

# Chromatin-remodeling enzymes in control of Schwann cell development, maintenance and plasticity

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Gene regulation is essential for cellular differentiation and plasticity. Schwann cells (SCs), the myelinating glia of the peripheral nervous system (PNS), develop from neural crest cells to mature myelinating SCs and can at early developmental stage differentiate into various cell types. After a PNS lesion, SCs can also convert into repair cells that guide and stimulate axonal regrowth, and remyelinate regenerated axons. What controls their development and versatile nature? Several recent studies highlight the key roles of chromatin modifiers in these processes, allowing SCs to regulate their gene expression profile and thereby acquire or change their identity and quickly react to their environment.

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## Introduction

SCs originate from neural crest cells that also give rise to other cell types including sensory neurons, chondrocytes, melanocytes, smooth-muscle cells [1,2]. After specification in SC precursors, the lineage further differentiates into immature SCs that encircle bundles of axons of different calibers. Next, big caliber axons are sorted in a one-to-one relationship with SCs by a process called radial sorting which leads to the promyelinating stage. The last step of maturation is the myelination process where SCs build a thick myelin sheath rich in lipids around axons (Figure 1). Meanwhile, small caliber axons remain in bundles associated with non-myelinating SCs and persist as Remak bundles in adult nerves [3,4]. Myelin provides axonal insulation and fast conduction of electric signals along axons; its formation and maintenance are thus critical for neuronal functions. By contrast, myelin is detrimental for axonal regrowth after lesion,

because it contains growth inhibitory proteins [5]. However, SCs react quickly to an axonal lesion by dedifferentiating, digesting their own myelin — a process called myelinophagy [6] — and converting into repair cells [7,8] that foster axonal regrowth and guide axons back to their former target [9,10]. SCs then remyelinate regenerated axons (Figure 2). This remarkable SC plasticity allows the PNS to functionally regenerate after lesion.

This review is focused on the mechanisms of SC development, maintenance and plasticity after lesion controlled by chromatin-remodeling enzymes. Chromatin remodeling regulates the accessibility of genes for the transcriptional machinery, and thereby gene activation and repression. Changes of chromatin architecture are controlled by ATP-dependent nucleosome remodeling and by covalent modifications, either on DNA by methylation or on histones by various post-translational modifications including acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, ADP-ribosylation. Although our knowledge on these mechanisms is still very sparse, recent findings on the functions of chromatin-remodeling enzymes have significantly contributed to a better understanding of their critical functions in SCs.

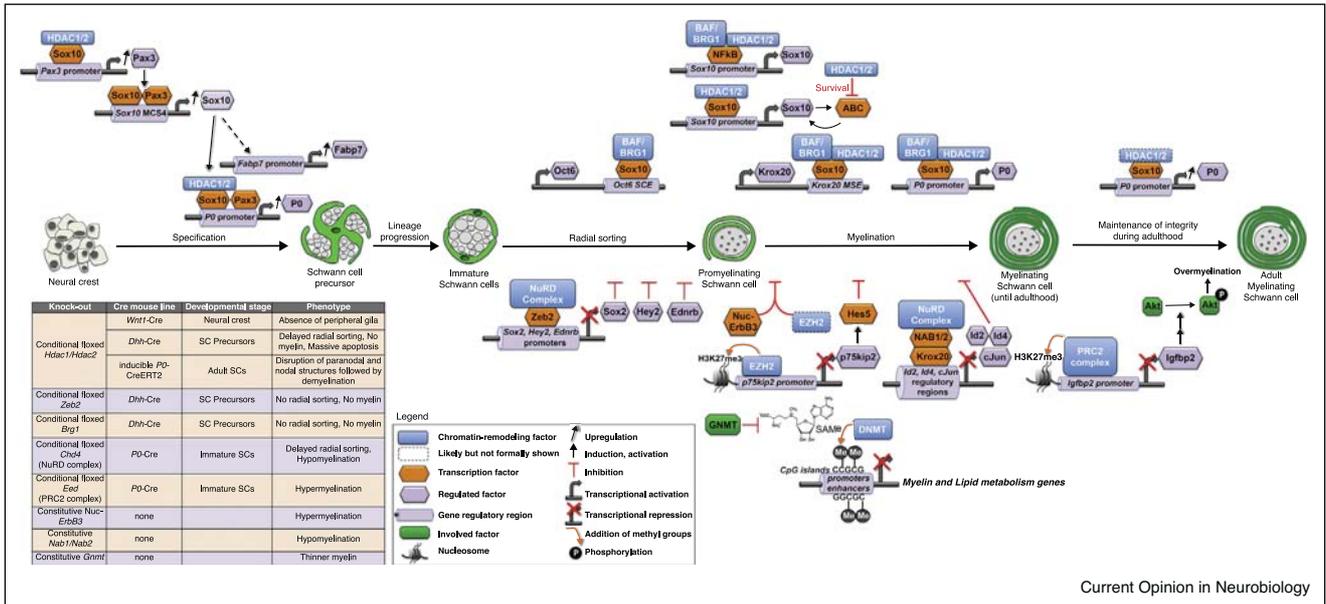
## Chromatin-remodeling factors controlling SC development, maintenance and plasticity after lesion

