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Functions of histone modifications and histone modifiers in Schwann cells

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Abstract

Schwann cells (SCs) are the main glial cells present in the peripheral nervous system (PNS). Their primary functions are to insulate peripheral axons to protect them from the environment and to enable fast conduction of electric signals along big caliber axons by enwrapping them in a thick myelin sheath rich in lipids. In addition, SCs have the peculiar ability to foster axonal regrowth after a lesion by demyelinating and converting into repair cells that secrete neurotrophic factors and guide axons back to their former target to finally remyelinate regenerated axons. The different steps of SC development and their role in the maintenance of PNS integrity and regeneration after lesion are controlled by various factors among which transcription factors and chromatin-remodeling enzymes hold major functions. In this review, we discussed how histone modifications and histone-modifying enzymes control SC development, maintenance of PNS integrity and response to injury. The functions of histone modifiers as part of chromatin-remodeling complexes are discussed in another review published in the same issue of *Glia*.

KEYWORDS

development, histone modifications, histone modifiers, injury response, maintenance of PNS integrity, regeneration, Schwann cells

1 | INTRODUCTION

Different cell types including Schwann cells (SCs), satellite glia, boundary cap cells, sensory neurons, chondrocytes, melanocytes, and smooth muscle cells originate from neural crest cells (Jacob, 2015; Woodhoo & Sommer, 2008). The first step of SC development is the specification of neural crest cells into SC precursors (SCPs), which will later generate SCs and endoneurial fibroblasts in the peripheral nervous system (PNS; Jessen & Mirsky, 2005). In addition, recent work has shown that SCPs are capable to generate melanocytes, parasympathetic neurons, mesenchymal stem cells, and adrenal chromaffin cells (Kastriti et al., 2019), thereby demonstrating multipotency capacities. Satellite glia, which are very closely related to SCs and found in dorsal root ganglia (DRG), and SCPs are generated twice during development: the first wave at embryonic day (E)11 in mouse embryos (Jacob et al., 2014) directly derives from neural crest cells and forms the SCPs of distal nerves and a subset of ventral root SCPs, while the second wave originates from boundary cap cells, themselves arising from neural crest cells, and forms the SCPs of dorsal roots and a subset of ventral root SCPs, satellite cells and DRG neurons (Maro et al., 2004). SCPs further differentiate to become immature SCs (at E13–E15 in mouse embryos), which encircle bundles of axons of different calibers and are also capable of producing factors that help to maintain their survival independently from axonal signals

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(Jessen & Mirsky, 2005). Around birth in mice, big caliber axons get sorted in a one-to-one relationship with SCs, which then wrap sorted axons one-and-a-half times without producing myelin yet. During this process called radial sorting, immature SCs further differentiate into promyelinating SCs (Nave & Schwab, 2005). The last step of the maturation process leads to two different cell types: myelinating and non-myelinating SCs. Promyelinating SCs that have sorted big caliber axons further differentiate into myelinating SCs, which build a thick myelin sheath rich in lipids around axons, while non-myelinating SCs remain associated with bundles of small caliber axons and persist throughout adulthood as Remak bundles (Jessen & Mirsky, 2005; Jessen, Mirsky, & Lloyd, 2015; Nave & Werner, 2014; Pereira, Lebrun-Julien, & Suter, 2012; Salzer, 2015).

One of the unique aspects of the PNS is its capacity for regeneration. This is in large part due to the ability of SCs to convert into repair cells to promote regeneration (Jessen & Mirsky, 2005, 2008; Jopling, Boue, & Izpisua Belmonte, 2011). Traumatic injury of the PNS and loss of axonal contact causes SCs to lose their differentiated morphology, downregulate myelin genes, upregulate some markers of the immature stage, and re-enter the cell cycle. At the same time, SCs convert into repair cells that upregulate genes and secrete factors promoting axon growth, neuronal survival, and macrophage invasion (Jessen & Mirsky, 2016). Morphologically, SCs transform into cells with long parallel processes that allow them to form regeneration tracks called bands of Büngner (Chen, Yu, & Strickland, 2007; Gordon et al., 2009; Vargas & Barres, 2007), which help guide regenerating axons to their original targets (Isaacman-Beck, Schneider, Franzini-Armstrong, & Granato, 2015). Finally, SCs re-differentiate into myelinating and non-myelinating SCs that envelop the regenerated axons to either re-myelinate them or to re-build Remak bundles in association with small caliber axons.

There are many transcription factors involved in SC developmental process, SC plasticity and regenerative capacity after lesion (Jacob, 2015, 2017; Jessen & Mirsky, 2019a, 2019b; Sock & Wegner, 2019; Stierli, Imperatore, & Lloyd, 2019; Svaren & Meijer, 2008). Among those, the promyelinating factors Sox10, Oct6, and Krox20 (also known as Egr2) have major functions in the myelination and remyelination processes (Weider & Wegner, 2017). Sox10 is expressed in neural crest cells and is required for each step of SC development, for the maintenance of PNS integrity and for remyelination after lesion (Bremer et al., 2011; Britsch et al., 2001; Finzsch et al., 2010; Frob et al., 2012; Jessen & Mirsky, 2005; Kuhlbrodt, Herbarth, Sock, Hermans-Borgmeyer, & Wegner, 1998; Paratore, Goerich, Suter, Wegner, & Sommer, 2001). Sox10 has the ability to upregulate its own expression and induces the expression of Oct6, which plays an important role in the differentiation process from promyelinating to myelinating cells (Bermingham Jr. et al., 1996; Jaegle et al., 1996); Sox10 and Oct6 together activate the expression of Krox20, which in turn activates the expression of myelin genes together with Sox10 and is thus essential for myelination (Ghislain et al., 2002; Kuhlbrodt et al., 1998; Topilko et al., 1994). After an injury, a different set of transcription factors controls SC demyelination and conversion into repair cells (Jessen & Arthur-Farraj, 2019). Among those, cJun is a master inducer of the switch into the repair phenotype (Arthur-Farraj et al., 2012; Gomez-Sanchez et al., 2015). Other factors such as Sox2 and Notch, which are negative regulators of SC myelination, are also involved in the regeneration process after lesion (Gökbuget et al., 2015; Parrinello et al., 2010; Roberts et al., 2017; Woodhoo et al., 2009; Wu et al., 2016).

