NEURAL REGENERATION RESEARCH
August 2017, Volume 12, Issue 8
www.nrronline.org

INVITED REVIEW

Transcriptional inhibition in Schwann cell development and nerve regeneration

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How to cite this article: *Quintes S, Brinkmann BG (2017) Transcriptional inhibition in Schwann cell development and nerve regeneration. Neural Regen Res 12(8):1241-1246.*

Abstract
Schwann cells, the myelinating glial cells of the peripheral nervous system are remarkably plastic after nerve trauma. Their transdifferentiation into specialized repair cells after injury shares some features with their development from the neural crest. Both processes are governed by a tightly regulated balance between activators and inhibitors to ensure timely lineage progression and allow re-maturation after nerve injury. Functional recovery after injury is very successful in rodents, however, in humans, lack of regeneration after nerve trauma and loss of function as the result of peripheral neuropathies represents a significant problem. Our understanding of the basic molecular machinery underlying Schwann cell maturation and plasticity has made significant progress in recent years and novel players have been discovered. While the transcriptional activators of Schwann cell development and nerve repair have been well defined, the mechanisms counteracting negative regulation of (re-)myelination are less well understood. Recently, transcriptional inhibition has emerged as a new regulatory mechanism in Schwann cell development and nerve repair. This mini-review summarizes some of the regulatory mechanisms controlling both processes and the novel concept of "inhibiting the inhibitors" in the context of Schwann cell plasticity.

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doi: *10.4103/1673-5374.213537*

Accepted: *2017-06-28*

Key Words: *Schwann cell; Zeb2; myelin; transcription factors; regeneration; remyelination; neuropathy*

Schwann Cell Development and Plasticity
Schwann cells form the lipid-rich myelin sheath enwrapping peripheral nerve axons thereby facilitating saltatory impulse conduction and providing trophic support. After nerve injury and, to some extent, in peripheral neuropathies, Schwann cells show a remarkable plasticity, which is a prerequisite for successful nerve regeneration. Schwann cells develop from the neural crest, a transient highly motile cell population giving rise to a multitude of derivatives, including enteric ganglion cells and melanocytes. Their differentiation from Schwann cell precursors to immature Schwann cells and finally mature myelinating and non-myelinating Schwann cells is governed by a multitude of factors, some Schwann cell-intrinsic, others stemming from the axon or the extracellular matrix (Jessen and Mirsky, 2005). After peripheral nerve injury, Schwann cells form repair cells, a process which partially recapitulates early Schwann cell development. These highly specialized cells gain unique features, such as the ability to phagocytose myelin and form regenerative tracts (Bands of Büngner) for axons to reinervate their targets. Repair Schwann cells share some properties with the immature Schwann cells in development and have therefore often been considered to be de-differentiated. However, in addition to the re-expression of immature genes, repair Schwann cells activate injury-related genes, such as those coding for neurotrophins, recruitment of macrophages and phagocytosis, thereby actively supporting nerve repair (Jessen and Mirsky, 2016). Some transcripts, such as oligodendrocyte transcription factor 1 (Olig1), glial cell-derived neurotrophic factor (Gdnf), sonic hedgehog (shh) or artemin are exclusively expressed in the repair cell and absent or only detectable at very low levels in immature cells (Arthur-Farraj et al., 2012; Fontana et al., 2012). This cell type conversion should therefore rather be considered as a transdifferentiation, similar to that observed in other cell types (Jessen et al., 2015).

Positive Regulation of Peripheral Nerve Myelination and Repair
The cascade of transcriptional activators driving peripheral myelination and redifferentiation after nerve injury has been well defined (reviewed in Jessen and Mirsky, 2005). Briefly, the high mobility group (HMG)-domain transcription factor SRY-related HMG-box 10 (Sox10), which is already expressed in migrating neural crest cells, activates octamer-binding factor 6 (Oct6) by binding to a Schwann cell specific enhancer. Once induced, a complex of Sox10, Oct6 and the related transcription factor brain-2 (Brn2) leads to activation of early growth response protein 2 (Egr2, Krox20), a master regulator of the peripheral myelination program (Ghislain and Charnay, 2006). This positive cascade finally activates genes coding for integral myelin proteins and lipids. The transcription factor nuclear factor κB (NF-κB) is dispensable for developmental myelination, however axonal regeneration and remyelination after injury is delayed in conditional knockout mice (Morton et al., 2012). In addition, the peripheral myelination process is tightly regulated by a whole set of partially interconnected signaling pathways, which have been reviewed in detail before (Boerboom et al., 2017). One key factor during peripheral myelination is axo-

