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Negative Regulation of Myelination: Relevance for Development, Injury, and Demyelinating Disease

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ABSTRACT
Dedifferentiation of myelinating Schwann cells is a key feature of nerve injury and demyelinating neuropathies. We review recent evidence that this dedifferentiation depends on activation of specific intracellular signaling molecules that drive the dedifferentiation program. In particular, we discuss the idea that Schwann cells contain negative transcriptional regulators of myelination that functionally complement positive regulators such as Krox-20, and that myelination is therefore determined by a balance between two opposing transcriptional programs. Negative transcriptional regulators should be expressed prior to myelination, downregulated as myelination starts but reactivated as Schwann cells dedifferentiate following injury. The clearest evidence for a factor that works in this way relates to c-Jun, while other factors may include Notch, Sox-2, Pax-3, Id2, Krox-24, and Egr-3. The role of cell–cell signals such as neuregulin-1 and cytoplasmic signaling pathways such as the extracellular-related kinase (ERK)1/2 pathway in promoting dedifferentiation of myelinating cells is also discussed. We also review evidence that neurotrophin 3 (NT3), purinergic signaling, and nitric oxide synthase are involved in suppressing myelination. The realization that myelination is subject to negative as well as positive controls contributes significantly to the understanding of Schwann cell plasticity. Negative regulators are likely to have a major role during injury, because they promote the transformation of damaged nerves to an environment that fosters neuronal survival and axonal regrowth. In neuropathies, however, activation of these pathways is likely to be harmful because they may be key contributors to demyelination, a situation which would open new routes for clinical intervention.

THE CONCEPT OF NEGATIVE REGULATION OF MYELIN DIFFERENTIATION

One of the most striking features of myelinating Schwann cells is their plasticity, namely the fact that they are able to switch off the myelin program, re-enter the cell cycle and adopt again a phenotype that is broadly similar to that of immature Schwann cells in perinatal nerves. This similarity means that the process can be viewed largely as a reversal of differentiation or dedifferentiation.

Typically, Schwann cell dedifferentiation takes place when cells lose contact with axons in injured nerves. In this case it represents a beneficial injury response because the denervated and dedifferentiated cells in the distal stump of cut nerves promote axon regrowth and nerve repair. The instability of myelin differentiation can however also be harmful as evidenced in demyelinating neuropathies, where metabolic disturbances, immune assault, or genetic abnormalities lead to debilitating dedifferentiation and loss of myelin.

Dedifferentiated Schwann cells can readily redifferentiate and myelinate axons if conditions are appropriate. Therefore, these cells can potentially choose between two states throughout life: the myelinated state or the immature/denervated state.

Signals that drive myelination have been studied for a long time, and it is clear that cell-extrinsic signals of this kind are associated with axons. Exciting progress has also been made in identifying a group of cell-intrinsic factors in Schwann cells, including the transcription factors Krox-20 (Egr-2), Sox-10, Oct-6 (SCIP, Tst-1, POU3f1) and NFκB, which act as positive regulators of myelination. Together these factors coordinate and drive the myelination program, and inactivation of these genes impairs or prevents myelination.

In this article, we will discuss the possibility that, in a mirror image of myelination, dedifferentiation of myelinating Schwann cells also depends on the activation of specific intracellular signaling molecules (see Fig. 1).

In particular, we will examine the idea that Schwann cells contain negative transcriptional regulators of myelination that functionally complement positive regulators of myelination, such as Krox-20. These factors would potentially work to prevent myelination or myelin maintenance or be needed to drive Schwann cell dedifferentiation in injured or diseased nerves. We will also discuss the related issues of cell-extrinsic signals and cytoplasmic signaling cascades that promote Schwann cell dedifferentiation.

Because negative regulators of myelination drive a dedifferentiation program in myelinating cells they are likely to have a major role during injury, and to exert

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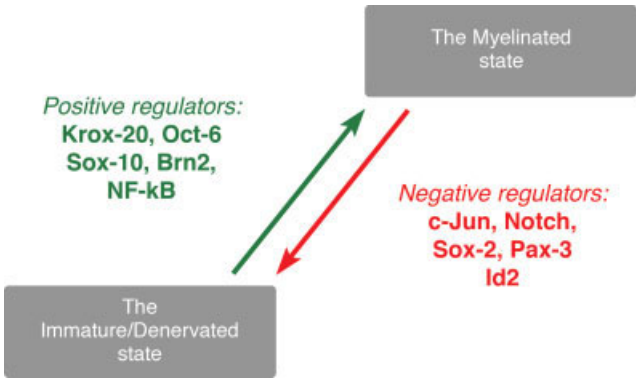

Fig. 1. A model of the transcriptional regulation of myelination. The myelination status of Schwann cells can be viewed as being determined by the balance between opposing signaling systems. Positive regulators (green) dominate in normal nerves, while the balance shifts to negative regulators (orange) in injured and pathological nerves. During development, negative regulators may also take part in timing the onset and rate of myelination. *In vivo* evidence for the negative regulators shown only exists for c-Jun and Notch at present, while the molecular identity of the positive regulators is better established (see text).

indirect control over nerve repair, since they promote the transformation of damaged nerves into an environment that fosters neuronal survival and axonal regrowth. Loss of myelin differentiation in demyelinating neuropathies may also involve inappropriate activation of these pathways, which would open new routes for clinical intervention. Correct timing of myelination in developing nerves is likely to involve interplay between positive and negative regulation, and in regrowing adult nerves, negative regulators may exert significant control over the timing and extent of remyelination.

POSITIVE REGULATORS OF MYELINATION

Before dealing with signals that inhibit or reverse myelin differentiation, it is useful to outline the signals that work in the opposite manner and promote myelination. Many of these mechanisms are reviewed in detail in other chapters in this volume.

All immature Schwann cells are likely to have an equivalent developmental potential, and their fate is determined by which axons they randomly associate with during development. The myelination program is selectively activated in cells that happen to envelop single large-diameter axons, pro-myelin Schwann cells, following the complex process of radial sorting (see Fig. 2) (Webster, 1971; Webster et al., 1973). Myelination involves an axonally signaled inversion of gene expression, as myelin genes are upregulated, while molecules that characterize immature Schwann cells are suppressed (Jessen and Mirsky, 2005). Those immature cells that remain associated with small diameter axons later give rise to mature non-myelinating cells. This process also involves axon-induced changes in molecular expression, albeit on a relatively restricted scale (see following section).

The sorting process, which results in the formation of a 1:1 ratio between axons and Schwann cells, is a precondition for myelination. But it is not a component of the myelin-specific differentiation program. This is because a large number of small unmyelinated axons also radially sort and achieve a 1:1 relationship with non-myelinating Schwann cells. In rodents, some 10–15% of unmyelinated axons are enveloped in this way, and in larger animals, including man, most unmyelinated axons have gone through radial sorting and exist in a 1:1 ratio with non-myelinating Schwann cells (Berthold et al., 2005; Sharghi-Namini et al., 2006).

