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Epigenetics in NG2 glia cells:

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Abstract

The interplay of transcription and epigenetic marks is essential for oligodendrocyte cell (OPC) proliferation and differentiation during development. Here, we review the recent advances in this field and highlight mechanisms of transcriptional repression and activation involved in OPC proliferation, differentiation and plasticity. We also describe how dysregulation of these epigenetic events may affect demyelinating disorders, and consider potential ways to manipulate NG2 cell behavior through modulation of the epigenome.

1. Introduction

NG2 glial cells are traditionally defined as oligodendrocyte progenitors (OPC) receiving synaptic inputs and with the ability to respond to a variety of extracellular stimuli by proliferating, migrating, differentiating or modulating brain homeostasis and plasticity (Barres et al., 1994a; Demerens et al., 1996; Fannon et al., 2015; Hernandez and Casaccia, 2015; Nishiyama et al., 1999; Pringle et al., 1992; Raff et al., 1983; Tsai et al., 2009; Wake et al., 2011). These biological responses result from the integration of environmental signals with the intrinsic properties of the cells. The latter ones might evolve with age as progenitors in the neonatal period show different responsiveness than their adult counterparts, in terms of their biological properties, including fate-choice decisions, proliferation, migration or differentiation rates (Chari et al., 2003; Windrem et al., 2004; Wolswijk and Noble, 1989; Young et al., 2013). It is likely that these changes result from modifications of the epigenetic landscape over time.

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Among well-defined epigenetic mechanisms this review will discuss: DNA methylation, chromatin modifications and remodeling and non-coding RNA.

DNA methylation is the only known epigenetic modification that directly modifies DNA components, by adding a methyl group at the C-5 position of cytosine residues at CpG dinucleotides (Eden and Cedar, 1994). This reaction is catalyzed by: the DNA maintenance methyltransferase DNMT1, which is responsible for the faithful transmission of DNA methylation from mother to daughter cells during replication and by the *de novo* methyltransferases DNMT3A and DNMT3B for the establishment of new methylation marks (Goll and Bestor, 2005; Lei et al., 1996; Okano et al., 1998). These enzymes are expressed in the CNS, where the DNA methylation level is higher than in any other tissues (Ono et al., 1993; Tawa et al., 1990). They have been shown to regulate survival and differentiation of neurons and astrocytes, while their role in the NG2 cells has not been thoroughly investigated (Fan et al., 2001; Noguchi et al., 2015; Takizawa et al., 2001; Wu et al., 2012b). DNA methylation at promoter regions is mainly associated with transcriptional repression, either by directly preventing the access of transcription factors to their binding sequence or by recruiting cofactors that modulate the chromatin environment (Schübeler, 2015; Smith and Meissner, 2013). Another modification of the DNA is the oxidation of 5-methylcytosine to 5-hydroxymethylcytosine (5-hmC) by the recently identified ten-eleven translocation (TET) enzymes, which are dynamically expressed in the oligodendroglial lineage (Branco et al., 2012; Tahiliani et al., 2009; Zhao et al., 2014). The low levels of 5-hmC initially found in the genome of embryonic stem cells led to the hypothesis that 5-hmC was only a short-lived intermediate associated with the removal of methyl groups from cytosine residues (Tahiliani et al., 2009). However, the abundance of 5-hmC in euchromatic regions, especially in the brain, suggested that it might also be an important epigenetic regulator of gene expression (Ficz et al., 2011; Münzel et al., 2010; Szulwach et al., 2011; Szwagierczak et al., 2010). Hydroxymethylation is characteristically enriched at gene bodies and transcription starting sites, where it has been associated with transcriptional activation and alternative splicing (Feng et al., 2015; Szulwach et al., 2011). In both human and mouse embryonic stem cells, hydroxymethylation enrichment at binding sites of pluripotency-associated transcription factors has been linked to regulation of cell lineage choice and differentiation (Ficz et al., 2011).

Histones H2A, H2B, H3 or H4 are protein components of the nucleosome, which defines the basic unit of chromatin. They can be subject to post-translational modifications including methylation, acetylation, sumoylation, phosphorylation, citrullination, ubiquitination, proline isomerization and ADP-ribosylation (Kouzarides, 2007). Addition or removal of these groups at specific amino acid residues on the tails of the histones, can either activate or repress gene expression (Jenuwein and Allis, 2001; Strahl and Allis, 2000). For example, acetylation of lysine 27 in histone H3 (H3K27ac) at active enhancers has been associated with transcriptional activation, whereas acetyl group removal by histone deacetylases (HDACs) is mainly linked to gene repression (Creyghton et al., 2010; Rada-Iglesias et al., 2011). Histone methylation marks, catalyzed by lysine-specific histone methyltransferase and arginine-specific histone methyltransferases, are also divided in two categories: methylation of lysine 4 in histone H3 (H3K4me1), usually enriched at enhancers, and dimethylation of arginine 3 in histone H4 (H4R3me2) are active histone marks, while

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trimethylation of lysines 9 or 27 in H3 (H3K9me3 and H3K27me3) are repressive marks, usually enriched in silenced genes (Di Lorenzo and Bedford, 2011; Mikkelsen et al., 2007; Shilatifard, 2006).

