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How Histone Deacetylases Control Myelination

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Abstract Myelinated axons are a beautiful example of symbiotic interactions between two cell types: Myelinating glial cells organize axonal membranes and build their myelin sheaths to allow fast action potential conduction, while axons regulate myelination and enhance the survival of myelinating cells. Axonal demyelination, occurring in neurodegenerative diseases or after a nerve injury, results in severe motor and/or mental disabilities. Thus, understanding how the myelination process is induced, regulated, and maintained is crucial to develop new therapeutic strategies for regeneration in the nervous system. Epigenetic regulation has recently been recognized as a fundamental contributing player. In this review, we focus on the central mechanisms of gene regulation mediated by histone deacetylation and other key functions of histone deacetylases in Schwann cells and oligodendrocytes, the myelinating glia of the peripheral and central nervous systems.

Keywords Histone deacetylases · Schwann cells · Oligodendrocytes · Development · Differentiation · Myelination

Introduction

Myelin is found in the vertebrate nervous systems and in some invertebrates, although its structure is different in invertebrates [1–3]. This lipid-rich structure, conserved among species, is necessary to avoid leakage of electric signals along axons and to ensure saltatory impulse conduction [4]. The chemical composition of myelin sheaths surrounding axons of the peripheral nervous system (PNS) differs from that found in the central nervous system (CNS) [5]. The reasons for these differences are not fully understood, all the more so as myelin in the PNS and CNS has apparently similar functions [4]. One pragmatic explanation is that the two types of myelin are produced by different cell types, Schwann cells in the PNS and oligodendrocytes in the CNS, that have different development origins. Although Schwann cells and oligodendrocytes exert comparable supportive functions towards axons, these two cell types differ in many ways. A Schwann cell myelinates only a single internode of a single axon, while an oligodendrocyte can myelinate up to 50 internodes [6, 7]. Even more striking are their different regenerative properties: Schwann cells can efficiently promote axonal repair, whereas oligodendrocytes cannot. Thus, only peripheral nerves can fully regenerate after an injury [8]. This is largely due to the remarkable plasticity of Schwann cells that can dedifferentiate and redifferentiate in case of damage to foster axonal regrowth and restore myelination. While the reasons for the differences between myelinating glia in the PNS and CNS remain enigmatic, differentiation and myelination processes of Schwann cells and oligodendrocytes have been and are still extensively studied. A large network of transcriptional activators and repressors are known to control each differentiation step to reach eventually the myelinating stage [7, 9–12]. Epigenetics came only recently into place to show how this transcriptional machinery is regulated by changes in chromatin architecture. The involvement of epigenetics in the regulation of the differentiation and myelination processes in oligodendrocytes, and more recently in Schwann cells, became now a very active area of investigation. We will discuss this recent progress with a particular focus on histone deacetylases (HDACs) and their epigenetic functions and other crucial roles in myelinating glia.

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Histone Deacetylases in Brief

The mammalian members of the HDAC family are, based on their structures, subdivided into four main classes. Class I (HDAC1, 2, 3, and 8), class II (HDAC4, 5, 6, 7, 9, and 10),