nally derived neuregulin 1 type III. Displayed on the axonal surface, neuregulin 1 (nrg1) type III promotes myelination and regulates sheath thickness by binding to erythroblastic leukemia viral oncogene homolog 2 (erbB2)/B3 receptors in the plasma membrane of Schwann cells (Michailov et al., 2004; Taveggia et al., 2005). This signal is transduced *via* the phosphoinositide 3 (PI3) kinase/protein kinase B (PKB, Akt)/mechanistic target of rapamycin (mTOR) pathway. PI3 kinase signalling is necessary for Schwann cell proliferation and survival *in vitro* and its inhibition delays the initiation of myelination in myelinating co-cultures (Maurel and Salzer, 2000). The kinase Akt regulates myelin sheath thickness and axon wrapping by nonmyelinating Schwann cells in the peripheral nervous system (PNS) (Domènech-Estévez et al., 2016). However, transgenic expression of a constituitively active Akt in mice showed no effect on PNS myelination (Flores et al., 2008). Deletion of mTOR from Schwann cells led to an arrest of myelination and a reduction of axonal size (Sherman et al., 2012). The critical importance of the interaction between Schwann cells and the extracellular matrix for axonal radial sorting and subsequent myelination has been demonstrated by different conditional mouse mutants (Nodari et al., 2007, 2008; reviewed in Colognato and Tzvetanova, 2011). In addition, G-protein-coupled receptors play important roles in peripheral nerve development and regeneration (Mogha et al., 2013, 2016). Recently, important functions for the evolutionary conserved Hippo signalling pathway in developmental peripheral myelination as well as in the generation of the repair cell, have been demonstrated, adding one more component to the constantly growing number of regulatory factors. The Hippo effectors yes-associated-protein (YAP) and transcriptional co-activator with PDZ-binding-motif (TAZ) bind to TEA domain transcription factors (TEAD) to regulate expression. Loss of Schwann cell Yap/Taz prevents their proliferation and axonal radial sorting (Poitelon et al., 2016) while increased activity of Yap/Taz leads to a catastrophic failure of regeneration in conditional merlin knockout mice (Mindos et al., 2017).

In addition to transcriptional control, epigenetic mechanisms also play an important role in the regulation of the peripheral myelination and remyelination program. Sox10 binding to Oct6 during Schwann cell development leads to the recruitment of Brahma-related gene 1 (Brg1) containing Brg1/Brm-associated factor (BAF) chromatin-remodeling complexes and the histone deacetylases 1 (HDAC1) and HDAC2 (Jacob et al., 2011; Weider et al., 2012). While HDAC2 primarily promotes myelination by transcriptional regulation of Sox10, Oct6 and myelin protein zero, HDAC1 is involved in the control of Schwann cell survival (Jacob et al., 2011). There is also evidence for the involvement of histone modification in the activation of genes after nerve injury (Ma et al., 2015).