It is clear that key signals that initiate and promote myelination are associated with larger diameter axons. Some of these are starting to be identified. Axon-associated neuregulin-1 controls myelin thickness in *in vivo* experiments and is also likely to be important for attaining correct axon-Schwann cell relationships necessary for the initiation of myelination (Michailov et al., 2004; Taveggia et al., 2005). Myelination in mice is reduced in the absence of β-secretase-1 (Bace 1), an endopeptidase that may act in peripheral nerves by cleaving neuregulin-1 and enhancing neuregulin-1 signaling (Hu et al., 2006; Willem et al., 2006). Studies using neuron-Schwann cell co-cultures also indicate that nectin-like (Necl) proteins on the axonal surface are required for myelination (Maurel et al., 2007; Spiegel et al., 2007).

Other cell-extrinsic signaling molecules that have been implicated in promoting myelination include steroid hormones, in particular, progesterone, brain derived neurotrophic factor (BDNF), glial cell line derived neurotrophic factor (GDNF), and insulin-like growth factor (IGF1/2) (Chan et al., 2001, 2004; Cheng et al., 1999; Höke et al., 2003; Melcangi et al., 2003; Schumacher et al., 2004). Progesterone can be expected to be present in the endoneurial Schwann cell environment, while BDNF, GDNF, and IGF1/2 can be secreted by several cells, including Schwann cells and neurons. It is unclear which cell type might be the relevant source of these secreted signals during myelination or whether they are associated with axonal surfaces when presented to Schwann cells. To what extent these factors promote myelination by affecting neurons or by direct effects on Schwann cells also remain to be unambiguously determined.

One of the earliest effects of axonal myelination signals on Schwann cells is activation of the transcription factor Krox-20. This protein is an essential driver of the myelination program and is needed for the formation and maintenance of the myelin sheath (Decker et al., 2006; Topilko et al., 1994). It promotes cell cycle exit and resistance to apoptotic death, activates a large number of myelin genes and suppresses markers of the immature Schwann cell stage, all of which are events that characterize the transition of the immature phenotype to myelinating cells. Genetic inactivation of *Krox-20* specifically affects the myelination program, because radial sorting and attainment of 1:1 relationships between axons and Schwann cells take place normally, while the formation of myelin sheaths is blocked (Topilko et al., 1994).

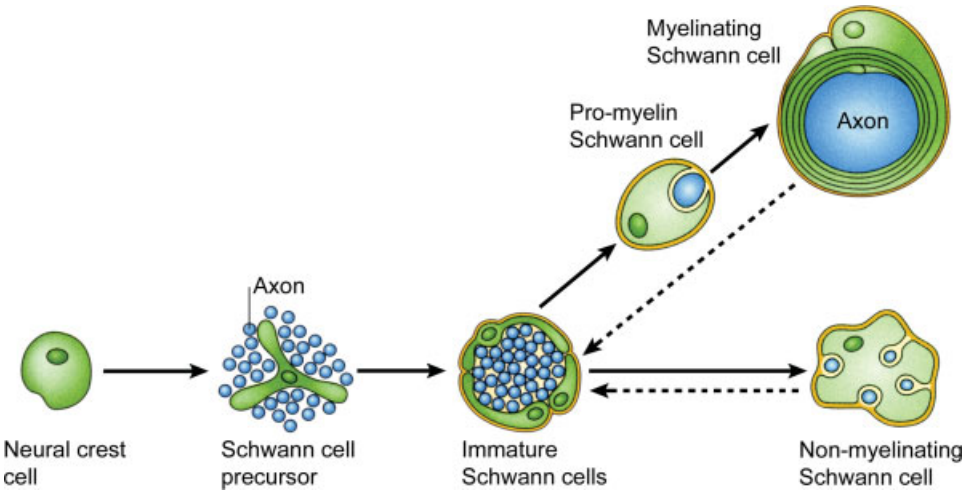

Fig. 2. The Schwann cell lineage. The main stages in the development of Schwann cells in limb nerves of rodents. Myelination starts around birth and mature non-myelinating cells appear about 2 weeks later. These transitions are essentially reversible (stippled arrows). (Adapted from Jessen and Mirsky, 2005, Nat Rev Neurosci 6:671–682.) [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Other pro-myelin transcription factors include Oct-6 and to a lesser extent Brn-2. These are important in immature Schwann cells for the correct timing of myelination, and in addition, Sox-10, which besides its importance for the generation of Schwann cell precursors (SCPs), is required for Oct-6 expression in immature Schwann cells and the activation of myelin genes (Bermingham et al., 1996; Britsch et al., 2001; Jaegle et al., 1996; Schreiner et al., 2007) [reviewed in (Jessen and Mirsky, 2005; Topilko and Meijer, 2001)]. *In vitro* experiments indicate that the myelination machinery also includes the transcription factor NFκB and that this factor may act as a mediator of cyclic AMP (cAMP) signaling (below) (Nickols et al., 2003; Yoon et al., 2008).

cAMP has long been known to activate myelin genes and mimic many of the effects of axonal myelin signals in isolated Schwann cells *in vitro* (Lemke and Chao, 1988; Morgan et al., 1991). There is increasing evidence that the cAMP pathway is indeed involved in normal myelination, and that the effects of cAMP may be mediated by NFκB and CREB (Yoon et al., 2008; Arthur-Farraj P, Mirsky R, Jessen KR, unpublished). Other signaling cascades that have been found to promote myelination include the phosphatidylinositol-3-kinase (PI3K)-Akt and p38 MAP kinase pathways (Fragoso et al., 2003; Haines et al., 2008; Maurel and Salzer, 2000; Ogata et al., 2004).

A number of molecules that control radial sorting have now been identified. These include laminin and laminin receptors, the GTPases Rac and Cdc2, focal adhesion kinase (FAK), and leucine-rich, glioma-inactivated 4 (LGI4) (Benninger et al., 2007; Bermingham et al., 2006; Grove et al., 2007; Nodari et al., 2007; Saito et al., 2007; Yu et al., 2005). It is also possible that neuregulin-1 is needed for the sorting process. As discussed above, sorting is distinct from myelination. But because the formation of myelin depends on sorting, the signals that control sorting are also, indirectly, needed for myelination. Nevertheless, for clarity it is better to maintain a clear distinction between the molecular control of sorting, a process required for the development of both myelinating and non-myelinating cells, and the signals that control the myelination program. In some cases, of course, the same molecule may be involved in the control of both processes.