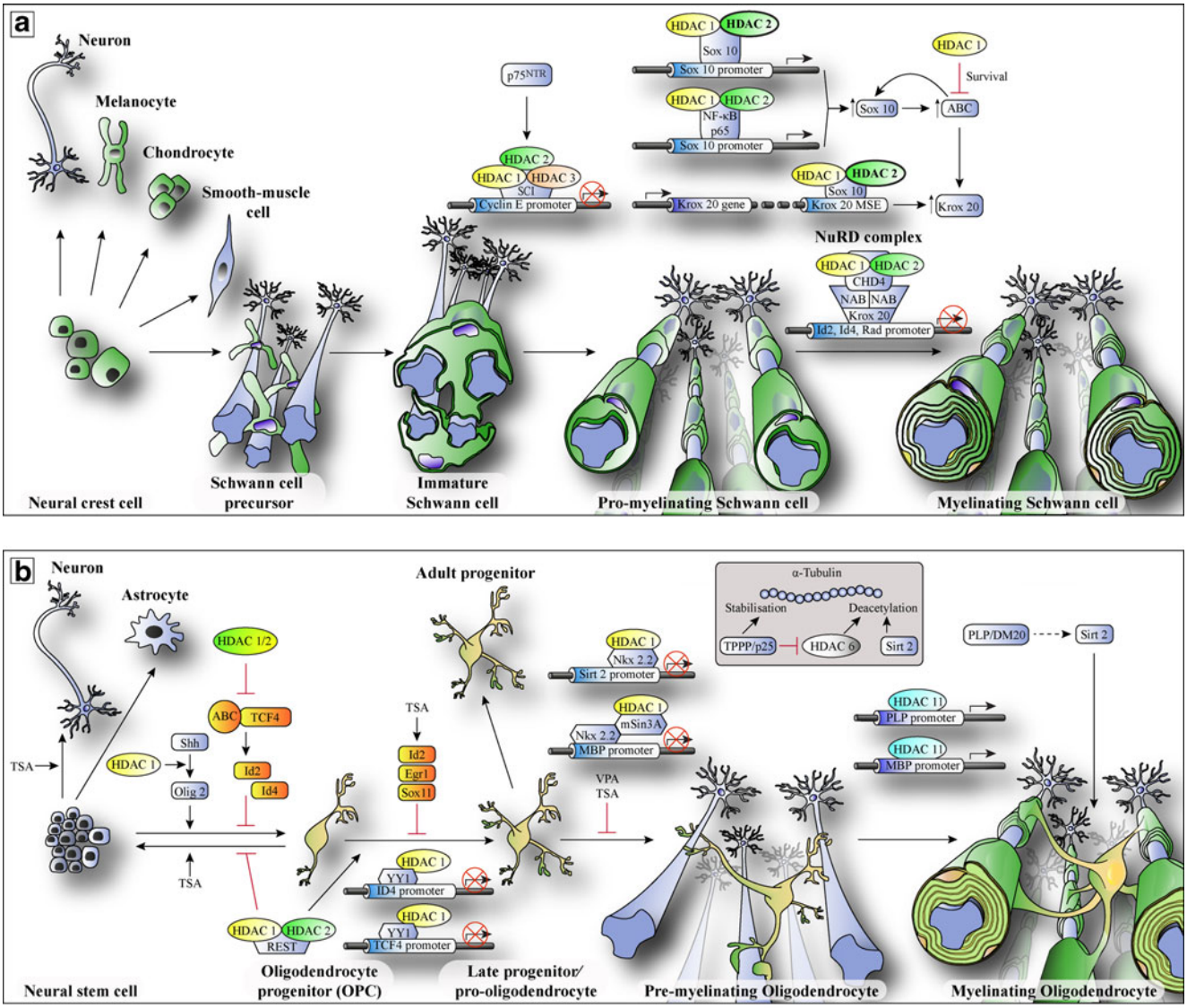

Fig. 1 HDACs control the differentiation and myelination processes of Schwann cells (**a**) and oligodendrocytes (**b**). In **a**, the *bold font* emphasizes the involvement of HDAC2 compared to HDAC1 in the depicted mechanism. In **b**, the *inset* illustrates a potential role of alpha-tubulin deacetylation mediated by HDAC6 and Sirt2, in the differentiation process of oligodendrocytes. HDAC6 appears *gray* since its expression in oligodendrocytes has not been proven in vivo. The *dashed arrow* between PLP/DM20 and Sirt2 indicates that the presence of Sirt2 in oligodendrocyte myelin is linked to PLP/DM20 expression by a yet unknown mechanism

and class IV (HDAC11), the "classical" HDACs, are structurally related and need the presence of Zn^{2+} to be active [13], whereas class III HDACs, the sirtuins (Sirt1–7), are a group of enzymes dependent on NAD^{+} and structurally unrelated to the classical HDACs [14]. Three members of this group, Sirt4, Sirt6, and Sirt7, are commonly described as part of the class III HDACs. However, these three sirtuins, as well as the variant C of HDAC9 (also called HDPR), do not exhibit deacetylase activity [15–18].

