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Chromatin remodeling and epigenetic regulation of oligodendrocyte myelination and myelin repair

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A B S T R A C T

Oligodendrocytes are essential for the development, function, and health of the vertebrate central nervous system. These cells maintain axon myelination to ensure saltatory propagation of action potentials. Oligodendrocyte develops from neural progenitor cells, in a step-wise process that involves oligodendrocyte precursor specification, proliferation, and differentiation. The lineage progression requires coordination of transcriptional and epigenetic circuits to mediate the stage-specific intricacies of oligodendrocyte development. Epigenetic mechanisms involve DNA methylation, histone modifications, ATP-dependent chromatin remodeling, and non-coding RNA modulation that regulate the chromatin state over regulatory genes, which must be expressed or repressed to establish oligodendrocyte identity and lineage progression. In this review, we will focus on epigenetic programming associated with histone modification enzymes, chromatin remodeling, and non-coding RNAs that regulate oligodendrocyte lineage progression, and discuss how these mechanisms might be harnessed to induce myelin repair for treatment of demyelinating diseases such as multiple sclerosis.

1. Introduction

Oligodendrocytes (OLs) are a type of glial cell whose main function in the central nervous system (CNS) is to myelinate axons, ensuring the promotion of rapid, energy-efficient action potential propagation. A failure in myelin repair after OL damage contributes to the persistence of demyelination in debilitating diseases such as multiple sclerosis (MS) and leukodystrophies (Franklin and Gallo 2014). OLs differentiate from OL precursor cells (OPCs) that arise from multipotent neural progenitor cells (NPCs). The transition from NPCs to primitive OPCs (uncommitted OPCs, which are *Olig1/2*$^{+}$*/PDGFRa*$^{-}$), to committed OPCs (e.g., *PDGFRa*$^{+}$*/NG2*$^{+}$), to mature OLs requires a series of complex changes involving an intricate network of interactions among transcription factors and epigenetic mechanisms (Emery and Lu 2015; Zuchero and Barres 2013). Epigenetic mechanisms alter gene expression without actual changes in DNA sequence and induce subtle yet impactful regulatory influences. Epigenetic mechanisms involve histone modifications and variants, DNA methylation, ATP-dependent chromatin remodeling, and non-coding RNAs (Allis and Jenuwein 2016).

Recent studies have revealed that epigenetic regulation is critical for OPC formation, maturation, and myelination. This knowledge should guide development of strategies to foster efficient remyelination to treat demyelinating diseases such as MS and leukodystrophies. Additionally, the understanding of myelination and remyelination may have an impact on human health that extends beyond these diseases per se to regeneration. Neuronal function cannot be fully restored until regrown axons have been properly myelinated. Accordingly, visual function was restored in mice only after regrown retinal axons had been myelinated (Bei et al. 2016).

Chromatin remodeling is mainly mediated by histone modifying enzymes and ATP-dependent chromatin remodeling complexes. The histone-modifying enzymes modify the N-terminal tails of histone proteins, thereby changing chromatin structure or providing docking sites for the recruitment of specific proteins or enzymes that carry out chromatin remodeling or transcriptional regulation. Histone modifications occur on specific amino acids in histone tails and include acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, and ADP-ribosylation (Kouzarides 2007). Of these modifications, histone acetylation has been shown to regulate OL lineage progression (Marin-Husstege et al. 2002; Shen et al. 2005; Ye et al. 2009; Zhang et al. 2016). Histone acetylation states can be regulated by histone acetyltransferases (HATs; “writers”) (Marmorstein and Zhou 2014), and histone deacetylases (HDACs), the “erasers”). Histone acetylation state is recognized by bromo-, PHD-, Tudor-, and WD40-domains containing proteins (Chiang 2014; Gacias et al. 2014; Yun et al. 2011). There are four classes of HDACs in mammals, assigned based on their similarity to

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their yeast homologs and other factors: class I contains HDAC1, -2, -3, and -8; class II contains HDAC4, -5, -6, -7, -9, and -10; class III contains SIRTs 1–7, also called Sirtuins, which are NAD-dependent; and class IV contains only HDAC11 (Glaser 2007; Thiagalingam et al. 2003). ATP-dependent chromatin remodelers use energy from ATP hydrolysis to unwrap or disrupt association between DNA and histones, slide/reposition nucleosomes along DNA, exchange one histone variant for another, or to evict nucleosomes from DNA (Allis and Jenuwein 2016; Xu et al. 2013). This review provides an overview of recent studies of chromatin remodeling and epigenetic mechanisms that regulate OL lineage progression and myelination in the CNS, particularly focusing on roles of histone modifications, ATP-dependent chromatin remodeling, and non-coding RNAs.