In addition to transcription factors, a number of studies carried out in SCs have uncovered the critical roles of histone modifiers in controlling SC development, plasticity and repair programs through the regulation of transcription factor activity. Indeed, histone modifications change the architecture of chromatin by modulating the compaction of nucleosomes; this regulates the accessibility of DNA for transcription factors and the activation of their target genes, resulting in either activation or repression (Nocetti & Whitehouse, 2016; Strahl & Allis, 2000). In the histone code hypothesis, histone modifiers are the writers of histone modifications and histone readers recognize and bind these modifications, which allows the recruitment of the transcriptional machinery to the readers binding sites and thereby causes gene activation or repression. Among the many known histone readers, we can cite bromodomain proteins which bind acetylated histones, and chromobarrel and chromodomain proteins which bind some lysine-methylated histones (reviewed in Musselman, Lalonde, Côté, & Kutateladze, 2012). Histones can undergo various post-translational modifications including, for the most described modifications, methylation, acetylation, phosphorylation, ubiquitination, sumoylation, ADP ribosylation, and the less studied or recently identified modifications biotinylation, citrullination, proline isomerization, crotonylation, lysine 2-hydroxyisobutyrylation, glutamine 5 serotonylation, lysine benzoylation (Andrews, Strahl, & Kutateladze, 2016; Zhao, Yue, Li, & Li, 2019). Acetylation, ubiquitination, sumoylation, biotinylation, and crotonylation occur exclusively on lysine (K) residues, whereas methylation can occur on all three basic amino acids lysine, arginine (R) and histidine, although methylation of histidine residues is rare. Phosphorylation occurs on serine and threonine, ADP ribosylation on arginine, aspartic acid and glutamine, and citrullination converts arginine residues into citrulline. Acetylation and methylation are the modifications that have been the most frequently studied and that have been reported in SCs. This review will thus thereafter focus on the functions of these modifications in SC biology.

2 | HISTONE ACETYLTRANSFERASES (KATS) AND HISTONE DEACETYLASES (HDACS)

KATs (also known as HATs) are enzymes that add acetyl groups to lysine residues of histone tails, which leads to less condensed chromatin and promotes the access for the transcriptional machinery. HDACs are chromatin-remodeling enzymes that can remove acetyl groups from histone tails (de Ruijter, van Gennip, Caron, Kemp, & van Kuilenburg, 2003; Jacob, 2017; Michan & Sinclair, 2007). Removal of acetyl groups leads to locally more condensed chromatin that limits or selects DNA access for the transcriptional machinery. KATs and HDACs

are thus able to control transcriptional activity (Hodawadekar & Marmorstein, 2007). KATs are known as transcriptional co-activators, whereas HDACs are mostly described to act as transcriptional corepressors, although several studies have shown that HDACs can also participate to transcriptional activation (Greer et al., 2015; Jacob, 2017; Wang et al., 2009). KATs and HDACs do not bind DNA directly, they thus need a DNA binding partner, such as a transcription factor, to modify histones. In addition to modifying histones, KATs and HDACs can acetylate and deacetylate other targets including several transcription factors, and can thereby control the activity of these transcription factors (Deckert & Struhl, 2001; Greer et al., 2015; Jacob et al., 2014; Jacob, Lebrun-Julien, & Suter, 2011; Wang et al., 2009). There are several families or classes of KATs and HDACs. KATs are subdivided into five different families: Gcn5-related acetyltransferases (GNATs), the MYST (for MOZ, Ybf2/Sas3, Sas2 and Tip60)-related KATs, p300/CBP KATs, the general transcription factor KATs, and the nuclear hormone-related KATs (Carrozza, Utley, Workman, & Côté, 2003; Torchia, Glass, & Rosenfeld, 1998). HDACs are subdivided into four different classes: the classical HDACs constituted by Class I, Class II, and Class IV HDACs, which need Zn^{2+} to be active, and Class III HDACs that are NAD^{+}-dependent (de Ruijter et al., 2003; Jacob, Lebrun-Julien, & Suter, 2011). There are 18 known mammalian HDACs: HDAC1, 2, 3, and 8 belong to Class I, HDAC4, 5, 6, 7, 9, and 10 are Class II HDACs, HDAC11 is the only member of the Class IV, and Class III is constituted by seven sirtuins.