SCHWANN CELL DEDIFFERENTIATION DURING WALLERIAN DEGENERATION

Nerve transection triggers a set of changes in the nerve stump distal to the injury that are collectively referred to as Wallerian degeneration (reviewed in Chen et al., 2007; Fu and Gordon, 1997; Raivich and Makwana, 2007; Scherer and Salzer, 2001; Stoll et al., 2002; Vargas and Barres, 2007). The major events are: axon death, invasion of blood-borne macrophages, collapse of myelin sheaths together with ingestion and breakdown of the myelin material, a transient phase of Schwann cell proliferation, and a reversal of molecular expression from that characteristic of mature myelinating and non-myelinating cells back to one that resembles the immature state. In the case of myelinating cells this involves downregulation of a large number of genes related to myelination (reviewed in Jessen and Mirsky, 2005; Mirsky et al., 2008; Scherer and Salzer, 2001). This includes enzymes that provide for cholesterol synthesis, structural proteins such as P_0, myelin basic protein (MBP), and membrane associated proteins such as myelin associated glycoprotein (MAG) and periaxin (Buchstaller et al., 2004; D'Antonio et al., 2006; Leblanc et al., 2005; Nagarajan et al., 2001, 2002; Verheijen et al., 2003). This switch-off is accompanied by the activation of another group of molecules, most of which are normally found on immature cells prior to myelination. This

includes L1 and NCAM, p75 low affinity neurotrophin receptor (p75NTR) and glial fibrillary acidic protein (GFAP) (reviewed in Scherer and Salzer, 2001). A number of growth factor genes are also activated in the Schwann cells of injured nerves, including NGF, BDNF, and GDNF, as are genes for cytokines including tumor necrosis factor (TNF)α, interleukin (Il)-1β, Il-6, leukaemia inhibitory factor (LIF) and macrophage chemoattractant protein-1 (MCP-1) (Boyd and Gordon, 2003; Curtis et al., 1994; Meyer et al., 1992; Shamash et al., 2002; reviewed in Stoll et al., 2002; Subang and Richardson, 2001).

The loss of the myelin sheath and myelin gene expression, and the reappearance of a set of protein markers of immature cells (L1, NCAM, p75NTR, GFAP and others), means that immature cells in developing nerves and "denervated cells" (the cells in the distal stump of cut nerves) show obvious similarities (reviewed in Jessen and Mirsky, 2005; Mirsky et al., 2008). In major features therefore this process represents dedifferentiation.

However, the molecular phenotype of immature cells and adult denervated cells is not identical. There are at least three documented differences: N-cadherin is *in vivo* suppressed to low levels on immature cells prior to myelination, but is strongly activated in cut nerves (Thornton et al., 2005; Wanner et al., 2006). Integrin α1β1 is also absent from immature cells but present on denervated cells (Stewart et al., 1997a). Conversely, the lipid antigen 04 is a marker of immature Schwann cells and expressed on both myelinating and non-myelinating adult cells but downregulated on denervated cells (Mirsky et al., 1990). In addition to this, it is unclear whether the high cytokine and growth factor expression that characterizes denervated cells, at least transiently, reflects that seen in immature cells. Gene profiling experiments also indicate a number of genes expressed at high levels in denervated cells compared with immature ones (Araki et al., 2001; Bosse et al., 2006; D'Antonio et al., 2006; Le et al., 2005). Future work is likely to establish more clearly that expression of a distinct set of "injury related genes" is superimposed on the immature state to generate the denervated Schwann cell phenotype. To reflect the present uncertainty in this area, we refer here to the phenotype of these cells as the immature/denervated state.

At a risk of digression, it may be noted that immature cells in developing nerve are also known to differ from mature non-myelinating (Remak) Schwann cells, because the mature cells are P_0 mRNA negative, α1β1 and α7β1 positive and galactocerebroside positive (Jessen et al., 1987; Lee et al., 1997; Previtali et al., 2003; Stewart et al., 1997a). The mature cells also differ from denervated cells, because denervated cells are P_0 mRNA positive, and galactocerebroside and O4 negative. In sum, peripheral nerve trunks in development, maturity and injury include at least three major categories of Schwann cell that do not make myelin, immature Schwann cells, mature non-myelinating (Remak) cells, and denervated cells; these cells show extensive similarities, but are already known not to be identical in molecular expression, a divergence that is likely to increase with further work.

It should be noted that what we refer to in this review as dedifferentiation or transition to the immature/denervated state is by some authors referred to as "activation." This term acknowledges the part played by gene upregulation in the dedifferentiation process, and highlights the fact that it involves upregulation of cytokines and appearance of phagocytic activity, all of which are reminiscent of the activation of macrophages and microglia.

The breakdown of the myelin sheath is carried out by Schwann cells and invading macrophages (reviewed in Koeppen, 2004; Vargas and Barres, 2007). There is evidence that the contribution of macrophages to myelin clearance is modest during the first week or so after injury (Perry et al., 1995). Macrophages, attracted by elevated Schwann cell expression of factors such as MCP-1, LIF, and TNFα, increase in importance at later stages. This implies that myelinating cells pass through a state that is remarkably effective in phagocytosing and degrading proteins and lipids, as they revert back to the immature/denervated state. This "macrophage-like" Schwann cell state remains to be fully characterized.

Three of the events that we have discussed, namely the switch-back towards gene expression that resembles the immature state, the activation of additional injury related genes, and Schwann cell breakdown of myelin, are likely to be important for generating an environment that fosters axonal regrowth and repair after injury. The gene regulatory programs that control these functions in Schwann cells and how they are integrated are only beginning to be determined.

NEGATIVE REGULATORS OF MYELIN DIFFERENTIATION: TRANSCRIPTION FACTORS AND TRANSCRIPTIONAL REGULATORS THAT DRIVE THE DEDIFFERENTIATION PROGRAM (ACTIVATION) OF MYELINATING SCHWANN CELLS

Negative regulation of gene transcription is a common component in the control of many genes. Negative regulators of myelination might be expected to negatively control the transcription of myelin-related genes, but they should also activate genes that characterize denervated cells (see Fig 1). Negative transcriptional regulators of myelin differentiation could also be expected to have the following features: (1) they might be active in immature cells before they myelinate, although this is not obligatory; (2) they should be inactive in myelinating cells; (3) they should be activated under conditions that lead to Schwann cell dedifferentiation, e.g. in injured nerves; (4) they would be expected to oppose pro-myelin signals (Krox-20, cAMP elevation, axonal myelination signals); (5) inactivation of such regulators should inhibit dedifferentiation. We will now examine the transcription factors c-Jun, Sox-2, Pax-3, Krox-24 (Egr-1, NGF1A/zif268), and Egr-3 and the transcriptional regulators Notch and Id2 in the light of these ideas.

c-Jun

c-Jun is a major component of the AP-1 transcription factor complex and forms together with JunB and JunD the mammalian Jun protein family (Mechta-Grigoriou et al., 2001). c-Jun is involved in a large number of cellular functions. Many of them depend on N-terminal phosphorylation of c-Jun carried out by Jun N-terminal kinases (JNKs). Other actions of c-Jun are phosphorylation independent. Even these functions of c-Jun may be responsive to changes in JNK activity, however, because JNK activates transcription of the *c-Jun* gene and can therefore potentially control c-Jun protein levels (Angel et al., 1988).