Negative Regulators of Peripheral Nerve Myelination and Repair

The positive signals driving peripheral myelination described above have been well defined. The function of negative regulators of myelination and the mechanisms suppressing them to allow Schwann cell maturation are less well understood. These factors are especially interesting as they are expressed in immature Schwann cells, inactivated in myelinating Schwann cells, and, in many cases, re-expressed after nerve injury and in peripheral neuropathies. This implies that some of them may play important roles in the establishment and maintenance of the repair Schwann cell or in creating a favourable environment for nerve regeneration. However, just as important as their activation in pathological conditions is the need to silence them again to allow re-differentiation and remyelination. A multitude of pathways and second messenger systems have to be precisely balanced during peripheral nerve myelination (Boerboom et al., 2017). The PI3 kinase/Akt/mTOR pathway is counteracted by the phosphatase and tensin homolog (PTEN), which dephosphorylates PtdIns (3,4,5)P3, thereby ensuring the correct myelin sheath thickness. Inactivation of PTEN in Schwann cells leads to focal hypermyelination of PNS axons and causes a tomaculous neuropathy (Goebbels et al., 2010). PTEN activity is potentiated by the scaffolding protein discs large homolog 1 (Dlg1) and mice lacking Dlg1 specifically from Schwann cells display transient hypermyelination (Noseda et al., 2013). Furthermore, DNA damage-inducible transcript 4 protein (Ddit4) has been identified as a sustained negative regulator of PNS myelination, as loss of expression results in increased PI3kinase/Akt/mTOR activity and persistent hypermyelination (Noseda et al., 2013). The p38 mitogen-activated protein (Map) kinase also functions as an inihibitor of PNS myelination. P38 MAPK inactivation in myelinating co-cultures promotes myelination and lack of the major isoform p38alpha in conditional knockout mice accelerates developmental myelination (Roberts et al., 2017). An imbalance of PI3 kinase and Map kinase signalling has been demonstrated in a rat model for Charcot-Marie-Tooth disease 1A (CMT1A) and may have implications for other peripheral neuropathies (Fledrich et al., 2014).

Secreted molecules have also been implicated in negative regulation of myelination. Collagen triple-helix containing 1 (Cthrc1) led to prolonged proliferation and delayed myelination when transgenically overexpressed in mice (Apra et al., 2012). Endothelin 1 binding to the endothelin receptor B has been shown to delay lineage progression of Schwann cells and Ednrb-deficient rats display premature expression of S100 beta protein, a marker for immature Schwann cells (Brennan et al., 2000).

In addition to these pathways, several transcription factors function as inhibitors of peripheral myelination. The pluripotency factor Sox2 has been shown to repress myelin gene expression *in vitro* (Le et al., 2005) and, together with Sox10, interacts with positive transcription elongation factor b in Schwann cells (Arter and Wegner, 2015). During regeneration of peripheral nerves, Sox2 acts downstream of EphrinB2 to mediate sorting through relocalization of N-cadherin (Parrinello et al., 2010). More recently, the role of Sox2 as a negative regulator of myelination was

confirmed *in vivo*. Maintained Sox2 expression in a transgenic mouse line led to increased proliferation and suppression of myelination during development and reduced functional recovery after injury (D.B. Parkinson personal communication).

The transmembrane receptor Notch is cleaved upon ligand binding and its intracellular domain (NICD) enters the nucleus to function as a transcriptional regulator. This signalling pathway is active in Schwann cell precursors, needs to be inactivated to allow final maturation and is then again re-activated in the repair Schwann cell to drive demyelination after injury (Woodhoo et al., 2009). Notch promotes the generation of Schwann cells from precursors and inhibits myelination by opposing Krox20. Furthermore, activation of Notch signalling in adult mice led to myelin breakdown (Woodhoo et al., 2009).

The activator protein 1 (AP-1) transcription factor c-Jun inhibits the induction of myelin gene expression by Krox20 and cyclic adenosine monophosphate (cAMP) and enforced expression inhibits myelination *in vitro* (Parkinson, 2004; Parkinson et al., 2008). While dispensable for Schwann cell development, c-Jun controls nearly all processes occurring in Schwann cells after nerve injury. Schwann cells lacking c-Jun are unable to form Bands of Büngner and provide sufficient neurotrophic support after injury, which leads to extensive loss of sensory neurons in conditional knockout mice (Arthur-Farraj et al., 2012). In addition, Schwann cell c-Jun controls myelin debris removal by Schwann cells after injury, so-called myelinophagy (Gomez-Sanchez et al., 2015). Elevated c-Jun levels have also been found in a mouse model for CMT1A and exert a protective effect on the survival of sensory neurons in this pathological context (Hantke et al., 2014).