Most HDACs can remodel chromatin by the removal of acetyl groups from histone tails [13, 14]. This favors condensed chromatin architecture that limits DNA access for transcription factors. Thus, HDACs control transcriptional activity by their epigenetic functions, but also through non-epigenetic regulation [19, 20]. Indeed, HDACs can deacetylate a wide range of transcription factors, as well as other proteins, and thereby modulate their activity. In addition to their deacetylase activity, two members of the sirtuin group, Sirt2 and Sirt3, can act also as mono-ADP-ribosyl transferases [21, 22]. Two other sirtuins, Sirt4 and Sirt6, act only as mono-ADP-ribosyl transferases [15, 16], and the enzymatic activity of Sirt7 is not known [17].

Most HDACs can theoretically deacetylate histones and remodel chromatin. However, their subcellular localization is not always compatible with this function. HDAC3 and class II HDACs shuttle from the nucleus to the cytoplasm, HDAC1

and Sirt1 are mostly nuclear but under certain circumstances can be exported to the cytoplasm, HDAC6 and Sirt2 are predominantly cytoplasmic, and Sirt3 and Sirt5 belong to the mitochondrial compartment [13, 14]. In addition, Sirt4 is also found in mitochondria and Sirt7 in the nucleolus [14]. To be localized in the nucleus, HDACs need a nuclear localization signal (NLS) or a binding partner that has an NLS [13]. Similarly, the HDACs possessing a nuclear export signal can be exported to the cytoplasm [13, 23], usually by utilizing the cellular export factor CRM1 [24, 25]. Even when nuclear, HDACs do not bind to DNA directly and can deacetylate histones only within complexes through interaction with DNA-binding proteins. These protein complexes often comprise two different HDACs: HDAC1 and HDAC2, HDAC6 and HDAC11, HDAC3 and a class II HDAC, HDAC10 and a class I or class II HDAC, a class I HDAC and a sirtuin [13, 26]. What is the functional relevance of recruiting two different HDACs into the same protein complex? The activity of HDACs themselves can be regulated by acetylation and deacetylation [27], opening the possibility that one HDAC of the complex deacetylates histones, while the other HDAC regulates the activity of the first HDAC, or of another protein of the complex. Consistent with this hypothesis, Sirt1 can be recruited to the mSin3A/HDAC1 complex to modulate the histone deacetylase activity of HDAC1 [26]. However, in most cases, the significance of two HDACs in the same complex remains unknown.

Because histone deacetylation results in chromatin compaction that limits DNA access for transcription factors, HDACs are commonly seen as transcriptional corepressors acting within complexes, such as NuRD, Sin3, CoREST, NCoR/silencing mediator of retinoid and thyroid hormone receptors (SMRT), the best characterized multiprotein complexes containing class I HDACs [28]. However, recent studies show that HDACs do not always silence gene expression, but can instead participate also in transcriptional activation [29–32]. Indeed, the study of Wang et al. [30] shows that both histone acetyltransferases (HATs) and HDACs are bound to transcriptionally active genes and proposes that HDACs function to reset chromatin modification states and to maintain an adequate level of acetylation to keep genes active. In addition, low levels of HATs and HDACs are found at the promoter of primed genes, where HATs and HDACs act in concert to poise genes for further activation [30].

HDACs in Control of Schwann Cell Differentiation

Schwann cells, the myelination-competent glia of the PNS, need to undergo several steps of differentiation to reach the myelinating stage. This journey starts with neural crest cells, a stem cell population which also gives rise to other cell types including sensory neurons, melanocytes, chondrocytes, and smooth muscle cells. After the specification step into the glial cell lineage, Schwann cell precursors differentiate into immature Schwann cells that surround bundles of axons of different calibers. The next differentiation step determines whether a Schwann cell will become myelinating or non-myelinating. While small caliber axons remain in bundles associated with non-myelinating Schwann cells, large caliber axons are sorted into a one-to-one relationship with Schwann cells. This process, called radial sorting, leads to the pro-myelinating stage, where a Schwann cell forms one-and-a-half wraps around an axon, but no myelin yet. During the last differentiation step, Schwann cells produce a thick myelin sheath around sorted axons (Schwann cell development is reviewed in [9, 10]).