Nucleosome-remodeling complexes, DNA methylation/demethylation, histone acetylation/deacetylation and methylation/demethylation enzymes have been shown to hold key functions in SCs (Figures 1 and 2).

### Nucleosome-remodeling complexes

Nucleosome-remodeling complexes use ATP to destabilize the interaction between DNA and histones. This local chromatin destabilization results in nucleosome sliding and repositioning that can also lead to adjacent nucleosome ejection or insertion. These changes of chromatin structure modify DNA accessibility, and can lead to either transcriptional activation or repression. Nucleosome-remodeling complexes are classified into different families, based on their composition and activity: SWI/SNF, ISWI, INO80/SWR1 and NuRD complexes [11]. Among those, the SWI/SNF and the NuRD complexes are known to regulate aspects of SC development and plasticity after lesion (Figures 1 and 2). Two subtypes BAF and PBAF of SWI/SNF complexes are known; they owe their enzymatic activity to their ATPase subunit BRM or BrG1 [12]. The NuRD complex comprises

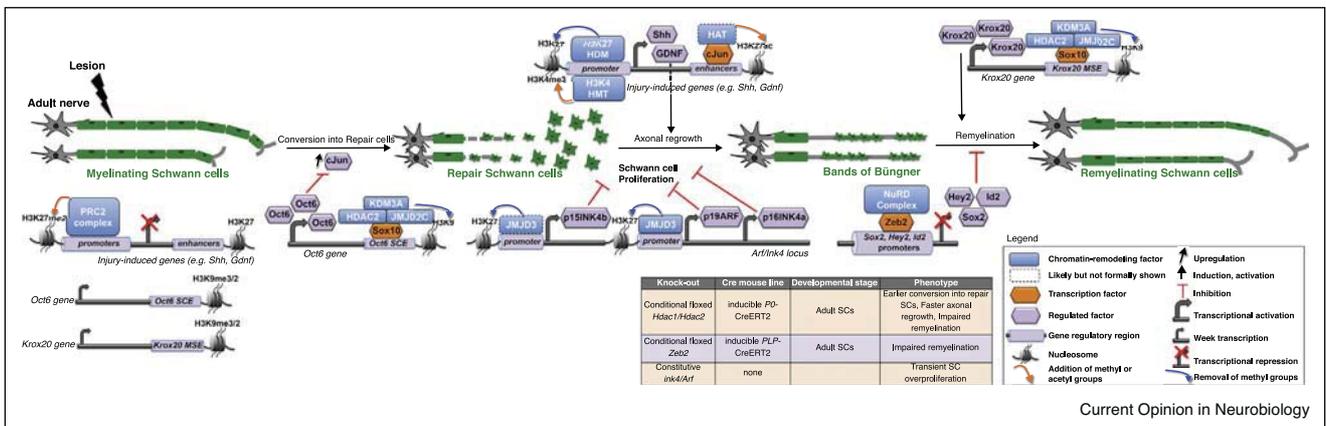
Figure 1



Current Opinion in Neurobiology

Chromatin-remodeling enzymes and associated mechanisms regulating SC development and maintenance. Activating mechanisms are depicted above and inactivating mechanisms underneath SC stages. The table lists mouse mutants and their phenotypes used to identify these mechanisms.

Figure 2



Current Opinion in Neurobiology

Chromatin-remodeling mechanisms regulating SC plasticity after lesion. Activating mechanisms are depicted above and inactivating mechanisms underneath regeneration stages. The table lists mouse mutants and their phenotypes used to identify these mechanisms.