The functions of the two transcription factors paired box 3 (Pax3) and inhibitor-of-differentiation 2 (Id2) in Schwann cells are less well defined. Both are re-expressed after nerve injury and have been shown to antagonize myelin gene expression *in vitro* (Le et al., 2005; Doddrell et al., 2012), however, *in vivo* evidence is still lacking. *In vitro* evidence also suggests roles for further factors in negative regulation of myelination. Oxysterols expressed in a Schwann cell line and sciatic nerve have been shown to repress expression of myelin protein zero (MPZ) and peripheral myelin protein 22 (PMP22) by liver X receptor (LXR) a and b activation and inhibition of Wnt/beta-catenin signalling (Makoukji et al., 2011). Heinen et al. (2008) demonstrated that deletion of the cyclin-dependent kinase inhibitor 1 (Cdnk1c, also known as p57Kip2) leads to the induction of myelin genes in cultured Schwann cells and accelerates myelination in cocultures (Heinen et al., 2008). Moreover, they demonstrate, that Cdnk1c is downstream of enhancer of zeste homolog 2 (EZH2) and Hes5 acts as an inhibitor of myelin gene expression (Heinen et al., 2012).

Negative regulators of myelination are absent or expressed at very low levels in mature Schwann cells and are re-expressed in the repair Schwann cell to promote regeneration (Jessen and Mirsky, 2016). This requires mechanisms actively suppressing differentiation inhibitors in a timely manner during development and in order to allow re-maturation and remyelination. It has so far remained elusive how this is accomplished, while the positive feedback loops in Schwann cell development and peripheral nerve regeneration have been well established. Direct transcriptional repression is one possibility to silence genes stalling Schwann cell maturation in development and re-differentiation after nerve injury.

Zeb2-Mediated Transcriptional Inhibition as a Novel Mechanism Promoting Schwann Cell Differentiation

The transcription factor Zinc finger E-box-binding homeobox 2 (Zeb2, also known as Smad-interacting protein (Sip) 1) is a member of the Smad-interacting protein family acting downstream of transforming growth factor-β (TGFβ) and bone morphogenetic protein (BMP) signaling pathways and plays an important role in neural crest cells (Van de Putte et al., 2007). Zeb2 acts as a transcriptional inhibitor by binding to E-box like sequences in the promotors of target genes (Verschueren et al., 1999; Conidi et al., 2011). Zeb2 protein is highly expressed at early developmental stages in the Schwann cell lineage, while mature Schwann cells are Zeb2-negative (Quintes et al., 2016; Wu et al., 2016). Schwann cell-specific inactivation of Zeb2 in mice not only stalled Schwann cell maturation at the pre-myelin stage, but also led to consistently high expression levels of genes known as negative regulators of the peripheral myelination program, the endothelin receptor B (Ednrb) and Sox2 pointing to a possible direct repression by Zeb2. The transcriptional repressor hairy/enhancer-of-split related with YRPW motif protein 2 (Hey2) was also highly expressed in Zeb2-deficient Schwann cells (Quintes et al., 2016). Hey2 had not been described in Schwann cells before, however, the transcriptional repressor acts downstream of Notch signalling, a highly important pathway in Schwann cell development and plasticity (Woodhoo et al., 2009). We could show, that Zeb2 inhibits transcription of the above-mentioned factors by direct binding, thereby facilitating Schwann cell maturation. Additionally, Zeb2 recruits the histone deacetylases HDAC1 and 2 and NurD chromatin remodelling complexes to suppress Notch/Hey2 signalling (Wu et al., 2016). In mutant mice, Zeb2-deficient Schwann cells failed to sort axons and did not myelinate them. However, conditional Zeb2-knockout mice survived into adulthood, meaning that mutant Schwann cells were able to provide at least basic trophic support to axons (Quintes et al., 2016). When we additionally deleted either one of the maturation inhibitors Ednrb or Hey2 in Zeb2-deficient Schwann cells, axonal radial sorting improved to some extent, however, double-mutant Schwann cells were still unable to myelinate. This points to a highly complex regulatory transcriptional network with finely tuned activators and inhibitors during Schwann cell maturation (**Figure 1**).