The process of Schwann cell differentiation is tightly regulated by intracellular and extracellular cues, and only when all necessary signals are perfectly orchestrated can peripheral nerves become fully functional. Transcription factors play a central role in this process [10]. Among the many factors involved, Sox10, Oct6, and Krox20 are major transcription factors controlling gene expression at early and/or late stages of Schwann cell differentiation. Sox10 is necessary for each differentiation step including the specification from neural crest cells to the glial cell lineage [33–37], Oct6 is important to induce the transition from the pro-myelinating to the myelinating stage [38], and Krox20 is absolutely required for PNS myelination [39]. The regulation of expression of these transcription factors is only partially understood, but includes that Sox10 and Oct6 act synergistically to induce Krox20 expression [40], while Oct6 expression depends on Sox10 and NF-kappaB [41, 42].

As for the regulation of Sox10 expression in Schwann cells, little was known until two independent but related studies identified HDAC1 and HDAC2 as positive regulators of Sox10 expression. We [31] and Chen et al. [32] deleted HDAC1 and HDAC2 in the Schwann cell lineage by crossing mice expressing the Cre recombinase under the control of *Desert hedgehog* regulatory sequences with mice carrying *floxed Hdac1* and *floxed Hdac2* genes. Both studies found that these two class I HDACs together are absolutely required for Schwann cell myelination, with HDAC1/2-double null Schwann cells being arrested at the immature or the pro-myelinating stages. In addition, we showed that concomitant depletion of HDAC1 and HDAC2 results in massive Schwann cell apoptosis, leading to complete loss of Schwann cells 2 weeks after birth. We also demonstrated that both HDACs interact with Sox10 upon induction of Schwann cell differentiation to bind to the Sox10 promoter and the Krox20 MSE (myelinating Schwann cell element). However, only HDAC2 acts in synergy with Sox10 to activate the transcription of Sox10 and Krox20, identifying HDAC2 as major regulator of the

transcriptional program of myelination. Chen et al. [32] discovered an additional mechanism regulating the Sox10 gene: HDAC1 and HDAC2 interact with and deacetylate NF-kappaB, while the NF-kappaB/HDACs complex binds to the Sox10 promoter and leads to an increase of the activating histone mark H3K4me3 (trimethylated lysine 4 of histone H3). In the absence of HDAC1 and HDAC2, NF-kappaB is acetylated by P300/CBP resulting in an increase of the repressing histone mark H3K9me3 on the Sox10 promoter. Whether and how the two mechanisms are interconnected—the one identified by us involving HDAC interaction with Sox10 and the mechanism described by Chen et al., involving HDAC interaction with NF-kappaB—remains to be elucidated.

We found also that HDAC1 limits the level of active beta-catenin (ABC), the downstream effector of the Wnt pathway, to maintain Schwann cell survival at the immature and pro-myelinating stages [31]. ABC is kept at low steady-state levels before myelination starts and increases when myelination has started, negatively correlated with HDAC1 expression. Furthermore, Sox10 increases the levels of ABC, and in turn, ABC increases expression of Sox10 and Krox20. This suggests that ABC acts as an enhancer of the myelination process after its induction, consistent with recent results that identified Wnt/beta-catenin signaling as driver of PNS myelin gene expression and myelination [43]. However, ABC signaling can be efficiently adjusted, possibly by activation of negative feedback loops, since expression of constitutively active beta-catenin in mice does not result in increased myelin thickness [32]. In contrast, inactivation of beta-catenin in mice leads to delayed myelination, further supporting a critical role of ABC in the myelination process [44].

