizer et al. 2002), activating genes important in axon regeneration such as growth-associated protein 43 (GAP-43) (Cafferty et al. 2004). Studies in STAT3-conditional knockout mice show that STAT3 is required for survival of lesioned motor neurons (Schweizer et al. 2002), but the effect on peripheral nerve regeneration has not been investigated.

GAP-43, myristoylated alanine-rich C kinase substrate, and cytoskeleton-associated protein 23. GAP-43, myristoylated alanine-rich c kinase substrate (MARCKS), and cytoskeleton-associated protein (CAP) 23 are plasmalemma-associated PKC substrates and can regulate actin assembly and function in axon elongation (Frey et al. 2000, Laux et al. 2000). Both GAP-43 and CAP 23 are induced by peripheral nerve injury and are expressed at high levels in the growth cone during regeneration. Transgenic mice overexpressing both GAP-43 and CAP 23 in their DRG neurons enable growth of lesioned central axons into a peripheral nerve graft (Bomze et al. 2001). Because GMC (GAP-43-MARCKS-CAP-23) can interact with calmodulins (Dunican & Doherty 2000, Gerendasy 1999), GMC may be involved in the signaling pathway by which receptor-mediated calcium fluxes regulate growth cone activity.

LIF: leukemia inhibitory factor

The signaling pathways we discussed are all related in peripheral axon regeneration. For example neurotrophic factors could be involved in the induction of cAMP (Cai et al. 1999) and activation of intrinsic growth capacity, whereas IL-6 is a downstream effector gene in the cAMP signal pathway. During PNS regeneration, all these molecules and signaling pathways are tightly coordinated to ensure successful regeneration (**Figures 1** and **2**).

RESPONSES OF SCHWANN CELLS IN PERIPHERAL REGENERATION-DEDIFFERENTIATION, PROLIFERATION, AND REMYELINATION

The three major players that regulate Schwann cell dedifferentiation/proliferation and remyelination during peripheral regeneration are (*a*) ECM proteins, (*b*) neurotrophic factors, and (*c*) hormones (summarized in **Table 1**).

Table 1 A summary of various factors implicated in regulation of Schwann cell responses during peripheral nerve regeneration

Factors	Effects on Schwann cells	References
ECM proteins and related molecules		
Laminins	radially sorts axons during remyelination	Chen & Strickland 2003, Masaki et al. 2000
Dystroglycan	maintains myelin sheath and regulation of myelin thickness	Masaki et al. 2000, Saito et al. 2003
L-periaxin	maintains myelin sheath and regulation of myelin thickness	Williams & Brophy 2002
tPA/Plasminogen	clears fibrin to promote remyelination	Akassoglou et al. 2000, 2002
Fibrin	Inhibits remyelination	Akassoglou et al. 2002
Neurotrophic factors and receptors		
BDNF	promotes remyelination	Zhang et al. 2000
$p75^{NTR}$	mediates myelin-promoting effect of BDNF	Song et al. 2006
FGF-2	promotes Schwann cell proliferation but inhibits remyelination during regeneration	Jungnickel et al. 2004a, 2006
TGF-β	enhances Schwann cell–trophic effect to regrowing axons	Rogister et al. 1993, Sulaiman & Gordon 2002
Intracellular regulators		
PI 3-kinase/Akt signaling	promote remyelination	Ogata et al. 2004
Cyclin D1	Is required for regeneration-specific Schwann cell proliferation	Atanasoski et al. 2001, Kim et al. 2000
Ski	arrests TGF-β-mediated proliferation and promotes remyelination	Atanasoski et al. 2004
Hormones		
Progesterone	promotes remyelination	Koenig et al. 1995
Thyroid hormone	promotes remyelination	Voinesco et al. 1998
Erythropoietin	stimulates Schwann cell proliferation and decreases expression of TNF-α in Schwann cells	Campana et al. 2006, Li et al. 2005

Radial sorting of axons: promyelinating Schwann cells extend cytoplasmic processes into axonal bundles, separating these bundles to form a 1:1 ratio with individual axons

Oct-6: Octamer-binding transcription factor 6, also known as SCIP/Tst-1

Krox20: also known early growth response 2 protein (Egr-2)

ECM Proteins and Related Molecules

ECM molecules play a critical role in axon myelination during development and in remyelination after injury in the PNS (Bunge 1993, Bunge et al. 1986). Laminin is one of the most important ECM proteins involved in remyelination. However, some extracellular proteases also regulate remyelination, such as the plasminogen activator (PA)/plasminogen system.