3 | HISTONE METHYLTRANSFERASES AND HISTONE DEMETHYLASES

Lysine methyltransferases and arginine methyltransferases (KMTs and PRMTs, respectively; also known as HMTs) are enzymes that catalyze the addition of methyl groups to target residues of histone tails, while histone demethylases (KDMs for lysine demethylases; also known as HDMs) remove these methyl groups from target residues. The outcome of histone methylation depends on the location of the target amino acid and in the case of arginine methylation on the exact position of the methyl group on the target residue (Dieker & Muller, 2010; Jenuwein & Allis, 2001; Tsai & Casaccia, 2019). Histone methylation marks associated with transcriptional activation are located on H3K4, H3K36, H3K79, H3R17, H3R26, and H3R42 (recently identified, Casadio et al., 2013), whereas repressive methylation marks are located on H3K9, H3K27, H3K64 (recently identified, Lange et al., 2013), H4K20 and H3R8. Methylation of H3R2 and H4R3 can also occur and leads to either transcriptional activation or repression depending on the enzyme that adds the methyl groups to the arginine residue (Pattaroni & Jacob, 2013). Methyltransferases are subdivided into three families: the SET-domain-containing proteins and DOT1-like proteins that methylate lysine residues, and the protein arginine *N*-methyltransferases that methylate arginine residues. KDMs are classified into two families, the amine oxidases and the Jumonji C (JmjC) domain-containing proteins (Pattaroni & Jacob, 2013). These two families of demethylases demethylate lysine residues and among them, some have been shown or proposed to also demethylate arginine residues (Walport et al., 2016; Zhang, Jing, Li, He, & Guo, 2019).

4 | FUNCTIONS OF HISTONE MODIFICATIONS AND HISTONE MODIFIERS IN SC DEVELOPMENT

4.1 | Acetylation and deacetylation

HDAC1 and HDAC2 (HDAC1/2) have key functions during SC development, in the maintenance of PNS integrity and in the remyelination process after lesion. These two class I HDACs are highly homologous and can efficiently compensate for the loss of each other. For this reason, the ablation of HDAC1 or of HDAC2 often does not lead to any obvious phenotype or only to a mild transient phenotype (Jacob, Christen, et al., 2011), and ablation of both HDACs is usually necessary to identify their functions. HDAC1/2 are highly expressed during SC specification and are upregulated again soon after birth in SCs of mouse peripheral nerves (Jacob et al., 2014; Jacob, Christen, et al., 2011). HDAC1/2 levels remain high during the active phase of developmental myelination and decrease when the myelination process is complete to remain expressed at low but steady levels during adulthood (Jacob, Christen, et al., 2011). We showed that HDAC1/2 are required for the specification of neural crest cells into SC precursors. Indeed, conditional ablation of HDAC1/2 in neural crest cells by crossing *Hdac1* and *Hdac2* floxed mice with mice expressing the Cre recombinase under the *Wnt1* promoter leads to the absence of peripheral glia specification and strongly reduced Sox10 and Pax3 expression (Jacob et al., 2014). In this study, we demonstrate that HDAC1/2 interact with Sox10 to activate the promoter of *Pax3*, another key transcription factor for SC specification (Auerbach, 1954; Franz, 1990; Olaopa et al., 2011). In turn, Sox10 and Pax3 activate together the *Sox10* MCS4 enhancer (also called U3 enhancer) to maintain high Sox10 levels necessary for inducing the expression of the early determinants of the SC lineage Fatty acid binding protein 7 (Fabp7) and Myelin protein zero (P0). While Sox10 seems to indirectly activate the *Fabp7* promoter, HDAC1/2, Sox10, and Pax3 are recruited to the *P0* promoter to induce its activation and the expression of P0 (Jacob et al., 2014). HDAC1/2 also hold critical functions later in development during the myelination process, as shown by radial sorting delay, absence of myelin and massive SC apoptosis in mouse mutants where HDAC1/2 have been deleted in SCs after the specification of the lineage by crossing *Hdac1/2* floxed mice with mice expressing the Cre recombinase under control of the *Dhh* promoter (Jacob, Christen, et al., 2011). Interestingly, this work allowed to identify specific primary functions for HDAC1 and HDAC2: while HDAC1 maintains SC survival in early postnatal SCs by preventing precocious increase of active beta-catenin levels, HDAC2 acts together with Sox10 to activate the transcription of *Sox10*, *Krox20* and *P0* and thereby induces the myelination program (Jacob, Christen, et al., 2011). In a similar study, Chen et al. (2011) show that the absence of

HDAC1/2 prevents SC developmental myelination and leads to low Sox10 expression in SCs, consistent with the study published by Jacob, Christen, et al. (2011). However, in contrast to the study of Jacob, Christen, et al. (2011), the study of Chen et al. (2011) does not identify a major SC apoptosis phenotype in the absence of HDAC1/2 and proposes a different mechanism of action of HDAC1/2 in SC myelination. Indeed, Chen et al. (2011) report that HDAC1/2 interact with NFkB to activate the *Sox10* promoter and thereby induce myelination. A third study (Morton et al., 2013) demonstrates however that activation of NFkB in SCs is dispensable for in vivo myelination, suggesting that the action of HDAC1/2 in promoting NFkB activity is likely to have minor functions in the myelination process.

The functions of other HDACs including HDAC3 and HDAC4 have also been investigated in SCs. The first study on HDAC3 shows that HDAC3 forms a transcriptional repressor complex together with HDAC1, HDAC2, and SC factor 1/positive regulatory domain protein 4 (SC1/PRDM4), a p75NTR-interacting zinc finger protein (Chittka et al., 2004). This complex represses *Cyclin E* transcription through the binding of SC1/PRDM4 to the *Cyclin E* promoter and causes cell proliferation arrest (Chittka et al., 2004). More recently, Gomis-Coloma et al. (2018) reported that cAMP activates the shuttling of HDAC4 from the cytoplasm to the nucleus of SCs. HDAC4 then binds to the *cJun* promoter and prevents the expression of cJun by recruiting the repressor complex NCoR1/HDAC3, thereby allowing SC differentiation and myelin gene expression. The inhibitor of SC myelination cJun is known to antagonize Krox20 expression (Parkinson et al., 2008). Gomis-Coloma et al. (2018) show that expression of constitutively active HDAC4 can on its own induce the expression of Krox20 and myelin genes. These findings suggest that HDAC3 contributes to promote the SC differentiation and myelination processes. However, this appears somewhat in contradiction with the studies of Rosenberg et al. (2018) and He et al. (2018) showing a hypermyelination phenotype when HDAC3 is ablated in SCs. Discrepancies also exist in the HDAC3 mechanism of action proposed in the two latter studies: while Rosenberg et al. (2018) report that HDAC3 allows the switch from developmental myelination to a homeostasis program that maintains myelination in adults, the work of He et al. (2018) indicates that HDAC3 directly antagonizes the myelination program. The functions of HDAC3 will therefore need to be further clarified by additional studies.