HDAC1 and HDAC2 also play a role in Krox20/Nab2-mediated transcriptional repression of Id2 and Id4, two inhibitors of myelination, and of Rad, a gene involved in Rho signaling [45–47]. Rad inhibits Rho signaling, which controls Schwann cell migration and the length of myelinated segments [48, 49], and is downregulated during myelination [50]. The Krox20/Nab2 complex may also repress other genes, including Oct6 and myc [46]. Krox20 associates with Nab2 to repress the transcription of target genes by the recruitment of the NuRD complex containing HDAC1 and HDAC2 [45, 46]. This mechanism occurs during the Schwann cell myelination process, and its disruption leads to severe hypomyelination [51].

HDAC1, HDAC2, and HDAC3 have been implicated in repression of the cyclin E gene through interaction with Schwann cell factor 1 (SC1), a p75 neurotrophin receptor-interacting protein and member of the PR/SET (positive regulatory/suppressor of variegation, enhancer of zeste, trithorax) domain-containing zinc finger protein family [52]. Upon nerve growth factor induction, SC1 translocates to the nucleus, binds to the cyclin E promoter, and recruits HDAC1, HDAC2, and HDAC3 to repress cyclin E transcription, resulting in cell proliferation arrest. These studies have not been conducted in Schwann cells, but the expression of SC1 and $p75^{NTR}$ in Schwann cells [53] is consistent with the hypothesis that this mechanism may mediate the obligatory cell cycle exit before induction of Schwann cell myelination.

Besides class I HDACs, Sirt2, a member of the class III HDACs, is likely to be involved in Schwann cell differentiation. Sirt2 has been identified as a constitutive protein of the myelin sheath, with enrichment in paranodal regions [54].

In summary, the elucidation of functional roles of HDACs in the differentiation and myelination program of Schwann cells has recently made major steps forward. It is clear now that these proteins play a key role in Schwann cell biology. However, the studies are still at the beginning, and more work is needed to fully unravel how histone deacetylation and other central roles of HDACs orchestrate the different steps of the Schwann cell differentiation process, including the specification from neural crest cells into the glial cell lineage. In addition, our current knowledge is restricted to only a few members of the HDAC family, requiring further studies to address the functions of other HDACs expressed in Schwann cells.

Multitasking HDACs in Oligodendrocyte Differentiation

Oligodendrocytes, the myelination-competent glia of the CNS, originate from neural stem cells (or neuroepithelial precursor cells), which also give rise to neurons and astrocytes. As with Schwann cells, oligodendrocytes need to go through several steps of differentiation before producing myelin. The first step consists in the specification from neural stem cells into oligodendrocyte progenitor cells (OPCs). OPCs then progress to differentiate into late progenitors, also called pro-oligodendrocytes or oligodendroblasts. A fraction of these cells persists in the adult nervous system as adult progenitor cells, while the majority will progress into the premyelinating (or immature) oligodendrocyte stage to eventually reach the mature myelinating stage (oligodendrocyte development reviewed in [11, 55–57]). Again as with Schwann cells, the differentiation process of oligodendrocytes is controlled by a complex network of transcription factors, which differs slightly depending on the origin of the oligodendrocyte progenitor pool [12]. Among these factors, Sox9 and Olig2 are early essential transcription factors that are necessary for the specification step into the oligodendrocyte lineage [58–61]. Further differentiation also necessitates Olig2, which induces expression of Sox10, Nkx2.2, and platelet-derived

growth factor receptor (PDGFR)-alpha [62–65]. Sox9 also remains expressed and appears to have functions similar to those of Sox10 on the activation of PDGFR-alpha expression [66]. As for terminal differentiation, Olig1, Olig2, Sox10, and the recently identified myelin gene regulatory factor play major roles in the activation of myelin protein expression [61, 65, 67–69]. In order to fine-tune this transcriptional network, inhibitors of differentiation such as Id2 and Id4, Sox5, Sox6, and Hes5 prevent precocious differentiation [70–75].