Laminins and their receptors. Laminins are primary components of the Schwann cell basal lamina and are required for proper ensheathment and myelination of axons. Disruption of laminins in the PNS results in aberrant Schwann cell differentiation, including lack of radial sorting of axons and severe hypomyelination (Yang et al. 2005, Yu et al. 2005). The development of laminin-deficient Schwann cells is arrested at the premyelinating stage. These Schwann cells have inappropriately persistent expression of Oct-6 and low expression of Krox-20 owing to impaired interaction between axons and Schwann cells. In addition, Schwann cell proliferation and survival are severely impaired (Yu et al. 2005). Studies of laminin-deficient peripheral nerves indicate that laminins are crucial for Schwann proliferation, differentiation, and survival.

Upon nerve injury, Schwann cells in the distal stump lose contact with degenerated axons, leading to Schwann cell dedifferentiation followed by a series of proliferations (Stoll & Muller 1999). Subsequent Schwann cell redifferentiation is triggered when the Schwann cells recontact the regenerated axons. Oct-6 expression is transiently upregulated at this point in regeneration, which indicates that Schwann cells redifferentiate to a time point similar to the premyelinating stage of nascent Schwann cell development (Scherer et al. 1994, Zorick et al. 1996). Following Oct-6 expression, Schwann cells in regenerating nerves reacquire expression of Krox-20 (Zorick et al. 1996). As regeneration proceeds, Oct-6 expression is downregulated and followed by persistent Krox-20 expression and reinduction of myelin-specific genes as in normal development (LeBlanc & Poduslo 1990, Zorick et al. 1996). These results suggest that remyelination of Schwann cells recapitulates development in terms of the timing and sequence of gene-expression pattern.

Therefore, it is not surprising that laminins play a similar role in remyelination. Laminins may induce redifferentiated Schwann cells to separate axons and regulate Schwann cell proliferation and survival during regeneration. In support of this hypothesis, when Schwann cells lose contact with axons during axon degeneration, laminin expression is downregulated. Laminins are then progressively upregulated as Schwann cells begin to ensheath and remyelinate regrowing axons (Masaki et al. 2000). Moreover, application of the retrograde dye fluororuby distal to the injury of laminin-deficient sciatic nerves shows a decreased number of labeled motor neurons in the spinal cord, again indicating the importance of laminin in peripheral nerve regeneration (Chen & Strickland 2003).

Remyelinating Schwann cells upregulate expression of laminin receptors β1 integrin and dystroglycan (Lefcort et al. 1992, Masaki et al. 2000). Schwann cells that lack β1 integrin fail to segregate axons properly but exhibit unaffected cell proliferation and apoptosis (Feltri et al. 2002). In contrast with β1 integrin-deficient Schwann cells, conditional ablation of dystroglycan in Schwann cells results in abnormal folding of myelin sheaths and reduction of sodium channels at the nodes of Ranvier, but it does not severely affect radial sorting of axons (Saito et al. 2003). These results suggest β1 integrin and dystroglycan play distinct roles in Schwann cell myelination. β1 integrin is critical for axonal sorting at the promyelinating stage, whereas dystroglycan is required later for folding and maintaining the myelin sheath.

Nodes of Ranvier: regularly spaced interruptions of the myelin sheath and the site where most sodium channels in the axon are concentrated

Although the importance of these laminin receptors in Schwann cell development has been studied extensively, their roles in regeneration remain unclear. However, a study in L-periaxin-deficient mice may shed some light on the involvement of the laminin receptor in regeneration (Williams & Brophy 2002). L-periaxin is a component of the dystroglycan-dystrophin-related protein-2 complex and is involved in the linkage between the ECM and Schwann cell cytoskeleton. During PNS development, L-periaxin-null mice show abnormal folding of myelin sheaths and hypermyelination similar to dystroglycan-null mice (Gillespie et al. 2000). Following nerve injury, L-periaxin-deficient mice can undergo remyelination but recapitulate the mutant phenotypes of hypermyelination during regeneration. This observation indicates that laminins may employ a similar set of receptor complexes for nerve repair.