In summary, HDACs are key enzymes for SC development. Histone acetylation also seems to play a role in the SC developmental process. Indeed, Lopez-Anido et al. (2016) have shown that major enhancer regions of the myelin gene *Pmp22*, which is highly expressed in SCs, are marked by H3K27 acetylation (H3K27Ac) before birth in mouse peripheral nerves. These H3K27Ac marks prime the *Pmp22* gene for its subsequent activation by transcription factors including Sox10 and Krox20. In addition, binding motives for the TEA domain (Tead) family of transcription factors are localized in enhancer regions of *Pmp22* which are marked by H3K27Ac, and Tead1 activates *Pmp22* enhancers (as well as the *Krox20* gene) together with the co-activators Yap and Taz (Grove et al., 2017; Lopez-Anido et al., 2016), which have been shown by several independent groups to hold critical functions in the SC myelination process (Deng et al., 2017; Fernando et al., 2016; Grove et al., 2017; Poitelon et al., 2016).

4.2 | Methylation and demethylation

Histone methylation enzymes also have critical functions in the development of the nervous system (Pattaroni & Jacob, 2013). In the context of the present review, Strobl-Mazzulla, Sauka-Spengler, and Bronner-Fraser (2010) demonstrated that the H3K9 demethylase JMJD2A is essential for the specification of neural crest cells in chick embryos. Indeed, loss of JMJD2A causes depletion of neural crest specifier genes including *Sox10*, *Slug* (also known as *Snail2*), *Wnt1*, *FoxD3*, and Sox8. Chromatin immunoprecipitation analyses show that H3K9me3 marks regulate neural crest specifier gene expression and that JMJD2A binds to regulatory regions of these genes (Strobl-Mazzulla et al., 2010). In this study, Strobl-Mazzulla et al. (2010) also show that in neural crest cells *Sox10* and *Slug* gene bodies are marked by H3K36 methylation, which is a mark of actively transcribed genes. NSD3 is a H3K36 methyltransferase that catalyzes mono- and dimethylation of H3K36 and also promotes H3K36 trimethylation in gene bodies (Rahman et al., 2011). Jacques-Fricke and Gammill (2014) report that NSD3 knockdown in chick embryos during neural crest specification impairs expression of *Sox10* and *Slug*, and also of the neural plate border gene *Msx1* and the neural crest transcription factors *Sox9* and *FoxD3*. Specification of neural crest cells also requires H3K4 methylation, as shown by impaired expression of the neural crest specifier genes *FoxD3*, *Slug*, and *Twist* upon knockdown in *Xenopus laevis* of KMT2D, a KMT catalyzing H3K4 mono-, di-, and trimethylation (Schwenty-Lara, Nehl, & Borchers, 2019).

In comparison to the specification of neural crest cells, the functions of histone methylation enzymes in the specification of SC precursors has been a lot less described, except for the KMT EZH2, which catalyzes the trimethylation of H3K27, a repressive methylation mark, which, however, does not appear to be required for the specification of neural crest cells into SC precursors (Schwarz et al., 2014). Later in the developmental process, EZH2 has been reported to be necessary for SC maturation and myelin gene expression in culture (Heinen et al., 2012). In this study, Heinen et al. (2012) show that EZH2 inactivates the promoter of *p75kip2* by H3K27me3 marks, which prevents the expression of p75kip2 and p75kip2-dependent expression of Hes5 (Heinen et al., 2012), a transcriptional repressor of myelin genes (Liu et al., 2006). However, the function of EZH2-mediated H3K27 methylation in SCs does not seem critical for SC myelination in vivo. Indeed, the study of Ma et al. (2015) reports that ablation of the PRC2 subunit Eed in SCs by crossing floxed *Eed* and *P0*-Cre mouse lines, which inactivates the PRC2 complex and thus prevents EZH1/EZH2-mediated H3K27me3, does not affect developmental myelination and instead causes hypermyelination at the adult stage. In this study, the authors show that inactivation of the PRC2 complex results in impaired repression of the *Igfbp2* promoter, subsequently leading to increased expression of Igfbp2, which promotes Akt-dependent myelination. Alternatively or in addition, since

Neuregulin (NRG)1 Type 1 is a strong activator of the myelination process (Stassart et al., 2013), this hypermyelination phenotype could be due to increased expression of NRG1 Type 1 observed at 2 months of age in SCs of *Eed* mutant mice (Ma, Duong, Moran, Junaidi, & Svaren, 2018).

H3K27me3 marks have other important functions during SC maturation: nuc-ErbB3, an alternative transcript from the ErbB3 locus which binds to a specific DNA motif, has been shown to control H3K27 methyltransferase activity and total levels of H3K27me3 (Ness et al., 2016). Inactivation of nuc-ErbB3 by a point mutation disabling its nuclear localization but preserving the function of the ErbB3 receptor causes sciatic nerve hypermyelination during postnatal development and correlates with loss of H3K27me3 marks on the promoters of genes including *Sox10* and *Hdac1*, and thus with the derepression of these genes (Ness et al., 2016), likely promoting myelination.