Adding to this already complex network and to a large degree, overlaying it as sort of master regulators, several members of the HDAC family have been identified as central regulators of the differentiation process. Studies addressing the functions of HDACs in oligodendrocyte differentiation started with the use of the broad HDAC inhibitors trichostatin A (TSA) [76] and valproic acid (VPA) [77]. These inhibitors have a large spectrum of activity and can target virtually all classical HDACs, although VPA is considered more specific towards class I HDACs. Using these pharmacological approaches, Marin-Husstege et al. [78] showed that HDAC activity is necessary for the differentiation of OPCs in cell cultures. Later, the same group confirmed the initial findings in vivo by showing that HDAC activity is critical for the induction of myelination in the rat corpus callosum. They hypothesized that HDACs promote the myelination process in oligodendrocytes by repressing the transcription of inhibitors of myelination [79]. Once the myelination process has started in oligodendrocytes, HDAC activity is no longer required. The authors correlated these observations with an increase in the repressive histone mark H3K9me3 and with heterochromatin protein 1 (HP1)-alpha expression at later stages of postnatal development. Of note, acetylation and deacetylation of histones are dynamic and reversible modifications, whereas H3K9me3 and HP1-alpha binding occurring after histone deacetylation are more stable marks associated with heterochromatin.

Other studies using TSA demonstrated that HDAC inhibition in neural stem cells favors the neuronal fate, while inhibiting differentiation into OPCs. Furthermore, TSA is able to reprogram OPCs into neural stem-like cells capable of neurogenesis [80]. This plasticity induced by HDAC inhibition involves re-expression of the stem cell marker Sox2 by reactivation of the Sox2 promoter through chromatin decompaction. In addition, HDAC inhibition by TSA correlated with the reactivation of a dozen other genes that mark the stem cell state, and with silencing of oligodendrocyte lineage-specific genes [80]. BMP signaling is also capable of reprogramming OPCs into neural stem-like cells [81]. Since HDACs have been shown to inhibit BMP signaling in several different systems [82, 83], it is possible that HDACs favor differentiation into OPCs by inhibiting BMP signaling. However, Lyssiotis et al. [80] showed that gene expression induced by BMP2 in OPCs does not completely overlap with the effect of TSA treatment. Furthermore, TSA induces OPC reprogramming even when BMP signaling is shut off. This indicates that HDACs promote differentiation into OPCs in complex ways with other contributions unrelated to BMP signaling.

Humphrey et al. [84] reported that overexpression in neural stem cells of HDAC1, HDAC2, or HDAC3 mutants, where enzymatic activity is strongly reduced or lost, results in increased oligodendrocyte differentiation. The reasons for these surprising effects are not clear. Finally, Swiss et al. [85] established a list of "TSA-sensitive" genes during the differentiation process of OPCs into mature oligodendrocytes. Among these genes, the authors identified Id2, Egr1, and Sox11 as early targets of HDACs, regulated immediately after induction of differentiation. Indeed, these three proteins prevent oligodendrocyte differentiation and need to be silenced for induction of the differentiation process [70, 85]. Later markers of oligodendrocyte differentiation such as myelin genes were not found in this study to be regulated by histone acetylation and deacetylation [85].

In summary, the use of pharmacological HDAC inhibitors provided a proof of concept that histone deacetylation is crucial for oligodendrocyte differentiation. The next challenge was, and still partially remains, the identification of potential specific functions of individual members of the HDAC family. HDACs were primarily considered as general histone deacetylases. Although compensation may occur between closely related HDACs, an increasing number of studies are identifying specific/primary functions of single HDACs. The first targeted study was carried out in zebrafish where zHDAC1 was knocked out [86] (Note that the zebrafish harbors only one HDAC1/HDAC2-like gene called here zHDAC1). The authors show that zHDAC1 is necessary for specification of OPCs. zHDAC1-null neural stem cells continue to express Sox2 and fail to express Olig2 required for specification into the oligodendrocyte lineage. Sonic hedgehog (Shh) is normally expressed in zHDAC1 mutant hindbrain; however, the absence of zHDAC1 renders Shh signaling inefficient in inducing Olig2 expression.