c-Jun levels are high in cultured Schwann cells from perinatal nerves, even when maintained in simple media. c-Jun appears therefore to be constitutively expressed by Schwann cells (Monuki et al., 1989). It is present in immature Schwann cells in late embryonic and neonatal nerves, but suppressed in individual cells as the pro-myelin transcription factor Krox-20 is activated and myelination begins (Parkinson et al., 2004, 2008). In cultured Schwann cells, enforced expression of Krox-20 is sufficient to suppress c-Jun protein expression. Krox-20 is also involved in suppressing c-Jun *in vivo*, because c-Jun remains high in Krox-20 null nerves where myelination is blocked. *In vitro* experiments indicate that suppression of c-Jun is obligatory for myelination, because Schwann cells with enforced Jun expression are inhibited from myelinating axons in co-cultures, and in such cells, induction of myelin genes by Krox-20 or cAMP is suppressed. Conversely, myelin gene expression is increased in c-Jun null Schwann cells (Parkinson et al., 2008).

c-Jun is rapidly upregulated after nerve injury, a procedure that triggers Schwann cell dedifferentiation (De Felipe and Hunt, 1994; Parkinson et al., 2008; Shy et al., 1996). To determine the function of c-Jun under these conditions, we generated a conditional knockout of *c-Jun* in Schwann cells (Arthur-Farraj et al., 2007). Myelination during development is not overtly affected in these mice, in line with the finding that c-Jun is normally suppressed as myelination starts (above). However, after injury there is a marked delay in myelin sheath degradation (Parkinson et al., 2008) (see Fig. 3). Partly this is due to reduced ability of *c-Jun* null Schwann cells to digest myelin. But there is also a delay in the inactivation of myelin genes and an apparent failure to activate normal expression of molecules that characterize denervated cells including L1, p75NTR and N-cadherin (Arthur-Farraj et al., 2007). This is important because it shows that following injury, c-Jun is required for Schwann cells to dedifferentiate and adopt the molecular phenotype of the immature/ denervated state. A notable feature of nerves without *c-Jun* in Schwann cells is a dramatic loss of regenerative ability and functional recovery following injury (Arthur-Farraj et al., 2007).

The key role of axonal integrity in controlling the switch from a c-Jun negative, Krox-20 positive cell that maintains myelin differentiation, to a c-Jun positive, Krox-20 negative dedifferentiating cell is clearly illustrated in experiments on the Wld^S mouse. In this mouse axonal degeneration and myelin degradation following nerve cut are delayed by 2–3 weeks. We find that during this period of myelin maintenance in spite of axotomy, Krox-20 expression is maintained and c-Jun remains suppressed. By the time axons eventually degenerate and myelin sheaths start to collapse, c-Jun is strongly expressed while Krox-20 is no longer present (see Fig. 4).

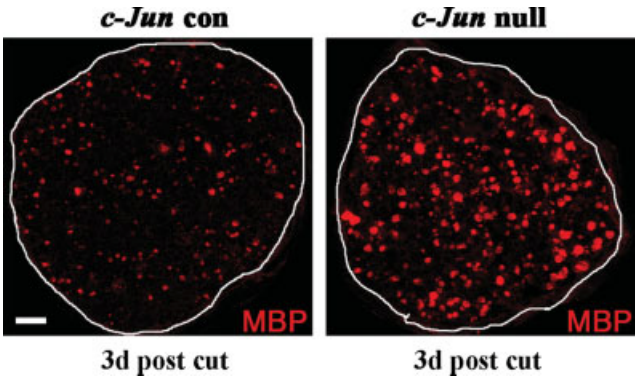

Fig. 3. c-Jun drives dedifferentiation *in vivo*. Transverse sections of whole mouse sciatic nerves immunolabeled to show MBP. Note delayed loss of myelin in *c-Jun* null nerves compared with controls, 3 days after transection of nerves of 5-day-old mice. Bar, 10 μm. © Parkinson et al., 2008. Originally published in *The Journal of Cell Biology* doi:10.1083/jcb.200803013. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Notch

Notch is a transmembrane receptor protein that, following binding to a ligand, is cleaved to generate an intracellular fragment, the Notch intra-cellular domain (NICD). This acts in the nucleus as a transcriptional regulator (Schweisguth, 2004). Notch signaling promotes the generation of a number of glial cells in the CNS and *in vitro* experiments have indicated a comparable function for Notch in Schwann cell development (e.g. Morrison et al., 2000; reviewed in Wang and Barres, 2000). In embryonic nerves, Notch signaling correctly times the generation of immature Schwann cells from SCPs *in vivo*, and controls Schwann cell proliferation (Woodhoo et al., 2007).

Notch also acts postnatally as a negative regulator of myelination. It is selectively downregulated in cells that start myelination and suppressed by Krox-20 *in vitro*. Enforced NICD expression prevents myelination in co-cultures and myelin gene induction by cAMP. Also *in vivo*, myelination is delayed in mice in which Schwann cell NICD expression is transiently elevated around birth (Woodhoo et al., 2007).

NICD levels rise strongly in the distal stump of cut nerves (Woodhoo et al., 2007). We have generated a conditional knockout of Notch signaling in Schwann cells by inactivation of Notch 1 or by inactivating recombination