5 | FUNCTIONS OF HISTONE MODIFICATIONS AND HISTONE MODIFIERS IN THE MAINTENANCE OF PNS INTEGRITY

The continuous dialog between axons and glial cells is fundamental for myelin formation during development, myelin maintenance and remyelination after nerve injury. In disease, axon damage is observed after myelin damage, suggesting disturbed glia–axon signaling (Nave & Trapp, 2008). Krox20 in SCs is considered, together with Sox10, as a master transcription factor for initiation, regulation, and maintenance of peripheral myelination (Topilko et al., 1994). An imbalance of Krox20 expression results in demyelination or hypermyelination that jeopardizes the stability and function of axons. During myelination, axonal NRG1 Type III regulates the expression of Krox20 and Sox10 in SCs (Bremer et al., 2011; Pereira et al., 2012), while the continuous expression of Krox20 and Sox10 in myelinating SCs is required for myelin maintenance, as shown by tamoxifen-inducible SC-specific knockouts of these genes resulting in SC demyelination (Bremer et al., 2011; Decker et al., 2006).

Once myelination ensues, myelinating SCs transition to a homeostatic state where continuous expression of myelin genes is required to a level necessary for maintenance of the myelin sheath. The regulation of Krox20 during myelin homeostasis is key to maintain the myelin structure and avoid demyelination or hypermyelination. This regulation can be achieved by histone modifications (Salzer, 2015). For instance, H3K9me3 repressive marks are enriched at the Myelinating SC element (MSE) of the *Krox20* gene and at the SC specific enhancer (SCE) of the *Oct6* gene in adult SCs (Brügger et al., 2017), maintaining lower levels of *Krox20* and *Oct6* transcription as compared to developing SCs during the active myelination phase.

Other repressive histone methylation marks such as H3K27me3 also contribute to the maintenance of the myelinating state: mature myelinating SCs exhibit H3K27me3 marks on promoters of injury-induced genes through histone methyltransferase activity of the PRC2 complex (Ma et al., 2015), one of the two Polycomb repressor complexes (the other one being PRC1). The PRC2 complex is required for initial targeting of genomic regions (PRC Response Elements or PRE), while the PRC1 complex is required for stabilizing gene silencing and underlies cellular memory of the silenced region (Veneti, Gkouskou, & Eliopoulos, 2017). EZH2, one of the two KMTs that can be found in the PRC2 complex, catalyzes the di- and tri-methylation of H3K27. In adult SCs, these histone methylation marks are enriched at promoters of genes associated with injury response (Ma et al., 2015), thereby preventing inappropriate expression of injury-induced genes.

Acetylation of H3K27, a marker of active promoters and distal gene enhancers (Ernst et al., 2011), has been found to mark active enhancers of *Krox20* and *Sox10* during myelin maintenance (Hung, Sun, Keles, & Svaren, 2015), suggesting a function of H3K27Ac in maintaining appropriate levels of Krox20 and Sox10 in adults. HDACs also play a role in PNS myelin maintenance. For instance, HDAC1/2, which are expressed at low but steady levels in adult SCs, have critical functions in maintaining the structure of the paranodes and nodes of Ranvier by modulating the expression of P0. In this case, HDAC1/2 most likely act as co-factors of the transcription factor Sox10 to activate the *P0* promoter (Brügger et al., 2015), leading to maintained expression of P0. Ablation of HDAC1/2 in adult SCs leads to the decrease of P0 expression by 50% and to motor and sensory loss of function. These findings are paralleled by severe disruption of paranodes and nodes of Ranvier, while myelination is mildly affected. In addition to ensuring the cohesion between two adjacent myelin lamellae through its homophilic adhesion properties, P0 also maintains the stability of the paranodal and nodal complexes through interaction with neurofascins (Brügger et al., 2015). Although HDAC1/2 hold critical functions in the maintenance of the PNS integrity, their expression levels are low as compared to the active phase of myelination during postnatal development (Jacob, Christen, et al., 2011). Rosenberg et al. (2018) propose a model where SCs undergo a switch from the myelin biogenesis state during developmental myelination to a homeostasis state in adults, where myelin genes are transcribed at lower level as compared to the developmental active myelination stage. In this study, the authors show that HDAC3 is an inducer of myelin gene expression (in contrast to the study of He et al., 2018), but that HDAC3 is necessary for the transition into the homeostasis stage. Deletion of HDAC3 in SCs prevents this transition and instead leads to the maintenance of myelin biogenesis by HDAC2. This eventually leads to hypermyelination followed by demyelination, and to the development of a severe peripheral neuropathy in adult mice (Rosenberg et al., 2018).

Interestingly, a recent study reports on the functions of KDM8 (also known as JMJD5)—a rarely studied KDM in neuroscience—that demethylates H3K36me2 and thereby decreases the activation of the demethylated locus. In this study, Fuhrmann, Mernberger, Nist, Stiewe, and Elsasser (2018) ablated the POZ (POxvirus and Zinc finger) domain of the transcription factor Miz1 (Myc-interacting zinc finger protein 1) in SCs, which led to the development of a peripheral neuropathy within 90 days. The authors identified KDM8 as a direct

target of Miz1, which represses KDM8 expression. Deletion of the POZ domain of Miz1 in SCs results in increased KDM8 levels and decreased H3K36me2 marks at regulatory regions of cell cycle-related genes. This induces SC hyperproliferation and the development of a late-onset demyelinating neuropathy (Fuhrmann et al., 2018).