In accordance with the effects observed in Schwann cell development, re-maturation and regeneration after nerve

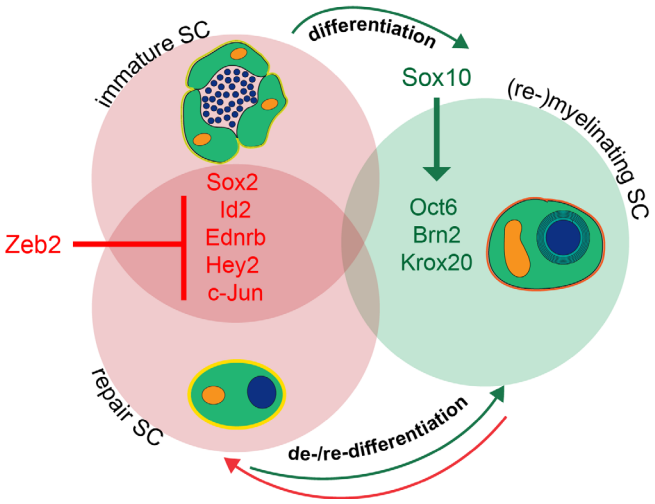

Figure 1 Schematic depiction of transcriptional regulation during SC development and nerve repair.
A number of transcriptional repressors (red) are active in both, the immature Schwann cell and the specialized repair Schwann cells. These factors are silenced by Zeb2 during Schwann cells development and nerve repair to allow maturation and re-differentiation. In mature and re-myelinating Schwann cells, transcriptional activators (green) drive expression of genes coding for myelin proteins and lipids. This cascade is driven by Sox10. A finely tuned equilibrium between negative and positive regulators of the (re-)myelination program is needed to ensure a balance between proliferation and differentiation of Schwann cells. Ednrb: Endothelin receptor type B; Hey2: hairy/enhancer-of-split related with YRPW motif protein 2; Oct6: octamer-binding factor 6; SC: Schwann cell; Sox2: sex determining region Y-box 2; Zeb2: zinc finger E-box-binding homeobox 2.

injury dramatically failed in mice with Zeb2-deficient Schwann cells (Quintes et al., 2016; Wu et al., 2016). Functional recovery of hind limb movement as well as remyelination was severely impaired. The absence of Zeb2 did not affect the formation of the repair cell or removal of myelin debris. Instead, the re-differentiation into remyelinating Schwann cells was hampered. Expression levels of Sox2 and Ednrb remained high in distal stumps of sciatic nerve of conditional Zeb2 mutant mice and Krox20 mRNA expression was low (Quintes et al., 2016). Aberrantly high Hey2 expression levels were not observed after nerve injury, which led us to hypothesize that this is a unique feature of Zeb2-deficient Schwann cells during development. We conclude, that Zeb2 acts as a potent transcriptional inhibitor and is crucial for the silencing of factors inhibiting Schwann cell maturation and re-differentiation. This "inhibition of inhibitors" is a novel concept in Schwann cell development and peripheral nerve regeneration.

The Repair Schwann Cell – Future Prospects for Peripheral Nerve Repair

While the degenerative and regenerative events occurring after an acute peripheral nerve injury (Wallerian degeneration) have been known since the nineteenth century, major progress has been made recently in understanding the pivotal role of Schwann cell plasticity during peripheral nerve regeneration. Sciatic nerve crush or transection has been used to study axon regrowth and remyelination in genetically altered mice, which has led to the identification of a multitude of factors controlling these processes. In the future it will be crucial to fully understand the function of each individual pathway and how they cooperate to enable nerve regeneration.

It has become clear, that the generation of the repair Schwann cell is not merely a passive de-differentiation or "going backwards" in development, but an active process, which is dependent on the AP1 transcription factor c-Jun (Arthur-Farraj et al., 2012; Jessen and Mirsky, 2016). Just as important as the generation of a proliferating, motile repair cell upon injury is the re-differentiation of this cell into a mature (or Remak) Schwann cell once it comes to remyelination. In contrast to Schwann cells lacking c-Jun, Zeb2-deficient Schwann cells are still able to form repair cells, however, in accordance with our data in development, they constantly show high mRNA expression levels of maturation inhibitors and their re-differentiation to mature myelinating cells is impaired. The resulting failure of nerve regeneration substantiates the importance of the silencing of transcription factors, which are needed to successfully activate the repair process, but at the same time, prevent remyelination (*e.g.*, c-Jun, Sox2, Pax3 and Id2).