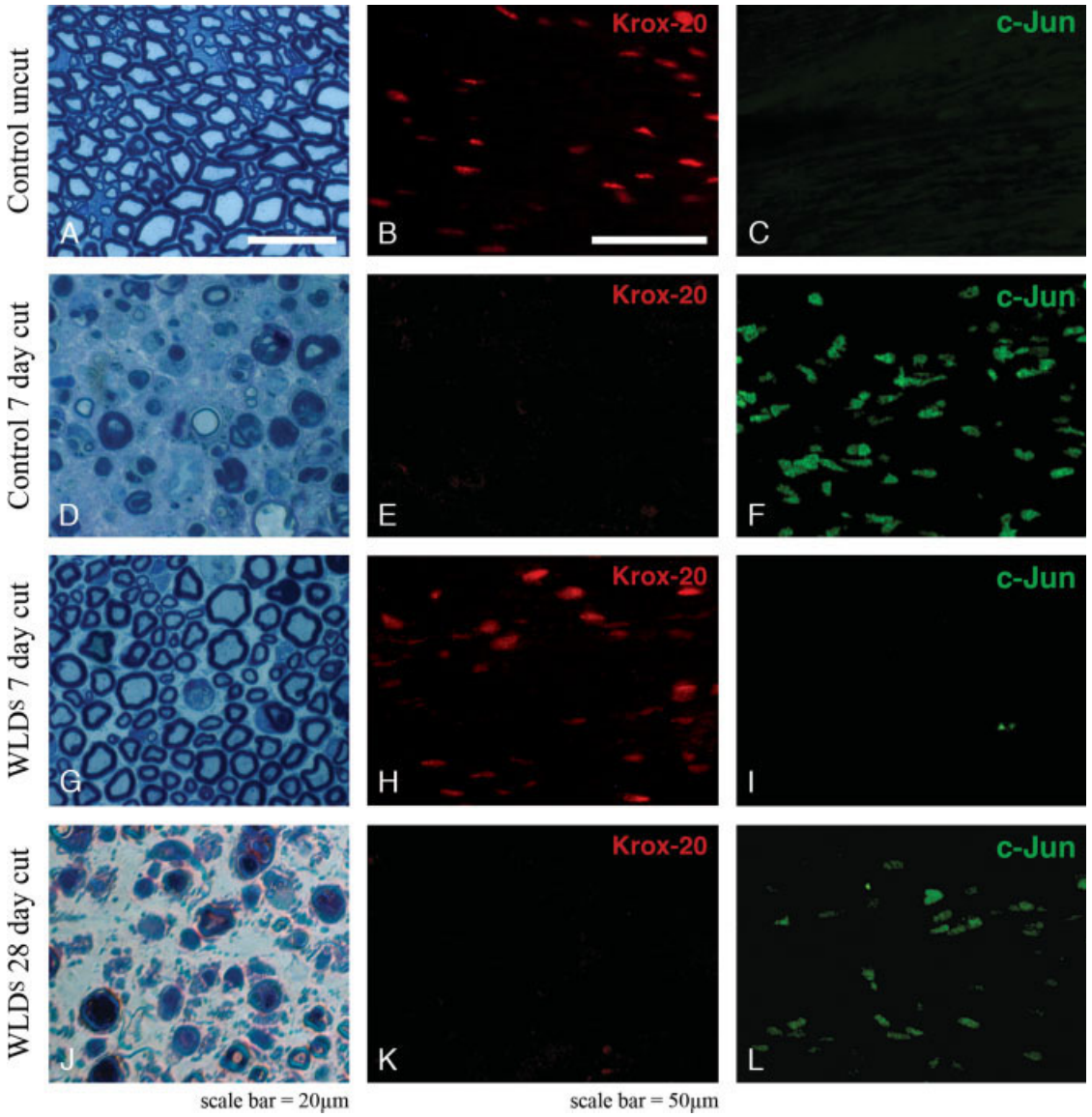

Fig. 4. In Wld^S nerves degeneration is delayed after nerve transection, together with downregulation of Krox-20 and up-regulation of c-Jun. (**A**–**C**) Wild-type nerve uncut. (A) Toluidine blue 1 μm section showing normal myelin. (**B** and C) Cryostat sections showing the expected Krox-20 expression in the nuclei of myelinating cells while c-Jun is undetectable. (**D**–**F**) Wild-type nerve 7 days after cut. (D) Toluidine blue 1 μm section showing the expected degeneration of axons and myelin. (**E** and F) Cryostat sections showing that Krox-20 is no longer detectable while c-Jun has appeared in Schwann cell nuclei. (**G**–**I**) Wld^Snerve 7 days after cut. (G) Toluidine blue 1 μm section shows preservation of axons and therefore myelin. (**H** and I) Cryostat sections showing that, as in uncut nerves, Krox-20 expression is maintained while c-Jun is undetectable in myelinating cells. (**J**–**L**) Wld^S nerves 28 days after cut. (J) Toluidine blue 1 μm section showing that by this time, axons and myelin are degenerating. (**K** and L) Cryostat sections showing that this is accompanied by the disappearance of Krox-20 and appearance of nuclear c-Jun. Scale bars A,D,G,J – 20 μm; B,C,E,F,H,I,K,L – 50 μm. This figure is provided by courtesy of Peter Arthur-Farraj from unpublished data. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

signal-binding protein Jkappa (RBP-Jκ), a transcription factor that is an essential component of the classical Notch signaling pathway (reviewed in Honjo, 1996). Following nerve transection in these mice, degeneration of myelin sheaths is delayed. Conversely, accelerated dedifferentiation is seen in nerves in which NICD expression in Schwann cells after injury is genetically enhanced (Woodhoo et al., 2007). Even activation of NICD in Schwann cells of intact nerves is sufficient to induce myelin loss (Woodhoo A, Mirsky R, Jessen KR, unpublished). All of this indicates that Notch signaling is potentially a powerful regulator of dedifferentiation in myelinating Schwann cells.

Sox-2

Sox-2 is a member of the SRY-related HMG box (SOX) family of transcription factors (Kamachi et al., 2000). These proteins are involved in numerous developmental processes, exemplified in Schwann cells by Sox-10, which has an essential function in the generation of

SCPs and during myelination (above) (Britsch et al., 2001; Schreiner et al., 2007). Sox-2 is co-expressed with c-Jun in the nuclei of immature Schwann cells before myelination. It is suppressed in myelinating cells *in vivo*, and *in vitro* enforced Krox-20 expression downregulates Sox-2. Enforced Sox-2 expression inhibits activation of myelin genes by Krox-20 or cAMP elevation, and inhibits myelination in co-cultures. It is upregulated following injury and co-expressed with c-Jun in the nuclei of dedifferentiating cells (Le et al., 2005; Parkinson et al., 2008).

Thus Sox-2 and c-Jun are extensively co-regulated and Sox-2 shows many of the features expected of a negative myelin regulator. There is evidence that c-Jun controls Sox-2 levels, at least partially (Parkinson et al., 2008), but how these proteins interact is not known. It also remains to be determined whether Sox-2 takes part in controlling the reversal of myelinating cells towards the immature/denervated state.

Pax-3

Pax-3 is a member of the paired box gene family (Tremblay and Gruss, 1994). *In situ* hybridization and RT-PCR experiments indicate that Pax-3 is expressed by immature Schwann cells and mature non-myelinating cells, but downregulated in myelinating Schwann cells *in vivo* (Blanchard et al., 1996; Kioussi et al., 1995). *In vitro*, Schwann cells express *Pax-3* mRNA and this is suppressed by cAMP elevation as myelin genes are induced. Importantly, enforced Pax-3 expression suppresses induction of myelin proteins by cAMP or Krox-20 without suppressing markers of the immature state such as L1 or NCAM (Kioussi et al., 1995; Slutsky et al., 2003; Parkinson DB, Mirsky R, Jessen KR, unpublished). In all of this, Pax-3 resembles c-Jun and Sox-2. Paradoxically, however, in early postnatal nerves of *Krox-20* null or heterozygous mice, *Pax-3* mRNA levels are lower than in control nerves (Leblanc et al., 2005). In adult nerves, Pax-3 is also upregulated after nerve transection, but it is not known whether it is involved in the control of dedifferentiation.