6 | FUNCTIONS OF HISTONE MODIFICATIONS AND HISTONE MODIFIERS IN PERIPHERAL NERVE INJURY RESPONSE

The process of SC response to peripheral nerve injury involves inhibition of myelination promoting genes and activation of regeneration promoting factors (Jessen & Mirsky, 2016). In the early stages following peripheral nerve injury, the activation of injury-related genes is promoted by the removal of the repressive histone mark H3K27me3 and the gain of the active histone mark H3K4me3, at their promoter regions. At the same time, ChIP-seq analysis using H3K27Ac-marked regulatory elements identified approximately 4,000 injury-induced enhancers. Enhancers of positive regulators of myelination like Krox20 and Sox10 exhibit loss of the active histone mark H3K27Ac, while enhancers of negative regulators of myelination like c-Jun, Shh, and GDNF gain H3K27Ac (Hung et al., 2015; Ma, Hung, & Svaren, 2016; Jessen & Mirsky, 2019b).

The requirement of histone modifiers in nerve injury response has recently been investigated. The acute phase of nerve injury response is regulated by HDAC2, which coordinates the action of other chromatin remodeling enzymes to induce the upregulation of Oct6, a key transcription factor for SC development (Brügger et al., 2017). Oct6 is an intermediate inducer of myelination (Jaegle et al., 1996): it is required for timely expression of the promyelinating factor Krox20 but needs to be downregulated for myelination to proceed (Ryu et al., 2007). HDAC2 interacts directly with the transcription factor Sox10 and recruits the H3K9 demethylases JMJD2C and KDM3A to de-repress and activate the *Oct6* promoter, which results in increased expression of Oct6 and subsequently prevents early upregulation of c-Jun after lesion (Brügger et al., 2017). Consistent with this, the authors show that ablation of HDAC1/2 or of Oct6 prevents Oct6 re-expression after lesion and leads to earlier and higher upregulation of c-Jun and to faster axonal regrowth. During the remyelination phase of nerve injury response, HDAC2 and Sox10 recruit again JMJD2C and KDM3A, but this time to the Myelinating SC element (MSE) of the *Krox20* gene, de-repressing and activating the transcription of *Krox20* and thus upregulating Krox20, which mediates remyelination. Ablation of HDAC2 and its homologous protein HDAC1 prevents Krox20 upregulation and leads to impaired remyelination (Brügger et al., 2017). Interestingly, a short-term 3-day treatment after lesion with the HDAC1/2 inhibitor Mocetinostat does not impair remyelination but accelerates axonal regrowth and functional recovery (Brügger et al., 2017). In this case, HDAC1/2 do not act as histone modifying enzymes but rather as protein mediators.

Studies have also revealed the role of HDAC3 in nerve injury response. He et al. (2018) report that in the early stages following injury, HDAC3 exerts an inhibitory effect through H3K27 deacetylation, which results in the silencing of genes encoding proteins with promyelinating functions, thus acting as a transcriptional repressor (He et al., 2018). Pharmacological inhibition of HDAC3 showed enhanced myelin growth and regeneration and improved functional recovery after peripheral nerve injury in mice (He et al., 2018). In this study, animals have been treated immediately after

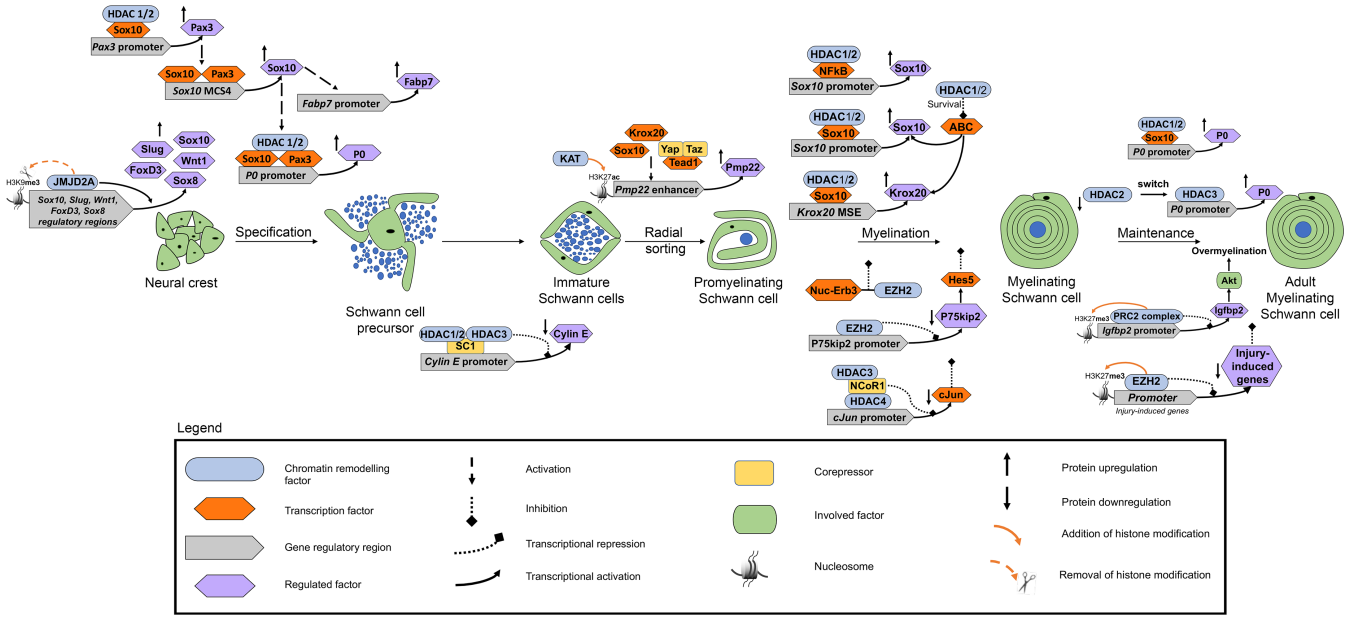

FIGURE 1 Histone modifications and histone modifiers in Schwann cell (SC) development and maintenance. Schematic representation of mechanisms related to histone modifications and histone modifiers in SCs during development and maintenance of peripheral nervous system (PNS) integrity