2. Histone modifying enzymes in oligodendrocyte development

2.1. Class I HDACs in oligodendrocyte lineage development

A series of studies have utilized different HDAC inhibitors to elucidate the role of HDACs in OPC specification and differentiation (Hsieh et al. 2004; Lyssiotis et al. 2007; Marin-Husstege et al. 2002). The treatment of NPCs with the HDAC class I inhibitor valproic acid (VPA) inhibits the specification of OPCs from NPCs and enhances specification toward neuronal differentiation, likely due at least in part to the effect of HDACs on the neurogenic transcription factor *NeuroD* (Hsieh et al. 2004). Although VPA inhibits myelination when used early in OL development, it does not have an effect when utilized after the onset of myelination (Shen et al. 2005), suggesting a stage-dependent switch in HDAC regulation. HDAC inhibitors trichostatin A (TSA) and sodium butyrate decrease differentiation of OPCs and disinhibit expression of *Id2*, *Egr1*, and *Sox11* in rats and *ID4* and *SOX2* in humans (Conway et al. 2012; Swiss et al. 2011), suggesting a role of class I HDACs in promoting OPC differentiation.

HDAC1 is vital for OPC specification in zebrafish through the promotion of *Olig2* expression and downregulation of *Nkx2.2* expression (Cunliffe and Casaccia-Bonnefil 2006). Simultaneous genetic ablation of both *HDAC1* and *HDAC2*, but not of the single genes alone, in OL lineage cells inhibits OPC proliferation and subsequent differentiation in the murine CNS, suggesting functional redundancy of HDAC1/2 in mammalian OPC development (Ye et al. 2009). HDAC1, along with HDAC3 and HDAC10, deacetylates the transcription factor Olig1 to promote OL differentiation (Dai et al. 2015), suggesting a non-histone-dependent effect of HDACs in OL development. Intriguingly, in neural stem cells (NSCs), ablation of *HDAC2* in conjunction with thyroid hormone triiodothyronine (T3) treatment increases expression of OL lineage genes through derepression of Sox8 and Sox10 expression, factors that promote the OL lineage (Castelo-Branco et al. 2014a), suggesting a stage-dependent function of HDACs in specification vs. differentiation in OL lineage development. Additionally, HDAC activity can be regulated by extrinsic signaling cues. Induction of sonic hedgehog signaling in OPCs promotes differentiation at least in part through HDAC1 and HDAC2, whereas treatment with bone morphogenetic protein 4 decreases HDAC activity and thus hinders differentiation (Wu et al. 2012).

HDAC1 and HDAC2 both work with corepressors and form repressive complexes such as the Sin3, nucleosome remodeling and deacetylating (NuRD), and Co-REST complexes (de Ruijter et al. 2003). HDACs are also often recruited and interact with transcription factors to target specific genes. The transcription factor YY1 recruits HDAC1 to the promoter regions of inhibitory genes such as *Id4* to repress their expression during OL differentiation (He et al. 2007). In addition, the HDAC1/2 repressor complex can compete with β-catenin to interact with TCF7L2 (also known as TCF4), a member of the TCF transcription factor family (Ye et al. 2009). When interacting with β-catenin, TCF7L2 serves as a repressor of OL differentiation, but TCF7L2 in conjunction with HDAC1/2 allows OL differentiation to occur (Ye et al. 2009). In mice, the chemotherapy drug 5-fluorouracil causes CNS demyelination via its interaction with TCF7L2 and consequent inhibition of the HDAC1/2-TCF7L2 interaction (Weng et al. 2014).