Plasminogen activator/plasminogen system and fibrin. The PA cascade is known primarily for intravascular fibrinolysis. However, it has also been implicated in physiological and pathological processes within the mammalian nervous system (Strickland 2001). There are two types of physiologic mammalian PAs: tissue-type (tPA) and urokinase-type (uPA). Both PAs are specific serine proteases that convert the zymogen plasminogen to plasmin. Unlike the PAs, plasmin has a broad range of substrates including fibrin,

Blood-nerve barrier: a diffusion barrier between the perineurium and the endothelium of endoneurial capillary

ERK1/2: extracellular regulated kinase 1 and 2

Trk: tropomyosine receptor kinase

the major proteinaceous component of blood clots, and ECM proteins.

Both peripheral neurons and Schwann cells are able to secrete PAs (Krystosek & Seeds 1984). Experimental sciatic nerve crush injury results in dramatically increased PA activity (Akassoglou et al. 2000, Bignami et al. 1982, Siconolfi & Seeds 2001a), a consequence of increased Schwann cell tPA-production (Akassoglou et al. 2000). Sciatic nerve crush experiments performed in tPA-deficient mice result in exacerbated axonal degeneration and demyelination and delayed functional recovery when compared with wild-type mice (Akassoglou et al. 2000, Siconolfi & Seeds 2001b). Administration of exogenous tPA to the injured sciatic nerves promotes axon regeneration, remyelination, and functional recovery (Zou et al. 2006), suggesting that tPA plays a protective role after nerve injury. Similarly injured plasminogen-deficient mouse sciatic nerves also show exacerbated damage. This damage correlates with increased deposition of fibrin(ogen) and is ameliorated by genetic or pharmacological depletion of fibrin(ogen) (Akassoglou et al. 2000). This evidence indicates that the protective function of tPA in nerve injury is mediated by the fibrinolytic activity of plasmin.

Deposition of fibrin has been implicated in a wide range of nervous system diseases (Akassoglou & Strickland 2002). In normal physiology, fibrin is not present within the peripheral nerve endoneurium. However, after nerve injury, blood-borne fibrinogen enters the extracellular space of peripheral nerves through a compromised blood-nerve barrier and is converted to fibrin within the injured nerve. Fibrin deposition inhibits not only Schwann cell migration but also remyelination during regeneration (Akassoglou et al. 2002, 2003). In vitro migration assays demonstrate that fibrin has a dose-dependent inhibitory effect on Schwann cell migration on fibronectin, perhaps because of its competition with the Schwann cell fibronectin receptor integrin αVβ8 (Akassoglou et al. 2003, Chernousov & Carey 2003). Additionally, the presence of fibrin in the Schwann cell endoneurium triggers ERK1/2 phosphorylation and downregulates expression of genes involved in myelin production and fibronectin. This arrests differentiation of Schwann cells, holding them in the predifferentiation proliferation state (Akassoglou et al. 2002).

Taken together, the data suggest that, upon injury, fibrinogen infiltrates the nerve and is converted to fibrin. Accumulation of fibrin prevents two crucial steps of peripheral nerve regeneration: migration and remyelination of Schwann cells. Coincident with fibrin deposition, tPA produced by Schwann cells activates the fibrinolytic cascade and helps in lysing fibrin, required for the reentry of the Schwann cell to its remyelinating state. The identification of the beneficial effect of the tPA/plasminogen system in peripheral nerve injury may provide a novel therapeutic strategy to promote nerve regeneration.

Neurotrophic Factors and their Receptors

The neurotrophic factors and their receptors are involved in peripheral nerve regeneration. Studies of neurotrophic factors during peripheral nerve regeneration have focused extensively on its influence in neuron survival and axonal outgrowth (Terenghi 1999). However, recent findings revealed that these factors also play important roles in regulating Schwann cell differentiation and axon remyelination.