Id2

Id2 belongs to the Id family of HLH transcription factors. Id proteins lack DNA binding motif but can bind to other members of the HLH family to suppress their function (De Candia et al., 2004; Lasorella et al., 2001). Id2 mRNA is expressed at relatively low levels during the embryonic phase of Schwann cell development. It is elevated as myelination starts around birth and downregulated again as myelination progresses (Stewart et al., 1997b; Thatikunta et al., 1999). Furthermore, microarray analysis indicates that Id2 levels are increased after injury (Le et al., 2005). In cultured Schwann cells, Id2 is upregulated by activation of cAMP pathways, in tandem with myelin-related genes. Generally, enforced expression of Id proteins blocks differentiation, and in line with this cAMP induced expression of the myelin gene P_0 is increased in cells where Id2 is suppressed using siRNA (Mager et al., 2008). It remains to be determined whether Id2 has a broader function in antagonizing myelination, and whether this factor is involved in organizing Schwann cell dedifferentiation.

Krox-24 and Egr-3

Although Krox-20 plays a central role in Schwann cell myelination, the role of other members of the family that are expressed in Schwann cells, namely Krox-24 and Egr-3, is less well-defined (Mercier et al., 2001; Topilko et al., 1997). In adult nerves Krox-24 is largely confined to non-myelinating cells (Küry et al., 2002; Topilko et al., 1997). After transection, levels of Krox-24 and Egr-3 rise as Krox-20 levels drop, but evidence for a role in promoting dedifferentiation is lacking and mice deficient in Krox-24 do not show impaired nerve regeneration (Araki et al., 2001; Harris, 2001; Nikam et al., 1995; Topilko et al., 1997; Jessen KR, Mirsky R, Harris BS, unpublished). Recent investigation of sciatic nerves of adult mice lacking either Krox-24 or Egr-3 or both of these genes together points to the possibility that they act in a complementary fashion. In adult nerves lacking both Krox-24 and Egr-3 there is an 82% reduction in p75NTR by qPCR, although significantly, mice deficient in either gene alone do not show diminished p75NTR expression. Individually, both Krox-24 and Egr-3 directly activate p75NTR in cultured Schwann cells, and *in vivo* loss of either gene alone fails to increase expression of the other. This indicates that in injured nerves Krox-24 or Egr-3 alone can activate p75NTR expression in the absence of the other (Gao et al., 2007; Nikam et al., 1995).

p75NTR, which is known to be expressed by immature Schwann cells, is suppressed in myelinating Schwann cells but reactivated in injured nerves (Jessen et al., 1990; Taniuchi et al., 1988). It is therefore possible that Krox-24 and Egr-3 together take part in promoting dedifferentiation. This remains to be tested in double mutant mice.

CELL–CELL SIGNALS AND CYTOPLASMIC SIGNALING PATHWAYS THAT PROMOTE DEDIFFERENTIATION OF MYELINATING CELLS

The expression and activation of transcription factors and transcriptional regulators can be decisively controlled by cytoplasmic signaling cascades, and therefore by cell-extrinsic signals that activate such pathways. Although the ability of cAMP pathways to activate Krox-20 and Oct-6 and suppress c-Jun provides clear examples of interactions between cytoplasmic signals and transcriptional regulators in Schwann cells, it remains true that relatively little is known about the integration of transcriptional mechanisms, cytoplasmic pathways and cell-extrinsic signals in these cells.

Although cell-extrinsic signals may well have a role in promoting dedifferentiation (below), it seems clear that the transition from the myelin phenotype to the immature/denervated state is not completely dependent on signals arising in injured nerves. This is because myelinating cells that are dissociated from axons and placed, even at low density, in simple culture media also stop expressing myelin proteins and re-express the common markers of immature cells. They therefore undergo major changes associated with dedifferentiation under conditions that are very unlikely to mimic the endoneurial environment in injured nerves. Nevertheless, it has long been recognized that *in vivo* Schwann cell dedifferentiation might be accelerated and influenced by cell-extrinsic injury-related signals, rather than resulting only from the absence of axonal signals that promote/maintain differentiation (e.g. Scherer and Salzer, 2001). One role for such signals could be the early initiation of myelin breakdown. The role of phospholipase A2 (PLA2), lysophosphatidylcholine (LPC), and matrix metalloproteinase-9 (MMP-9) in this context is discussed and reviewed elsewhere in this volume. It is also possible that endoneurial signals are important for driving myelinating Schwann cell dedifferentiation at a rate that is optimal for supportive interactions with regrowing axons and the promotion of repair. Lastly, such signals might be required for generating the complete phenotype of denervated cells. Evaluation of this possibility requires a comprehensive comparison of the phenotype of adult myelinating cells allowed to dedifferentiate *in vitro*, with that of cells in the distal stump of cut nerves.

We will now discuss some of the main signaling pathways that have been implicated in Schwann cell dedifferentiation.

ERK1/2 and Neuregulin-1

Although neuregulin-1 has been shown to promote myelination and control myelin thickness in a number of studies (see Positive regulators of myelination above), the idea that neuregulin-1 signaling can in certain contexts suppress myelin genes and contribute to demyelination has also received support from several quarters. In purified Schwann cell cultures, application of neuregulin-1 suppresses basal levels of P_0 expression (Cheng and Mudge, 1996). In myelinating neuron-Schwann cell co-cultures, high doses of neuregulin not only inhibit myelination but also induce demyelination (Guertin et al., 2005; Harrisingh et al., 2004; Zanazzi et al., 2001). Furthermore, there is *in vivo* evidence that demyelination is associated with ErbB2 activation in myelinating Schwann cell microvilli. These receptors are activated by 10 min after nerve cut but this activation is reduced at 3 h. There is a later rise in activation of ErbB2 receptors on denervated Schwann cells at 5-days post-transection which is maintained at 30 days (Carroll et al., 1997; Cohen et al., 1992; Guertin et al., 2005; Kwon et al., 1997). Levels of neuregulin-1 isoforms also rise from day 3 post-transection (Carroll et al., 1997). Caution is required however in interpreting these results to mean that neuregulin-1 has a role in promoting Schwann cell dedifferentiation. To ascertain this, the rate of dedifferentiation and other aspects of Wallerian degeneration need to be measured in mice in which neuregulin-1 signaling has been inactivated, either by cutting out neuregulin-1 or its receptors.

Although a role in dedifferentiation therefore remains unclear, neuregulin-1 appears not to be required for the burst of Schwann cell proliferation that follows nerve injury (Atanasoski et al., 2006). Furthermore, cut out of ErbB2 receptors in Schwann cells in uninjured adult nerves, using cre-lox technology, does not result in myelin breakdown, indicating that neuregulin-1 signaling is not needed for myelin stability (Atanasoski et al., 2006).