CHD3 or CHD4 as ATPase subunit, and has in addition deacetylase activity by the recruitment of HDAC1 and HDAC2 [13].

### DNA methyltransferases (DNMTs)

DNMTs transfer a methyl group from a methyl donor, generally S-adenosylmethionine (SAMe) to the carbon 5 of cytosines located within CpG dinucleotides [14]. Most CpGs in mammalian genomes are maintained

methylated across generations by DNMT1. By contrast, CpG islands in promoters and enhancers often remain unmethylated through active DNMTs exclusion. This usually requires recruitment of a transcription factor and other partners such as histone H3 lysine 4 (H3K4) methyltransferases (HMTs), a TET dioxygenase and a thymidine DNA glycosylase that erase/prevent methylation. Promoter silencing can however occur through *de novo* methylation at CpG islands by DNMT3A or DNMT3B,

and is usually preceded by repressive H3K9 methylation marks. Interestingly, in the case of very low availability of methyl donor, DNMT3A/B cannot methylate CpGs, but in contrast have been reported to actively participate in DNA demethylation [15].

#### Histone acetylation and deacetylation enzymes

Histone acetyltransferases (HATs) add acetyl groups to lysines of histone tails, which loosens the attraction between histones and DNA and results in chromatin decompaction that facilitates the access for the transcriptional machinery. By contrast, HDACs remove these acetyl groups, which leads to a more condensed chromatin that restricts DNA access [16]. HATs are thus commonly thought to act as transcriptional co-activators, whereas HDACs as transcriptional co-repressors. However, several studies have shown that HDACs can also participate in transcriptional activation [17–19]. HATs and HDACs cannot bind DNA directly and thus need a DNA-binding partner to modify histones. In addition, these enzymes can acetylate and deacetylate and thereby control the activity of non-histone targets including several transcription factors [20]; they are thus very powerful transcriptional regulators. Eighteen known mammalian HDACs are subdivided into four classes, based on their structure [21]. HDAC1 and HDAC2, two highly homologous class I HDACs that can usually compensate each other's functions, have been extensively studied in SCs.

#### Histone methylation and demethylation enzymes

HMTs catalyze the addition of methyl groups to target residues, whereas histone demethylases (HDMs) remove these methyl groups. Histones can be methylated on the three basic residues K, arginine (R) and histidine (His), although His methylation is rare. Activating methylation marks are located on H3K4, H3K36, H3K79, H3R17 and H3R26, and repressive methylation marks on H3K9, H3K27, H4K20 and H3R8, whereas methylation of H3R2 and H4R3 leads either to transcriptional activation or repression, depending on the exact location of the methyl group. There are several families of HMTs and K HDMs, but the existence of R HDMs is not clear [22].

#### Functions of chromatin-remodeling enzymes in SC development and maintenance of PNS integrity

SC development from specification of the lineage to terminal differentiation into myelinating cells and maintenance of myelination require transcriptional activation of genes that induce lineage differentiation and acquisition and maintenance of cell stage identity. HDAC1 and HDAC2 (HDAC1/2) and the BAF complex hold major functions in these processes. For differentiation to proceed, inactivating inhibitory mechanisms of SC differentiation is also necessary. In addition, preventing overmyelination is required for stable myelination and optimal nerve conduction. The NuRD complex as well

as DNA and histone methylation regulate these mechanisms. Current knowledge on this topic is discussed below and summarized in Figure 1.

#### HDAC1/2 control SC lineage specification

The transcription factor Sox10 is essential for SC lineage specification and the entire SC developmental process [23]. However, Sox10 is expressed in all neural crest cells. Thus, additional mechanisms direct Sox10-dependent specification into the SC lineage. Indeed, ablation of HDAC1/2 in neural crest cells by crossing *Hdac1/2* floxed mice with mice expressing the Cre recombinase (Cre) under control of the *Wnt1* promoter (*Wnt1*-Cre) prevents peripheral glia specification [24]. We show that HDAC1/2 and Sox10 interact to activate the promoter of the early lineage marker *Myelin protein zero* (*P0* [25]) and of *Pax3*, another key transcription factor for SC specification [26,27]. In turn, *Pax3* and Sox10 activate the *Sox10* MCS4 enhancer (also called U3 [28,29]) to maintain high levels of Sox10, which induces expression of *P0* and *Fatty acid binding protein 7* (*Fabp7*), another early peripheral glia marker [30].