Neurotrophins. The neurotrophin family includes NGF, BDNF, NT-3, and NT4/5 (Notterpek 2003). Neurotrophin signaling is mediated through two types of receptors, the high-affinity Trk receptor tyrosine kinases and the low-affinity $p75^{NTR}$ (Chao 2003). The $p75^{NTR}$ binds all four neurotrophins with similar affinity and acts as a coreceptor for Trk receptors. There are three different kinds of Trk receptors, each specific for a particular neurotrophin: (*a*) TrkA selectively binds NGF,

(*b*) TrkB is specific for BDNF and NT4/5, and (*c*) TrkC interacts preferentially with NT3 (Chao 2003).

An essential role of neurotrophins in peripheral nerve regeneration has been deduced from their differential expression patterns after nerve injury. Following peripheral nerve injury, the mRNA level of $p75^{NTR}$ is increased in Schwann cells distal to the nerve lesion (Heumann et al. 1987). Similarly, upon sciatic nerve transection, the mRNA level of BDNF is upregulated in the distal stump of injured nerves three days after injury and lasts for several weeks (Funakoshi et al. 1993, Meyer et al. 1992). In contrast, NT-3 mRNA levels decrease in the distal segment of the injured nerve shortly after nerve transection but return to normal after two weeks (Funakoshi et al. 1993, Meyer et al. 1992). Investigators initially thought that the differential expression of neurotrophins affected primarily the survival and differentiation of neurons during regeneration. However, a latter series of studies by Cosgaya and colleagues revealed that neurotrophins play a critical role in regulating Schwann cell myelination, as well (Chan et al. 2001, Cosgaya et al. 2002). Neurotrophins can both positively and negatively modulate myelination. Using in vitro and in vivo model systems, Cosagaya and colleagues have shown that addition of exogenous BDNF or depletion of endogenous NT3 enhances myelination, whereas addition of exogenous NT3 inhibits myelination (Chan et al. 2001). These results indicate that BDNF is a positive modulator and NT3 is a negative modulator of peripheral nerve myelination.

Additionally, Cosagaya and coworkers identified that the neurotrophin receptors $p75^{NTR}$, full-length TrkC, and a truncated isoform of TrkB known as TrkB-T1 are the major neurotrophic mediators during myelination (Cosgaya et al. 2002). Although $p75^{NTR}$ and TrkC are present at high levels during myelination, TrkB-T1 levels correlate with the course of myelination: It is induced at the onset of myelination, peaks at the maximum of myelination, and is gradually downregulated. Prevention of BDNF binding to TrkB or inhibition of Trk receptor–mediated tyrosine kinase signaling promoted myelin protein production and myelin formation, whereas blockage of $p75^{NTR}$ with antibodies showed inhibitory effects on myelination. In the presence of an inhibitor for Trk-mediated tyrosine kinase signaling in Schwann cell/neuronal cocultures, BDNF and TrkB-Fc (a scavenger receptor for BDNF) are still able to modulate myelination, suggesting that BDNF's effects are not mediated by the tyrosine kinase activity of the full-length TrkB receptor. In addition, $p75^{NTR-/-}$ mice exhibit reduced myelination with fewer myelinated axons and thinner myelin sheaths compared with normal mice. In comparison with wild-type nerves, neither injection of exogenous BDNF nor depletion of endogenous BDNF by scavenger receptor TrkB-Fc in $p75^{NTR}$-deficient sciatic nerves has any regulatory effect on myelination. These results demonstrate that the myelin-promoting effect of BDNF is mediated by $p75^{NTR}$. NT3 mediates its myelin-inhibitory effect via TrkC, whereas TrkB-T1 acts as an inhibitory regulator by competing with $p75^{NTR}$ for the availability of endogenous BDNF.