In line with the possibility that neuregulin-1 is involved in Schwann cell dedifferentiation, there is evidence that ERK1/2 activation could play a role in demyelination (Agthong et al., 2006; Harrisingh et al., 2004; Ogata et al., 2004; Sheu et al., 2000). Phospho-ERK1/2 levels rise rapidly in the distal stump after transection and remain high until at least 16 days later, and activation is delayed at sites distal to the transection site compared with segments adjacent to the cut site itself (Harrisingh et al., 2004; Sheu et al., 2000). In crushed nerves, ERK1/2 phosphorylation levels remain high for up to 1 month (Agthong et al., 2006). *In vitro*, selective activation of ERK1/2 signaling or alternatively overexpression of ras or raf, effector molecules upstream of ERK1/2, prevent Schwann cell differentiation in response to cAMP. Raf also induces downregulation of myelin proteins in cultures that have been induced to express myelin proteins in response to cAMP and demyelination in Schwann cell-DRG co-cultures (Harrisingh et al., 2004; Ogata et al., 2004). In the nerves of $P_0+/-$ mice, examined as a model for Charcot-Marie Tooth neuropathy, ERK1/2 activation is seen in the nuclei of some myelinating Schwann cells at 6 months of age, and is directly linked to the increased production of the macrophage attractant cytokine MCP-1 in the nerves of these mice (Fischer et al., 2008). This in turn is linked to macrophage recruitment and increased demyelination, thus providing a direct link between raised ERK1/2 activation and demyelination through the activation of macrophages (Carenini et al., 2001).

Together these studies suggest that high levels of ERK1/2 activation negatively regulate myelination. However, detectable levels of activated ERK1/2 are found in wild-type nerves (Fischer et al., 2008), and it remains possible that lower levels of activity in the ERK1/2 pathway are necessary for myelination and myelin maintenance.

Neurotrophin 3 (NT3)

Evidence from rat neuron-Schwann cell co-culture experiments suggests that NT3 can have an inhibitory effect on myelination (Chan et al., 2001). NT3 secretion

by isolated neurons is 2–10 times higher than secretion by isolated Schwann cells suggesting that neuronal NT3 is likely to be the major contributor to the effects seen. After addition of Schwann cells to the neurons, the NT3 levels drop sharply and are barely detectable by the time the neurons are induced to myelinate with ascorbic acid. NT3 is undetectable by ELISA assay 6 days after induction, when the peak number of myelin segments has been generated, providing a correlation between the onset of myelination and a drop in NT3 levels. Addition of exogenous NT3 at the time of ascorbate addition reduces both MAG and P_0 expression, and the number of myelin segments. Conversely, addition of soluble TrkC-Fc to sequester endogenously produced NT3 enhances the levels of MAG and P_0 and the number of myelin segments formed. Thus in the co-culture system there is clear evidence that NT3 suppresses myelination. Injection of NT3 in the vicinity of newborn sciatic nerve also produced a reduction in P_0 and MAG protein levels 2 days later, but when NT3 was injected twice (newborn and at 2 days) no difference in MAG and P_0 protein levels was seen at 4 days, indicating a transient inhibitory effect on myelination *in vivo*. Injection of Trkc-Fc to sequester NT3 produced a small but significant enhancement of levels at both 2 and 4 days (Chan et al., 2001).

In contrast to these results, examination of the brachial plexus of newborn *NT3*+/− mice revealed normal ensheathment, no change in the size or proportion of axons that had begun to myelinate, and no change in myelin thickness or in the number of myelin lamellae in the brachial plexus of newborn mice (Klein et al., 1994; Woolley et al., 2008). Furthermore, observations on a single *NT3*−/− mouse at postnatal day 3 showed significant defects in myelin thickness. In the *NT3*+/− mice there was also a small but significant decrease in myelin thickness and a substantial reduction in mRNA and protein for P_0 and MAG at postnatal day 21 (Woolley et al., 2008).

It is possible that in the *NT3*+/− mouse, neurons or Schwann cells are themselves adversely affected in ways that mask the effect of reducing NT3-mediated communication between them. Nevertheless, these observations suggest that *in vivo* NT3 plays no obvious role in regulating the onset and early events of myelination, while it may have a supportive function later in the myelination process (Woolley et al., 2008), thus contradicting the results obtained in both co-culture and by injection of either NT3 or TrkC-Fc in the vicinity of the newborn nerve. The different outcome of the co-culture experiments on the one hand and the direct knock-down of NT3 *in vivo* on myelination is paralleled in experiments in which the effects of transforming growth factor (TGF)β were examined in co-culture or *in vivo*. TGFβ inhibits myelination in co-cultures (Einheber et al., 1995), whereas knockout of TGFβ signaling specifically in Schwann cells has no effects on myelination but reduces Schwann cell proliferation and death in developing nerves (D'Antonio et al., 2006). This emphasizes the importance of timing and the context in which a particular molecule exerts its effects.

Purinergic Signaling

The possibility that neural activity delays Schwann cell differentiation has been raised recently in studies on purinergic signaling. Primary Schwann cells express purinergic receptors of the P2Y and P2X(7) subtypes in excised nerve preparations, and when the cells are acutely isolated *in vitro*, but not on long-term culturing. This indicates that axonal contact is required to maintain receptor expression and in line with this, activation of cAMP pathways, a procedure that in many ways mimics axonal signals, induces expression of purinergic receptors in cultured cells. The evidence that these purinergic receptors are important for axon-Schwann cell communication comes from experiments involving electrical stimulation of neurons in mouse neuron-Schwann cell co-cultures. This initially causes an increase in Ca^{2+} concentration in the soma of individual neurons, which is in turn followed by delayed calcium elevation in Schwann cells associated with neurites of the same cell. On electrical stimulation of neurons, ATP is released into the medium, and the Ca^{2+} elevation in Schwann cells is blocked by P2Y type purinergic receptor blockers or by the application of apyrase, which breaks down ATP. This strongly suggests that ATP is responsible for the Schwann cell Ca^{2+} response. Consistent with this, direct application of ATP induces an immediate large increase in intracellular Ca^{2+} in Schwann cells (Ansselin et al., 1997; Colomar and Amédée, 2001; Lyons et al., 1994, 1995). Purinergic activation of Schwann cells has functional effects, inhibiting both proliferation and Schwann cell differentiation, measured by 04 antigen expression and myelination in co-cultures (Fields and Stevens, 2000; Stevens and Fields, 2000). The effect of ATP on proliferation in the co-culture system is induced by the action of P_2Y_1 receptors. However, Schwann cells also express $A2_A$ adenosine receptors, which elevate intracellular cAMP levels and activate the ERK1/2 pathway (Stevens et al., 2004). Like ATP, adenosine inhibits Schwann cell proliferation acting via $A2_A$ receptors but does not inhibit 04 expression or myelination.

Thus both ATP and adenosine derived from neurons have the potential to inhibit Schwann cell proliferation, although they have differential effects on differentiation. During normal nerve development inhibition of proliferation is associated with the onset of myelination, and this inhibition takes place well after 04 antigen is first expressed (Stewart et al., 1993). Further studies will therefore be needed to determine how the complex effects of ATP signaling seen in these *in vitro* experiments integrate with other signals to generate the coordinated pattern of Schwann cell maturation, proliferation and myelination seen *in vivo*.