#### HDAC1/2 regulate radial sorting, SC survival, induction and maintenance of myelination

HDAC1/2 have also essential functions at later developmental stages and in the maintenance of integrity in adult nerves. Ablation of HDAC1/2 in SC precursors (by crossing *Hdac1/2* floxed mice with mice expressing Cre under control of the *Dhh* promoter) leads to radial sorting delay and virtual absence of myelin, followed by massive SC apoptosis [31]. We showed that HDAC1/2 maintain SC survival by limiting active-beta-catenin (ABC) levels and that they interact with Sox10 to activate the *Sox10* and *P0* promoters and the *Krox20* MSE (myelinating SC element [32]), a critical enhancer for expression of the major transcription factor of SC myelination *Krox20* [33]. In adult SCs, ablation of HDAC1/2 (using the tamoxifen-inducible CreERT2 under control of the *P0* promoter) leads to disruption of paranodal and nodal structures, followed by moderate demyelination due to 50% loss of *P0* expression, presumably caused by impairment of Sox10-mediated activation of the *P0* promoter [34]. Chen *et al.* [35] also showed that HDAC1/2 interact with the transcription factor NFkB to activate the *Sox10* promoter in SCs during developmental myelination. However *in vivo* NFkB inactivation leads to minor effects on myelination [36], therefore this mechanism may have a minor control over *in vivo* myelination.

#### The BAF complex ATPase BrG1 is required for radial sorting and myelination

Ablation of BrG1 in SC precursors (using floxed *Brg1* and *Dhh*-Cre mouse lines) prevents radial sorting and myelination [37,38]. Limpert and colleagues (2013) show that BrG1 interacts with NFkB to activate the *Sox10* promoter and suggest that this mechanism controls BrG1-dependent SC

myelination [37]. However, given the minor effect of *in vivo* NFκB inactivation on myelination [36], BrG1 interaction with NFκB is likely to have minor functions on SC myelination. Furthermore, while Sox10 levels are moderately [37] or not [38] affected in the absence of BrG1 in SCs, Oct6, Krox20 and P0 are virtually absent. Indeed, the BAF complex is recruited by Sox10 to the *Oct6* SCE (SC enhancer [39]), the *Krox20* MSE and the *P0* promoter to induce Oct6, Krox20 and P0 expression [38–40], and thereby controls the myelination process.

### The NuRD complex regulates radial sorting and myelination

As mentioned earlier, Krox20 is a major transcription factor of SC myelination, which is absolutely required for the activation of myelin genes and the production of peripheral myelin [33]. Interestingly, Krox20 can also act as a transcriptional repressor. Indeed, Krox20 can interact with the transcriptional repressors NAB1/2, which recruit the NuRD complex to silence expression of inhibitors of myelination including *Id2*, *Id4* and *cJun* at a late myelination stage [41–43]. Consistently, ablation of the NuRD complex ATPase CHD4 in immature SCs (using floxed *Chd4* and *P0*-Cre mouse lines) leads to increased expression of inhibitors of myelination and to hypomyelination [43]. Ablation of CHD4 also leads to delayed radial sorting [43]. At this earlier developmental stage, the NuRD complex may allow radial sorting by silencing the transcription of *Sox2*, *Hey2* and *Ednrb* [44<sup>••</sup>,45<sup>••</sup>], other inhibitors of SC differentiation, together with the transcription factor *Zeb2*. Indeed, *Zeb2* has been shown to recruit the NuRD complex in SCs [44<sup>••</sup>] and ablation of *Zeb2* in SC precursors (using floxed *Zeb2* and *Dhh*-Cre mouse lines) leads to upregulation of *Sox2*, *Hey2* and *Ednrb* and prevents radial sorting and myelination [44<sup>••</sup>,45<sup>••</sup>]. However, ablation of *Zeb2* results in a more severe phenotype as compared to ablation of CHD4 [43], suggesting that *Zeb2* acts also through CHD4-independent mechanisms. Alternatively, the different levels of phenotype severity between *Zeb2* and *Chd4* mutant mice could be due to the different Cre mouse lines used to generate these mutants.