Considering their expression patterns and roles in myelination, it is not surprising that these factors play similar roles in modulation of remyelination during nerve repair. Following nerve injury, the downregulation of NT3 allows for myelination as the upregulation of BDNF and $p75^{NTR}$ promotes remyelination. Once remyelination is complete, the expression of neurotrophins and their receptors returns to normal. In concordance with this idea, endogenous BDNF is required not only for axonal outgrowth but also for remyelination during nerve regeneration. For example, when injured nerves were deprived of BDNF by treatment with an anti-BDNF antibody, the size and number of regrowing axons were reduced (Zhang et al. 2000). Additionally, sciatic nerve crush experiments performed in $p75^{NTR}$-deficient mice showed that the number of myelinated axons and the

thickness of the myelin sheath were diminished in regenerated nerves compared with that of wild-type mice. The level of myelin gene expression in injured sciatic nerves during regeneration was also decreased in $p75^{NTR}$-deficient animals as compared with wild-type animals (Song et al. 2006).

Other neurotrophic factors

Basic fibroblast growth factor. FGF-2 is upregulated after nerve injury (Grothe et al. 1997) and has been studied for its role in supporting neurite outgrowth and sensory neuron survival during nerve regeneration (for a review, please see Grothe et al. 2006). However, studies of nerve regeneration from transgenic and knock-out mice of FGF-2 and its receptor provide evidence that the FGF-2 system also contributes to the regulation of Schwann cell proliferation and redifferentiation after nerve injury. In vitro, FGF-2 is a potent Schwann cell mitogen (Davis & Stroobant 1990) and a negative regulator of the myelin gene, myelin protein zero (P0) (Morgan et al. 1994). After sciatic nerve crush injury, transgenic mice overexpressing FGF-2 regenerate twice the number of axons as do control animals, but myelin sheath thickness was decreased. Using a BrdU-incorporation assay, mice overexpressing FGF-2 had increased proliferating cells distal to the crush site (Jungnickel et al. 2006). In contrast, after nerve crush, FGF-2-deficient animals have five times more regenerating myelinated axons with increased myelin thickness and axon diameter compared with wild-type mice (Jungnickel et al. 2004a). Because myelin thickness and the number and size of regenerating myelinated axons are the same for fibroblast growth factor receptor (FGFR3)-deficient and wild-type mice (Jungnickel et al. 2004b), the myelin-inhibitory effect of FGF-2 could be mediated via another receptor, e.g., FGFR1/2 (Grothe et al. 2006). Thus, FGF-2 may play another role in peripheral nerve regeneration in addition to its neurite-supportive effects by arresting Schwann cell differentiation and inducing their proliferation.

Glial-cell-line-derived neurotrophic factor. GDNF is a potent trophic factor for a subset of sensory and motor neurons (Terenghi 1999). After sciatic nerve crush, the mRNA level of GDNF and its receptor is rapidly induced in the distal segment of the injured nerve (Naveilhan et al. 1997). The effects of GDNF on enhancement of peripheral nerve regeneration are due mostly to its action on axonal outgrowth and neuronal survival. Investigators recently demonstrated that administration of GDNF to Schwann cell/neuronal cocultures and rat sciatic nerves stimulates Schwann cell proliferation and migration, leading to enhanced myelination (Hoke et al. 2003, Iwase et al. 2005). Thus, it is tempting to speculate that GDNF may also be involved in promoting remyelination.

Neuregulin-1. NRG1 is a family of proteins of more than 15 transmembrane and secreted isoforms resulting from alternative splicing. On the basis of the difference of amino terminal sequence, they can be divided into three major types: I, II, and III. The NRG1 type III protein expressed in axons is the major isoform responsible for the Schwann cell–trophic effect, mediated by the receptor tyrosine kinases ErbB2 and ErbB3. During peripheral nerve development, NRG1 isoforms are potent positive regulators at multiple stages of the Schwann cell lineage, including proliferation and survival of Schwann cells and their precursors as well as regulation of myelin thickness (for a review, see Jessen & Mirsky 2005).