Nitric Oxide Synthase

Following injury to the sciatic nerve, inducible nitric oxide synthase (iNOS) is upregulated in the distal stump although it is not clear to what extent this takes

place in Schwann cells rather than macrophages (Gonzalez-Hernandez and Rustioni, 1999; Lee et al., 2007; Levy and Zochodne, 1998; Levy et al., 1999, 2001). In *iNOS* null mice, uninjured nerves show no obvious abnormalities, but myelin breakdown, judged by morphological criteria, is markedly delayed after transection, nerve crush or chronic constriction injury (Levy et al., 2001). Taken together these results provide convincing evidence that lack of iNOS contributes both to delayed Wallerian degeneration, and delayed regeneration after injury.

Although upregulation of iNOS in Schwann cells in injured nerves *in vivo* remains to be unambiguously demonstrated, iNOS can clearly be induced in cultured Schwann cells by agents such as cytokines and double-stranded viral RNA (Gold et al., 1996; Lee et al., 2007). Interestingly, iNOS induction by viral RNA in this model depends on toll-like receptor 3 and requires activation of JNKs (Lee et al., 2007), suggesting a link between the c-Jun pathway and NO signaling in Schwann cell demyelination.

Other Agents Implicated in Negative Regulation of Myelination

In experiments on *Mycobacterium leprae (M leprae),* the causative agent in leprosy, exposure of myelinating neuron-Schwann cell co-cultures to the bacterium caused dimerization of Schwann cell ErbB2 neuregulin-1 receptors without the involvement of ErbB3. Through this unconventional mechanism *M leprae* increased ERK1/2 phosphorylation and caused demyelination that could be inhibited by the ERK1/2 blocker U0126 (Rambukkana et al., 2002; Tapinos et al., 2006).

Another potential mechanism for demyelination is described in recent reports showing that Schwann cell specific inactivation of the *Lpin1* gene caused myelin degradation and Schwann cell dedifferentiation (Nadra et al., 2008). Lipin1 is an enzyme that catalyzes the dephosphorylation of phosphatidic acid, which was found at elevated levels in the mutant nerves. On the basis of further analysis in cell culture it was concluded that the demyelination was caused by high levels of phosphatidic acid via a process that was blocked by ERK1/2 inhibitors.

The cyclin-dependent kinase inhibitor p57kip2, which is downregulated as postnatal nerves myelinate, has also been implicated in negative regulation of myelination, since RNA interference-based knockdown of p57kip2 in cultured Schwann cells induces modest expression of myelin proteins, including P_0 and MBP, and promotes myelination in co-cultures (Heinen et al., 2008).

It is also possible that unmyelinated axons suppress the myelin phenotype, much as myelinated axons promote it. This notion comes from work on the regulation of P_0 mRNA expression in the non-myelinating Schwann cells of the sympathetic trunk (Lee et al., 1997). Low basal levels of P_0 gene expression, which serve as a marker for the Schwann cell lineage, are first seen in SCPs and are found in all immature Schwann cells irrespective of whether they later form myelin or not (Jessen and Mirsky, 2005; Lee et al., 1997). This P_0 expression is axon-independent and constitutive. Although myelination involves axon-dependent amplification of this pre-existing P_0 gene expression, it is suppressed to undetectable levels during the maturation of non-myelinating cells. This suppression is axon dependent, since P_0 is reactivated in the distal stump of the transected sympathetic trunk, and in the non-myelinating cells of trunk when they are removed from axonal contact by dissociation and cell culture (Lee et al., 1997).

RELEVANCE FOR NERVE REPAIR

There is ample evidence that Schwann cell dedifferentiation is required for effective nerve regeneration. This includes the observations that regeneration is poor through intact, nondegenerated nerves *in vivo*, and compromised in the Wld^S mouse where myelin degeneration is delayed (Brown et al., 1992). Similarly *in vitro*, axon growth is blocked on cryosections from intact nerves, but not on sections from predegenerated nerves (Bedi et al., 1992). In line with this, regenerating axons are often associated with dedifferentiating Schwann cells containing myelin debris, but seldom with intact myelin sheaths in the same nerves (Fruttiger et al., 1995a). Further, dedifferentiating Schwann cells upregulate molecules such as tenascin-C that have been shown to accelerate axon growth *in vivo*, and the marked upregulation of growth factors and surface proteins such as L1 and N-cadherin during Wallerian degeneration is also likely to promote regeneration, because these molecules have been shown to support axon growth and/or neuronal survival in culture studies (Adcock et al., 2004; Fruttiger et al., 1995a,b; Schäfer et al., 1996; Wanner and Wood, 2002).

In so far as they promote the transition to the immature/denervated phenotype, negative regulators of myelination can therefore be expected to be important promoters of nerve repair. There is already some evidence for this. c-Jun is required for driving Schwann cell dedifferentiation (above) and in mice with conditional inactivation of *c-Jun* in Schwann cells, functional recovery is strikingly compromised following facial or sciatic nerve injury (Arthur-Farraj et al., 2007). Nitric oxide signaling promotes demyelination in injured nerves (above) and in mice lacking *iNOS*, regeneration of the sciatic nerve following crush is significantly delayed at 14 days after crush injury although by 6 weeks fiber numbers, size distribution and densities are similar to those seen in wild-type mice (Levy et al., 2001). After nerve transection a more substantial deficit in nerve regeneration is seen, including a delay in the appearance of a compound muscle action potential distal to the injury, and a long-lasting suppression of muscle potential amplitude, indicating a deficit in the number of axons that reach the motor endplates (Levy et al., 2001).

Although the general expectation is that, collectively, negative regulators of myelination should be important

for nerve repair, the signaling that controls axon regrowth likely involves a complex balance between a number of different factors. It may therefore prove hard to predict the overall effect on axonal growth that results from activation or inactivation of individual signaling systems in Schwann cells. Future work will determine whether improved understanding of the mechanisms that control the transition of differentiated Schwann cells to the immature/denervated state can be harnessed to improve the success of peripheral nerve repair.

CONCLUSIONS

This article presents the view that Schwann cells are likely to contain signaling pathways and transcriptional mechanisms that are negative regulators of myelination. The emerging idea of negative transcriptional regulators of myelination by factors such as c-Jun, Notch, Sox-2, Id2, Pax-3, Krox-24 and Egr-3 complements the already established notions about positive regulators of this process, including Krox-20, Sox-10, Oct-6 and others, and implies that myelination is determined by a balance between two opposing transcriptional programs.

Future work is likely to focus on the role of negative regulators in the development of peripheral neuropathies of both the hereditary and acquired kind. If they have a role in promoting demyelination in these conditions it may be possible to devise therapies that will prevent the demyelination, based on interference with these pathways. It will also be important to determine the links between the transcriptional program of demyelination and the cell–cell signals and cytoplasmic pathways that have also been implicated in Wallerian degeneration and the control of macrophage invasion. Finally, elucidation of the molecular mechanisms involved in Schwann cell dedifferentiation is likely to improve our understanding of how glial cells control axon regrowth after injury and how they can be manipulated to promote nerve repair.

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