OPCs can be reprogrammed in vitro into neural stem-like cells [80, 81]. The RE1-silencing transcription factor (REST) recruits HDAC1 and HDAC2 to stimulate OPC differentiation and inhibits reprogramming into neural stem-like cells [87]. The REST/HDAC complex represses several neuronal genes and thereby favors glial cell differentiation. Consistent with this, OPCs expressing a dominant-negative REST are not able to differentiate into mature oligodendrocytes and instead adopt a neuronal phenotype [87]. These findings indicate that the REST/HDACs complex is required for OPC differentiation.

Oligodendrocyte differentiation is inhibited by Wnt/ABC signaling [88–90]. Ye et al. [91] ablated both *Hdac1* and *Hdac2* simultaneously in the oligodendrocyte lineage by crossing mice expressing the Cre recombinase under control of the *Olig1* promoter with mice carrying *floxed Hdac1* and *floxed Hdac2* genes. In double mutant mice, the formation and differentiation of OPCs were severely impaired, and the ABC levels significantly increased. The authors found that TCF4 (also called TCF7L2), a member of the LEF/TCF family of proteins interacting with ABC, is a transcriptional activator of the inhibitors of differentiation Id2 and Id4 in OPCs. When HDAC1 and HDAC2 are absent, Id2 and Id4 are upregulated, while markers of oligodendrocyte differentiation (MBP (myelin basic protein) and CNPase (cyclic nucleotide phosphodiesterase)) are reduced. Consistent with previous findings [92], HDAC1 and HDAC2 compete with ABC to interact with TCF4, and TCF4/HDACs is a repressor complex necessary for oligodendrocyte differentiation. These findings suggest that HDAC1 and HDAC2 promote oligodendrocyte differentiation by disrupting the interaction of ABC with TCF4 and switching the role of TCF4 from an activator to a repressor of Id gene expression.

Oligodendrocyte differentiation is also inhibited by Notch signaling, which induces expression of the inhibitor of differentiation Hes5 [93–95]. HDAC1 has been shown to repress Notch signaling in a complex with SMRT [96, 97]. Thus, in addition to Wnt signaling, HDAC1 and HDAC2 may also negatively regulate Notch signaling to favor oligodendrocyte development. However, Ye at al. did not detect increased levels of Hes5 in double HDAC mutant OPCs, rendering this possibility unlikely [91].

Mouse genetic approaches have identified Ying Yang 1 (YY1) as an essential transcription factor for OPC differentiation and maturation in conjunction with HDAC1 [98]. Depletion of YY1 in the oligodendrocyte lineage, using mice expressing the Cre recombinase under control of the *Cnp* promoter and mice carrying a *floxed Yy1* gene, resulted in severe CNS hypomyelination. On the molecular level, YY1 recruits HDAC1 to repress the promoters of the inhibitors of myelination Id4 and TCF4 just after exit of OPCs from the cell cycle. Taken together, the data indicate that the YY1/HDAC1 complex is required in OPCs for progression of the differentiation process. As a side note, ablation of YY1 in the Schwann cell lineage resulted also in severe hypomyelination in the PNS [99]. However, this phenotype appears not to depend on HDAC functions. In Schwann cells, YY1 is a transcriptional activator of peripheral myelination that links neuregulin signaling with Krox20 expression. In the CNS, the same research group used the cuprizone-mediated demyelination–remyelination model to show that OPCs in young mice remyelinate axons more efficiently than OPCs in old mice [100]. Remyelination was accompanied by downregulation of the early progenitor markers Sox2 and Hes5 in young mice, whereas these two markers remained highly expressed in OPCs from old mice. The authors show that HDAC1 and HDAC2 are recruited to the promoters of Sox2 and Hes5 in cultured OPCs upon induction of differentiation and that this recruitment is more efficient in young mouse OPCs compared to old mouse OPCs. Furthermore, silencing of HDAC1 or HDAC2 resulted in the upregulation of Sox2 and prevented the expression of differentiation markers. These findings suggest that HDAC1 and HDAC2 promote OPC differentiation during remyelination by downregulating Sox2 and Hes5. This mechanism is age-dependent and may explain why remyelination becomes less efficient with age. Further understanding of how HDAC1 and HDAC2 are recruited to the promoters of Sox2 and Hes5 is necessary to attempt improving this recruitment for the enhancement of remyelination during aging. In addition, recently developed transgenic techniques that allow spatially and temporally regulated gene alterations of OPCs in development and regeneration are expected to be highly beneficial in advancing our knowledge [101–103].