After axotomy, neuregulins and their receptors, ErbB2 and ErbB3, are increased in injured sciatic nerve (Carroll et al. 1997). Application of glial growth factor 2 (GGF2), a soluble form of neuregulin-1, to an in vitro explant culture system designed to mimic entubulation repair of transected nerves shows

increased Schwann cell migration and neurite outgrowth (Mahanthappa et al. 1996). Animals treated with exogenous GGF2 in their injured sciatic nerves also show improved functional recovery (Chen et al. 1998), suggesting that neuregulin plays a role in peripheral nerve regeneration. However, a recent study using an inducible Cre-loxP system to disrupt ErbB2 in mature Schwann cells demonstrates that proliferation and survival of Schwann cells are not impaired in regenerating nerves after injury, and other ErbB receptor family members do not compensate for the loss of ErbB2 (Atanasoski et al. 2006). This indicates that the proliferation of Schwann cells during regeneration does not require NRG1/ErbB2 signaling.

NRG1/ErbB signaling is required for ensheathment and myelination of axons by Schwann cells during normal development (Michailov et al. 2004, Taveggia et al. 2005). The study also reveals that only the axonal membrane–associated form but not the soluble form of NRG type III rescues myelination in NRG1 type III$^{-/-}$ Schwann cell/neuronal cocultures, indicating that NRG1 type III needs to cooperate with other axonal signals to induce Schwann cell myelination (Taveggia et al. 2005). NRG1 may be effective only at later stages of regeneration when Schwann cells reconnect with axons. In concordance with this idea, the myelin-promoting effect of NRG1 is mediated by PI 3-kinase/Akt signaling (Taveggia et al. 2005), and enhanced myelination of regenerated axons has been demonstrated in an allogenic nerve graft infected with adenovirus-expressing constitutively active Akt (myrAkt) (Ogata et al. 2004). Determination of whether NRG1/ErbB signaling plays a role in remyelination requires further clarification.

Previous studies show that cyclin D1 is not required for Schwann cell proliferation during development, but the proliferation of Schwann cells after nerve injury is completely inhibited without cyclin D1 (Atanasoski et al. 2001, Kim et al. 2000). Together with the finding that NRG1/ErbB signaling is not required for Schwann cell proliferation during regeneration, these results introduce the idea that the developmental process of Schwann cells is not always identical to its regeneration, especially in proliferation. The molecular mechanism to control redifferentiation of denervated Schwann cells in regenerating nerves may be similar to differentiation of immature Schwann cells in developing nerves (see above discussion about expression of Oct-6 and Krox-20 following nerve injury), but the mechanisms that control Schwann cell proliferation during early regeneration and development are different.

Transforming growth factor-β. TGF-β is required for maintenance of the nonmyelinating, proliferating state of Schwann cells by promoting proliferation and inhibiting myelination during development. It also controls Schwann cell numbers by regulating Schwann cell survival (Jessen & Mirsky 2005). After nerve injury, TGF-β is induced in the distal stump of injured nerves (Scherer et al. 1993) and secreted by infiltrating macrophages and Schwann cells (Assoian et al. 1987, Ridley et al. 1989). Both in vitro and in vivo studies have shown that TGF-β can modulate the response of Schwann cells to nerve injury and enhance Schwann cell tropic effect to regrowing axons (Rogister et al. 1993, Sulaiman & Gordon 2002). A recent study identified the protooncogene Ski, a downstream component of TGF-β/Smad signaling pathway, as being involved in the regulation of the coupling of growth arrest and differentiation of Schwann cells during development and remyelination (Atanasoski et al. 2004). TGF-β blocks myelination by preventing Ski expression. Overexpression of Ski inhibits TGF-β-mediated Schwann cell proliferation. Expression of Ski in Schwann cell cultures upregulates both myelin genes and the cell cycle arrest gene p21, suggesting a role in promoting growth arrest and myelination of Schwann cells. Ski expression is decreased four days after nerve

injury and returns to a level found in uninjured nerves after axons have fully regenerated and remyelinated. These data suggest that Ski plays a role in arresting the Schwann cell cycle and promoting remyelination during regeneration.