### DNA demethylation adjusts myelin thickness

DNA demethylation of selected genes appears necessary for appropriate developmental myelination. Indeed, DNA demethylation at promoters and enhancers of myelin genes (*Mbp*, *Pmp22*, *Prx*, *Cnp*), transcriptional regulators of myelination (*Lgi4*, *Nab1*, *Nfatc1*) and lipid metabolism genes (*Scap*, *Srebf1*, *Hmgcr*, *Mvk*, *Pmvk*, *Dgat1*, *Lipe*, *Scd1*, *Abca2* and *Elov17*) correlates with upregulation of these genes during myelination [46<sup>••</sup>]. Simultaneously, expression of DNMTs decreases and expression of *Gadd45a* (growth arrest and DNA damage 45a), *Gadd45b*, and *Apobec1* (apolipoprotein B mRNA editing enzyme catalytic subunit 1), which promote DNA demethylation [47], increases [46<sup>••</sup>]. The principal methyl donor SAME

is converted into S-adenosylhomocysteine and N-methylglycine by Glycine N-methyltransferase (GNMT, [48]). Ablation of GNMT impairs this conversion and thus increases the availability of SAME, which results in a thin myelin phenotype in constitutive *Gnmt* mutant mice [46<sup>••</sup>,48]. These data provide further evidence that DNA demethylation of myelin-related genes allows SCs to build myelin sheaths of appropriate thickness during development.

### Involvement of repressive histone methylation marks in regulating myelination

Other repressive mechanisms mediated by H3K27me3 marks on gene promoters have been reported during the myelination process. Ness and colleagues (2016) identify Nuc-ErbB3, a nuclear variant of ErbB3, as a DNA-binding protein that promotes H3K27me3 at gene promoters presumably by activating the HMT EZH2. This study reports that loss of Nuc-ErbB3 (constitutive mouse mutant) leads to developmental hypermyelination [49]. Consistently, ablation of the PRC2 subunit *Eed* in immature SCs (using floxed *Eed* and *P0*-Cre mouse lines), that leads to inactivation of the PRC2 complex (mediating H3K27me3 through its HMT EZH2), results in hypermyelination in adults [50<sup>•</sup>]. This is due to impaired repression of *Igf1p2* that maintains the activation of Akt-dependent myelination [50<sup>•</sup>]. However, no defect in developmental myelination occurs in *Eed* mutants [50<sup>•</sup>]. A third study conducted in SC cultures proposes that loss of EZH2 leads in contrast to the inhibition of the myelination process through impaired inactivation of *p75kip2* transcription that promotes expression of the inhibitor of myelination *Hes5* [51]. These inconsistencies need to be resolved with additional *in vivo* studies.

### Functions of chromatin-remodeling enzymes in SCs after lesion

Regenerative properties of the PNS after lesion are to a large extent due to the plasticity of SCs that first de-differentiate and convert into repair cells in response to injury to foster and guide axonal regrowth, and second re-differentiate to remyelinate regenerated axons [3,5,7,10]. These different key steps of the regeneration process involve the dynamic regulation of many genes and thus the timed action of several transcription factors, which are known to promote either SC de-differentiation or re-differentiation after lesion. In comparison, our knowledge on the functions of chromatin-remodeling enzymes and their coordinated action with transcription factors after lesion is just emerging with recently published studies that are discussed below and illustrated in Figure 2.

### HATs, HDACs, HMTs and HDMs control the conversion into repair cells, their cell cycle and functions after lesion

In adult nerves, injury-induced genes are silenced by the PRC2 complex, which adds repressive H3K27me3 marks

at their promoter [52<sup>\*</sup>]. Upon injury, these genes are depressed by H3K27 demethylation and activated by H3K4 methylation at promoter regions and by H3K27 acetylation at enhancers, the latter correlating with recruitment of the transcription factor cJun [52<sup>\*</sup>,53], a major inducer of SC conversion into repair cells [54]. This mechanism allows the expression of injury-induced genes including *Shh* and the neurotrophic factor *Gdnf* [52<sup>\*</sup>], and thus promotes axonal regrowth after lesion.

De-differentiated SCs re-enter the cell cycle after injury. To prevent SC overproliferation that could lead to tumor formation, the *Arf/Ink4* locus is de-repressed by the HDM JMJD3 that demethylates H3K27 at the promoter of *p19Arf* and *p16Ink4a* and potentially also at the *p15Ink4b* promoter. These tumor-suppressor proteins then inactivate SC proliferation [55].