lesion and for several days with the HDAC3 inhibitor, leading to precocious remyelination. The relevance of such a treatment appears however unclear at this early time-point after lesion, since promoting remyelination too early is very likely to interfere with the conversion of SCs into repair cells and thus with axonal regrowth (Arthur-Farraj et al., 2012). In this context, it would be interesting to measure the levels of c-Jun early after lesion in SCs of mice treated with an HDAC3 inhibitor or where HDAC3 has been deleted. In this study, HDAC3 was shown to antagonize the myelinogenic neuregulin-PI3K-AKT signaling axis. Moreover, genome-wide profiling analyses revealed that HDAC3 represses promyelinating programs through epigenetic silencing while coordinating with p300 HAT to activate myelination-inhibitory programs that include the HIPPO signaling effector TEAD4 to inhibit myelin growth (He et al., 2018).

Recently, the role of non-coding RNAs in the regulation of gene transcription (Hawkins & Morris, 2008) has been described. First observed in doubly transformed tobacco plants, small double-stranded RNAs were shown to direct epigenetic changes such as DNA methylation to loci containing homology to the small RNA (Matzke, Primig,

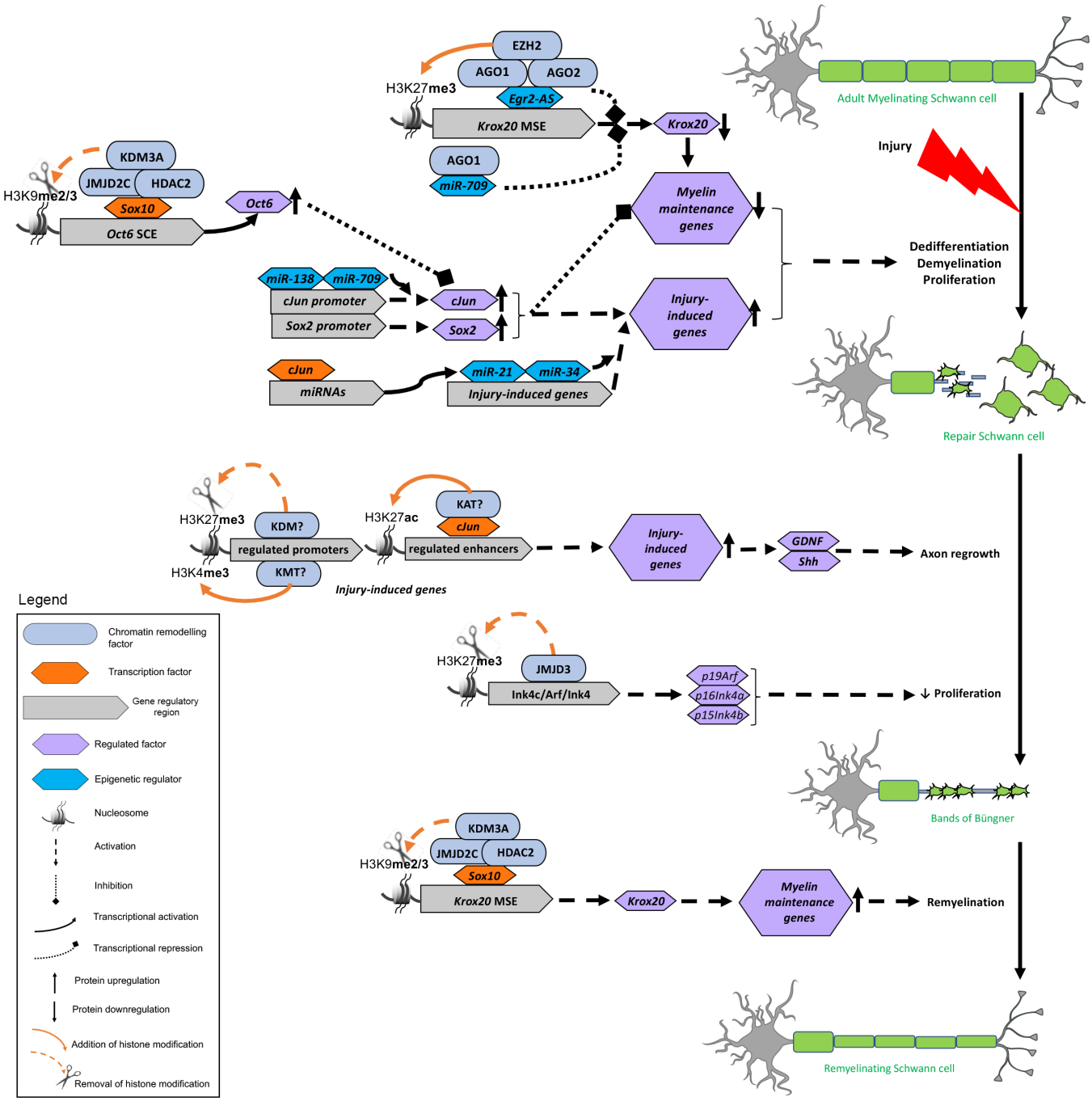

FIGURE 2 Histone modifications and histone modifiers in Schwann cells (SCs) after lesion. Schematic representation of mechanisms related to histone modifications and histone modifiers in SC response to injury and peripheral nervous system (PNS) regeneration