Hormones

Progesterone. Progesterone is another factor implicated in remyelination (Koenig et al. 1995). Blockage of the effect of progesterone by inhibiting its synthesis or receptor-mediated action decreases the thickness of myelin sheaths of remyelinated axons after injury. In contrast, administration of exogenous progesterone or its precursor to the injured site promotes myelin sheath formation. Progesterone-mediated enhancement of myelination likely occurs via stimulation of the promoters for the peripheral myelin protein 22 (pmp22) and P0 genes (Desarnaud et al. 1998) and via activation of transcription factors required for myelination (Guennoun et al. 2001, Mercier et al. 2001a). The direct effect of progesterone in promoting remyelination suggests its potential use as a therapeutic in nerve repair.

Thyroid hormones. The effect of thyroid hormones on responsive cells is mediated through nuclear triiodothyronine receptors (NT3R). Rat Schwann cells transiently express NT3R from late embryonic to early postnatal stages of peripheral nerve development. The expression of NT3R then disappears after postnatal day 10 (Barakat-Walter et al. 1993). However, after injury of an adult rat sciatic nerve, expression of NT3R is induced again in Schwann cells proximal and distal to the lesioned site (Barakat-Walter et al. 1992, 1993). Administration of thyroid hormones (T3) to an injured rat sciatic nerve results in increased nerve regeneration (Voinesco et al. 1998). The number, diameter of remyelinated axons, and myelin thickness of T3-treated nerves are significantly increased as compared with control nerves. The action of T3 on Schwann cells is most likely through the induction of transcription factors involved in Schwann cell differentiation (Mercier et al. 2001b).

Parathyroid hormone–related peptide (PTHrP) is widely expressed in the PNS and is upregulated in Schwann cells following sciatic nerve crush (Macica et al. 2006). Addition of PTHrP to dorsal root ganglion explants stimulates Schwann cell migration and phosphorylation of CREB proteins but does not affect proliferation and survival of Schwann cells (Macica et al. 2006). The function of PTHrP in peripheral nerve regeneration is still unclear. However, because increased phosphorylation of CREB by PTHrP mimics forskolin-mediated CREB activation, PTHrP could be involved in the dedifferentiation of Schwann cells during nerve regeneration.

Erythropoietin. Normally, Erythropoietin (Epo) and Epo receptors (EpoR) are expressed in axons and Schwann cells of the PNS (Campana & Myers 2001). After sciatic nerve crush, the expressions of Epo and EpoR are increased in Schwann cells (Li et al. 2005). Addition of exogenous Epo to injured sciatic nerves or primary Schwann cell cultures stimulates Schwann cell proliferation by activation of ERK/MAP (mitogen-activated protein kinase) kinase (Li et al. 2005). Systemic or local administration of Epo to animals reduces expression of tumor necrosis factor alpha (TNF-α) in Schwann cells at the injured site. Addition of Epo to TNF-α-treated primary Schwann cell cultures protects the cells from TNF-α-mediated cell death (Campana et al. 2006). These results suggest that Epo may facilitate peripheral nerve regeneration by increasing Schwann cell proliferation and decreasing TNF-α-mediated injury or death effects.

Table 1 summarizes the factors involved in regulating proliferation and remyelination of Schwann cells during peripheral nerve regeneration.

SUMMARY POINTS

1. Elevation of intracellular cAMP levels by peripheral nerve lesion plays a key role in the activation of neuronal intrinsic growth capacity. Successful functional regeneration depends on both permissive environment and neuronal intrinsic growth capacity.
2. The molecular program to control remyelination of denervated Schwann cells in regenerating nerves is similar to differentiation of immature Schwann cells in developing nerves, but the molecular mechanism that controls Schwann cell proliferation is different between regeneration and development.
3. The two major endogenous modulators of Schwann cell remyelination are ECM molecules and neurotrophic factors.

FUTURE DIRECTIONS/UNRESOLVED ISSUES

1. Most studies on regeneration have focused on how to promote axon elongation in the CNS. However, the exact molecular mechanism involved in successful peripheral axon regeneration is still not clear.
2. Because the role of the molecules involved in the activation of intrinsic growth capacity is still speculative, can blocking cAMP elevation or PKA activity abolish peripheral axon regeneration?
3. Although remyelination after injury recapitulates myelination during development in many ways, the exact similarity between these two processes remains to be determined.
4. The identification of the pathways that trigger dedifferentiation and proliferation of Schwann cells after injury is still unclear and requires future experimentation.

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