In a different study, Wei et al. reported that Nkx2.2 recruits an HDAC1/mSin3a complex to repress the MBP promoter in immature oligodendrocytes [104]. In addition, Ji et al. found that Nkx2.2 binds to and represses the promoter of the class III HDAC Sirt2 in CG4 cells, an oligodendroglial precursor cell line, and that Sirt2 promoted the differentiation of CG4 cells [105]. These results may appear contradictory to the described functions of HDAC1 in promoting oligodendrocyte differentiation. However, it is also conceivable that tightly regulated repression of precocious differentiation may be a prerequisite to adequate oligodendrocyte lineage progression.

In contrast to HDAC1, HDAC11 (the only mammalian class IV HDAC) can activate the myelin genes MBP and proteolipid protein (PLP). HDAC11 is recruited at the last step of oligodendrocyte differentiation to the promoters of these genes to activate their transcription by histone deacetylation [106]. Although conducted in vitro, using the oligodendrocyte cell line OL-1 and primary oligodendrocyte cultures, and not yet confirmed in vivo, this study supports an important function of HDAC11 in oligodendrocyte terminal differentiation and myelination. This putative function of HDAC11 is in accordance with its expression pattern in the mouse brain, showing strong expression in oligodendrocytes that increases during postnatal development [107].

HDAC6, a class II HDAC, is known to deacetylate alpha-tubulin, thereby destabilizing microtubules and regulating cytoskeletal dynamics [108]. Although HDAC6 expression by oligodendrocytes has not yet been clearly demonstrated in vivo [109], it is tantalizing that HDAC6-mediated microtubule destabilization is inhibited by TPPP/p25 which binds to HDAC6 and stabilizes microtubules by

preventing their depolymerization [110]. TPPP/p25 plays an important role in oligodendrocyte differentiation [111] and may mediate this effect by regulating HDAC6 and microtubule organization. Similar to HDAC6, Sirt2 is also an alpha-tubulin deacetylase [112]. In oligodendrocytes, Sirt2 is targeted to the myelin sheath in a PLP/DM20-dependent fashion and has also been found in paranodes [54], where its presence coincides with that of stathmin-1 at the start of myelin formation [113]. Sirt2 and stathmin-1 are both microtubule-destabilizing proteins. Their simultaneous presence during myelin formation suggests the existence of a microtubule regulatory network, which is likely to control process extension and membrane remodeling. Consistent with this, Ji et al. [105] showed that Sirt2 overexpression increases MBP expression and process extension in CG4 cells.

Conclusion

Among the transcription factors that control the differentiation and myelination processes, some are common and have similar functions in Schwann cell and oligodendrocyte development, but many of them are different or are differentially involved in both cell types. Consistent with this notion, the HDACs regulating differentiation and myelination act through distinct mechanisms in Schwann cells and oligodendrocytes. However, despite using largely different mechanisms of action, HDACs involved in the development of myelinating cells seem remarkably determined to guide both cell types through differentiation and myelination. Understanding the precise molecular and cellular functions of the different forms of HDACs, together with the identification of their individual targets, will help in designing new therapeutic strategies for repair of the PNS and CNS in neurodegenerative diseases and after injury. One of the main challenges will be to elucidate the complex interplay between the different members of the HDAC family, their potential compensatory mechanisms, and very importantly to determine how their expression and activities are regulated. In this regard, while a growing number of HDAC inhibitors are being developed, with increasing selectivity towards individual HDACs [114], the availability of HDAC activators is nearly inexistent. Given the strong commitment of HDACs to induce differentiation of myelinating cells, the possibility to increase their expression and activity is a promising strategy to be considered towards improvement of remyelination in diseases and after injuries of the nervous system.

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