Trnovsky, & Matzke, 1989). The phenomenon was termed small RNA-directed transcriptional gene silencing (TGS). TGS was later shown in *Arabidopsis thaliana* to require the action of RNA-dependent DNA methylation (Mette, Aufsatz, van der Winden, Matzke, & Matzke, 2000; Wassenegger, Heimes, Riedel, & Sanger, 1994) and members of the Argonaute protein family (Lippman, May, Yordan, Singer, & Martienssen, 2003). TGS is mechanistically distinct from the abundantly studied post-transcriptional silencing pathway, which requires Argonaute 2 (AGO2) and results in cleavage of the target mRNAs (Morris, 2009a). Notably, TGS results in long-term stable epigenetic modifications that can be passed on to daughter cells (Morris, 2009b). In human cells, there are two independent mechanisms that confer TGS: (a) a miRNA-directed mechanism and (b) a long-antisense RNA mechanism (Morris, 2009b). Both short (miRNA) and long (antisense) RNA-mediated TGS in human cells involve interaction of RNA with promoter regions (Kim, Saetrom, Snove Jr., & Rossi, 2008; Klase et al., 2007; Omoto & Fujii, 2005; Tan et al., 2009). We and others (Adilakshmi, Sudol, & Tapinos, 2012; Lin, Oksuz, Svaren, & Awatramani, 2018; Viader, Chang, Fahrner, Nagarajan, & Milbrandt, 2011) have shown that a specific cohort of miRNAs controls directly or indirectly the expression of positive and negative regulators of myelination and injury response such as Krox20, c-Jun, Sox2, Nanog, ID2, p75, QKI-6 through acute post-transcriptional gene silencing after PNS injury in vivo. Although miR-138 is dispensable for myelination (Lin et al., 2018), miR-138 and miR-709 show the highest affinity for binding and regulation of Krox20, c-Jun and Sox-2 expression (Adilakshmi et al., 2012), which are the main gene regulators of demyelination and conversion into repair SCs following PNS injury (Jessen & Mirsky, 2008). We also demonstrated that miR-709 is involved in regulating transcriptional gene silencing of *Krox20* through direct interaction of miR-709 with the *Krox20* MSE, which affects nascent transcription of *Krox20*, and through the formation of silencing complexes comprising the repressive histone mark H3K27me3, AGO-1, and miR-709 recruited to the *Krox20* promoter (Adilakshmi et al., 2012). Recently, Arthur-Farraj et al. (2017) identified c-Jun and Foxd3 as potential regulators of certain miRNA in repair SCs following nerve injury. After peripheral nerve injury, the expression of a long non-coding RNA antisense to the promoter of *Krox20* (Egr2-AS-RNA) is increased and correlates with decreased *Krox20* transcript and protein levels. In vivo inhibition of Egr2-AS-RNA following sciatic nerve injury reverts the Krox20-mediated transcriptional program and significantly delays demyelination. Egr2-AS-RNA gradually recruits H3K27Me3, AGO1, AGO2, and EZH2 on the *Krox20* promoter following sciatic nerve injury to mediate inhibition of *Krox20* transcription (Martinez-Moreno et al., 2017).

Following injury, SCs demyelinate, convert into repair cells and re-enter the cell cycle. Gomez-Sanchez et al. (2013) showed that the H3K27me3 demethylase JMJD3 (also known as KDM6B) is upregulated in SCs after lesion and stimulates the activation of the Ink4a/Arf locus by demethylating the promoter regions of *p19Arf*, *p16Ink4a* and potentially also of *p15Ink4b*, which prevents uncontrolled SC proliferation that could lead to tumor formation (Gomez-Sanchez et al., 2013). These findings are further supported by the study of Ma et al. (2018) showing increased expression of p19 and p16 in sciatic nerves of SC-specific *Eed* KO mice after sciatic nerve crush injury. In this mouse mutant, the EED subunit of the PRC2 complex is ablated, which prevents PRC2 complex-dependent H3K27 methylation.

The functions of histone modifications and histone modifiers in SCs during development, maintenance, and regeneration described above are summarized in Figures 1 and 2.

7 | CONCLUSION

During the past two decades, a growing number of studies have identified critical functions of histone modifications and histone modifiers in SC biology. This area of research is very likely to expand a lot further, due to the various types of possible modifications that histones can undergo. Indeed, recent progress in mass spectrometry methods and analyses has permitted to uncover novel histone modifications at a time-point where we are still far from fully understanding the functions of the previously known histone modifications. The good news is that there is a lot more work for the next generation of scientists on this topic, thus the scientific community working on the functions of histone modifications and histone modifiers is likely to grow substantially together with our knowledge!

We already know that histone modifiers hold key functions in regulating the activity and expression of transcription factors controlling SC development and SC functions in the maintenance of PNS integrity and its regeneration after lesion. The next step will be to put into practice what we have learnt. Indeed, many small-molecule inhibitors and activators of histone modifiers are already available and represent a tremendous potential for future treatment to restore myelination or promote axonal regeneration in the context of disease or trauma. In addition, it is very likely that modulators of histone modifiers will lead to treatments for peripheral nerve sheath tumors, which are mostly due to uncontrolled SC growth. Indeed, although not covered in this review, some peripheral nerve sheath tumors have been correlated with changes in histone modifications in addition to DNA methylation. For instance, inactivation of the PRC2 complex and loss of the repressive methylation mark H3K27me3 were found in clusters of genes deregulated in cases of malignant peripheral nerve sheath tumors (Lee et al., 2014; Rohrich et al., 2016). Another challenge for the design of efficient treatments with low toxicity will be to increase the specificity of the available compounds. Indeed, the overview of the different studies on histone modifiers demonstrates specific functions for each enzyme. It is therefore of utmost importance to be able to target specifically the enzyme involved in a given process, first to understand their individual function and second to use their function in human medicine.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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