In NSC culture, HDAC3, another class I HDAC, represses neuronal specification, thus promoting the OL lineage development (Castelo-Branco et al. 2014a). Whereas HDAC1/2-deficient OPCs do not adopt astrocytic fates, *Hdac3* deletion in the Olig1-expressing primitive OPCs (pri-OPC) leads to an increase in astrocytes with a concomitant loss of OL lineage cells, suggesting that HDAC3 functions as a molecular switch for OL and astrocyte lineage determination in the developing brain. In addition, HDAC3 appears to cooperate with acetyltransferase EP300 (also known as p300) to promote Olig2 expression and thereby prime and maintain OPC identity while inhibiting NFIA and Stat3-mediated astrogliogenesis (Zhang et al. 2016). While the roles of HDAC3 and p300 may seem conflicting, coordination between HDAC3 and p300 appears to exert activating effects with net HAT activity to initiate the transcriptional program for OPC specification (Zhang et al. 2016). In addition, HDACs may positively regulate gene transcription (Greer et al. 2015). Intriguingly, the deletion of DAD domains of both NCoR1 and SMRT in mice, which results in a lack of histone deacetylase activity in the NCoR/HDAC3 complex (You et al. 2013), does not lead to an oligodendrocyte-astrocyte fate switch and dysmyelination (Zhang et al. 2016). This suggests that HDAC3 activity is independent of NCoR1/SMRT-mediated histone deacetylation in oligodendrogenesis and that HDAC3 activity per se or HDAC3/NCoR-mediated transcriptional regulation or modification of non-histone substrates controls oligodendrocyte-astrocyte fate switching (Zhang et al. 2016).

Class II and class IV HDACs in oligodendrocyte lineage progression.

Class II HDACs only exhibit deacetylation function when recruited with class I HDACs and in complex with the SMRT/NCoR co-repressor (Fischle et al. 2000). Although both class I and class II HDACs function during tissue development, class I HDACs appear more important during brain development than are class II HDACs (Montgomery et al. 2009). It has been reported that HDAC6 is present in rat brain OLs, where it downregulates the acetylation of Tau (Noack et al. 2014), a microtubule-associated protein that is necessary for the transport of *MBP* mRNA in OLs, suggesting that HDAC6 may have a role in OL maturation and myelination (Richter-Landsberg 2016).

HDAC11 is found in both dentate gyrus granule neurons and mature OLs (Liu et al. 2008). During OL maturation in rats, HDAC11 deacetylates lysine 9 and lysine 14 of histone 3 (H3) bound to *PLP* and *MBP* myelin genes (Douvaras et al. 2016; Liu et al. 2009). Intriguingly, mechanical strain on OLs can increase levels of HDAC11 and promote OL differentiation (Jagielska et al. 2017). The specific role of class II HDACs and HDAC11 in CNS myelination in vivo requires further investigation.

Class III SIRTs in oligodendrocyte precursor cell differentiation.

SIRTs, class III HDACs that deacetylate K16 of histone 4, also play important roles in OL lineage development (Vaquero et al. 2007). In OPC specification, SIRT1 and SIRT2 have redundant functions involving nicotinamide phosphoribosyltransferase, a mammalian enzyme that catalyzes the synthesis of NAD^+ (Stein and Imai 2014). SIRT2 has been shown to deacetylate both histones and α-tubulin and to interact with HDAC6 in the myelin proteome (North et al. 2003; Roth et al. 2005). As OPCs differentiate into OLs, there is an increase of SIRT2 and α-tubulin acetylation (Li et al. 2007). SIRT2 may reduce α-tubulin acetylation in OLs and thus impede differentiation (Li et al. 2007; Tang and Chua 2008). In contrast, SIRT2 can also promote differentiation of CG4 oligodendroglial cells (Ji et al. 2011). Such conflicting roles of SIRT2 in OL differentiation should be studied further in a spatio-temporally specific manner to determine the precise mechanism through which SIRT2 regulates OL development and myelination. *SIRT2* mRNA is stabilized by the RNA-binding protein Quaking, and this stabilization promotes OL differentiation due to the sustained levels of SIRT2 (Thangaraj et al. 2017). The precise role of SIRT2 in oligodendroglial lineage differentiation and myelin maintenance remains to be