Even though the conversion of SCs into repair cells after lesion is efficient, it is interesting to point out that this process is not optimal and can be improved. Indeed, shortly after injury, HDAC2 is upregulated in SCs and mediates the assembly of a protein complex with the two H3K9 HDMs KDM3A and JMJD2C and the transcription factor Sox10, which is recruited to the *Oct6* SCE to demethylate H3K9 and induce *Oct6* transcription. In turn, *Oct6* slows down the upregulation of cJun [56<sup>\*\*</sup>]. Consistently, ablation of HDAC1/2 in adult SCs (using the tamoxifen-inducible *P0-CreERT2* mouse line) or a short-term treatment with the HDAC1/2 inhibitor Mocetinostat delays *Oct6* upregulation after lesion and leads to higher and earlier cJun upregulation, earlier conversion into repair cells and faster axonal regrowth [56<sup>\*\*</sup>].

#### HDAC1/2 and the NuRD complex promote remyelination after lesion

At the remyelination stage, the same protein complex assembled by HDAC2 after lesion (described above) is recruited to the *Krox20* MSE to demethylate H3K9 and activate *Krox20* transcription [56<sup>\*\*</sup>]. *Krox20* then induces remyelination. In the absence of HDAC1/2 in adult SCs, *Krox20* expression is strongly reduced. This results in impaired remyelination [56<sup>\*\*</sup>], indicating that HDAC1/2 are necessary for the remyelination process after lesion. Of note, a short-term HDAC1/2 inhibitor treatment after lesion (during the 3 days following lesion) does not interfere with the remyelination process, but leads to faster functional recovery due to faster and more efficient axonal regeneration, as mentioned above [56<sup>\*\*</sup>], thereby identifying a novel treatment to accelerate PNS regeneration after lesion.

To enable remyelination after lesion, it is also necessary to downregulate inhibitors of myelination such as Sox2, Hey2 and Id2. Similar to its function in developing SCs, the transcription factor *Zeb2* represses the promoter of these genes in conjunction with the NuRD complex to

silence their expression and thereby allow remyelination [44<sup>\*\*</sup>,45<sup>\*\*</sup>].

## Conclusion

In summary, each step of SC development, the maintenance of integrity in adult nerves and the regeneration process after a PNS lesion are controlled by chromatin-remodeling enzymes that either modify histones, DNA or remodel nucleosomes. The recent studies discussed in this review show that several chromatin-remodeling enzymes or events act in sync to regulate one cellular process. It appears also increasingly obvious that chromatin-remodeling enzymes are often targeted to a specific set of genes through their interaction with transcription factors, and thereby act as co-factors of these transcription factors to enable the regulation of their target genes.

Although recent findings have improved our understanding of chromatin-remodeling enzymes functions in SC development, maintenance and plasticity, a lot more work — preferentially carried out *in vivo* — is necessary to fully understand their functions and mechanisms of action, resolve inconsistencies, and potentially use and control them in disease contexts. In particular, it will be of major importance in future studies to analyze the coordinated action of different types of chromatin-remodeling enzymes, and elucidate their mode of activation and recruitment to specific target genes. Mass spectrometry combined with chromatin immunoprecipitation analyses will certainly reveal instrumental to identify dynamic protein complex formation and recruitment to specific loci depending on the developmental or regeneration stage.

## Conflict of interest statement

Nothing declared.

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This study (together with [39]) shows that Zeb2 is essential for radial sorting, SC myelination and remyelination after injury. The authors show that Zeb2 represses the transcription of inhibitors of myelination including Sox2, Hey2 and Ednrb during development. During remyelination after lesion, the authors find persistence of Sox2, Hey2 and Id2 expression in Zeb2 mutant peripheral nerves.

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This study shows that HDAC2 assembles a protein complex with the two H3K9 HDMs KDM3A and JMJD2C and with Sox10 to de-repress and activate *Oct6* transcription early after a PNS lesion. This complex is subsequently recruited to the *Krox20* MSE to de-repress and activate *Krox20* transcription at the remyelination stage. The authors demonstrate that inactivating this mechanism accelerates cJun upregulation, the conversion into repair cells and axonal regrowth, but impairs remyelination. However, short-term inactivation using an HDAC1/2 inhibitor accelerates regeneration and functional recovery without impairing remyelination, thereby identifying a novel treatment to improve PNS regeneration after lesion.