Induction of the repair mechanisms in Schwann cells leads to an adaptive cellular reprogramming (Jessen et al., 2015) of mature cells upon nerve injury, which is extremely interesting in regenerative medicine and peripheral neuropathy research. Understanding common molecular control mechanisms involved in both, developmental differentiation and regeneration after trauma or in peripheral neuropathies, will be valuable to develop new therapeutic strategies. However, one major challenge is the complexity of the regulatory network.

In addition, more research is needed in the analysis of transcription factors expressed in the neural crest and in developing Schwann cells and their possible role in Schwann cell plasticity after injury. As direct repression of maturation inhibitors is evolving as a novel concept in Schwann cell development and nerve regeneration, transcriptional inhibitors are moving into the focus. One way of identifying possible candidates of interest is to look at genes causative of human neurocristopathies, diseases characterized by malformations of neural crest derivatives. Patients carrying mutations in one of the two alleles of Zeb2 suffer from one of these rare disorders, Mowat-Wilson-Syndrome (Mowat et al., 1998). Notably, mutations in the Sox10 gene also lead to a neurocristopathy, Waardenburg syndrome (Bondurand et al., 2007). Recent data suggest that transcriptional repression by Zeb2 poses a counterpart to the transcriptional activator Sox10 during Schwann cell maturation (Quintes et al., 2016; Wu et al., 2016).

Another possibility is looking at physiological or patho-

logical processes known to require cellular reprogramming, such as the epithelial-to-mesenchymal transition (EMT), a process in which mature, stationary cells regain properties of immature cells such as the ability to migrate and loss of cell-cell contacts (Baum et al., 2008; Conidi et al., 2011). These massive phenotypical changes can be compared to the processes characterizing Schwann cell plasticity and adaptive cellular reprogramming after injury (Jessen et al., 2015). Zeb2 plays a pivotal role in EMT during tumor metastasis by repressing E-cadherin expression (Comijn et al., 2001). The analysis of Zeb2 function in Schwann cells thereby examplifies that by analyzing genes involved in rare diseases or cell type transitions new insights can be obtained for Schwann cell development and adaptive changes occurring during somatic healing. Moreover, specific inactivation of Zeb2-mediated transcriptional repression in Schwann cells also allowed the identification of novel inhibitors of myelination, such as the downstream effector of Notch signalling Hey2 (Quintes et al., 2016; Wu et al., 2016).

Transcriptional regulators are highly interesting as potential therapeutic targets, however, one enormous challenge for any future treatment trials will be to reach a finely tuned balance between proliferation and differentiation. It may prove too difficult to pharmacologically regulate the transcription factors themselves, because of their actions as activators or repressors depending on the regulated gene. In addition, unknown downstream targets may cause unwanted side effects. In the case of Zeb2, simultaneous activation of genes related to maturation and myelination cannot be excluded at the moment and additional direct and epigenetic mechanisms of gene silencing in the Schwann cell lineage remain to be elucidated. For therapeutic purposes, it may thus be more promising to focus on single downstream targets. Endothelin receptor antagonists have been used for the treatment of pulmonary hypertension and could be tested in models of nerve injury or peripheral neuropathies.

Some genes re-expressed in Schwann cells after acute nerve injury may also be involved in long-term maintenance of the repair capacity, which holds implications for nerve trauma, where regeneration of severed axons may take years, and peripheral neuropathies where Schwann cells are in a chronically de-differentiated state. Recently, the transcription factor Stat3 was identified to play a major role in long-term denervation by not only supporting the survival of long term denervated Schwann cells, but also maintaining their repair capacity (Benito et al., 2017).

Finally, any future therapeutical approach will have to be carefully timed in order to potentiate regenerative capacity of Schwann cells and at the same time prevent overproliferation and tumor development.

Author contributions: *SQ and BGB drafted, revised and accepted the final version of the manuscript.*
Conflicts of interest: *None declared.*
Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewer: *Patrick Küry, Heinrich-Heine-Universitat Duesseldorf, Germany.*
Additional file: *Open peer review report 1.*

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