In addition to histone modifications, chromatin structure can also been rearranged by ATP-dependent chromatin remodelers that are characterized by nucleosomal sliding activity (Sohn et al., 2007). The SWI/SNF complex has first been identified in yeast, and several members of this family, including BRG1 (or SMARCA4) and BRM (or SMARCA2), have later been described in mammalian cells and also in NG2 cells (Bischof et al., 2015; Hargreaves and Crabtree, 2011; Ho and Crabtree, 2010; Yu et al., 2013). Chromatin remodeling has been associated to both activation and repression of gene expression (Clapier and Cairns, 2009).

Recently described non-coding RNA are another epigenetic mechanisms regulating gene expression, notably during brain development (Derrien et al., 2012; Qureshi and Mehler, 2012) and in neurological disorders (Esteller, 2011). In this family, the 20-25 nucleotide-long micro-RNAs (miRNA), which are processed by RNA polymerase II and DICER, can form a complex with Argonaute to induce mRNA silencing or degradation (Huntzinger and Izaurralde, 2011; Lee et al., 2004). By their post-transcriptional role, miRNA can affect several mRNA transcripts that are encoded at distant genome loci (Lim et al., 2005).

These epigenetic marks modify the organization or the condensation of the chromatin, thus altering its access to transcription factors and their ability to modulate gene expression (Bernstein et al., 2007; Li et al., 2007; Yao and Jin, 2014).

2. Regulation of NG2 cells proliferation

OPC proliferate in response to several mitogens, growth factors and cytokines (Barres et al., 1994b, 1996; Canoll et al., 1996; Diemel et al., 2003; Noble et al., 1988; Ohya et al., 2007), and also to electrical activity (Barres and Raff, 1993; Demerens et al., 1996; Gallo et al., 1996; Li et al., 2010). NG2 tend to proliferate more in white matter regions (i.e. corpus callosum) than in gray matter areas (Psachoulia et al., 2009; Young et al., 2013). OPC cell cycle time increases significantly with age: from a 24-48 hours duration in neonatal brains to 18 days in adult (2 month-old) and up to 70 days in aged (8 month old) murine brains (Clarke et al., 2012; Hughes et al., 2013; Psachoulia et al., 2009; Simon et al., 2011; Young et al., 2013). In addition, OPC derived from young or old brains display different degrees of responsiveness to treatment with equivalent mitogen concentrations (Lin et al., 2009; Ruffini et al., 2004; Shi et al., 1998), thereby supporting the existence of a cell intrinsic mechanism regulating proliferation which is affected by age.

2.1. Cell cycle regulation

The decision of NG2 cells to enter the cell cycle or to arrest and start differentiating, is regulated at the G_1/S transition, which is characterized by the phosphorylation of the retinoblastoma protein, and consequent release of the E2F1-mediated expression of S-phase genes (Huang et al., 2002; Magri et al., 2014a; Swiss and Casaccia, 2010; Swiss et al., 2011). The E2F family is divided into two main categories: the activating E2F1, E2F2,

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E2F3A and E2F3B, which bind exclusively to Rb, and the repressing E2F4 and E2F5, which can also interact with other members of the retinoblastoma family (e.g. p107 and p130) (Beijersbergen et al., 1994; Lees et al., 1993; Magri et al., 2014a; Swiss and Casaccia, 2010). The phosphorylation of the pocket proteins Rb, p107 and p130 is mediated by cyclin-dependent kinase (CDKs), which in turn can be activated by cyclins or inhibited by CDK inhibitors (Casaccia-Bonnefil et al., 1997, 1999; Hannon et al., 1993; Xiao et al., 1996). The cyclin E/CDK2 and cyclin D/CDK4 complexes have been identified as those responsible for cell cycle progression of NG2 cells (Belachew et al., 2002; Huang et al., 2002; Jablonska et al., 2007; Nobs et al., 2013). The detection of overall lower levels of expression of the cell cycle activating components in adult OPC compared to their neonatal counterparts, could in part explain the lower proliferative rate of adult OPC (Belachew et al., 2002; Young et al., 2013). Conversely, decreased levels of cell cycle inhibitors, such as p27Kip is associated with increased proliferation and expansion of the progenitor pool during developmental myelination and myelin repair (Casaccia-Bonnefil et al., 1997, 1999; Crockett et al., 2005; Durand et al., 1998; Tikoo et al., 1998).

E2F family proteins can be regulated by several mechanisms including lysine acetylation, arginine methylation and nuclear export. E2F1 acetylation has been described in non-oligodendroglial cell types, and associated with increased half-life, increased DNA binding and enhanced expression of target genes (Martínez-Balbás et al., 2000; Marzio et al., 2000). Although E2F1 acetylation has not been yet reported in NG2 cells it is intriguing to take into account the possibility that a histone deaceylase (i.e. HDAC1) with the ability to remove the acetyl groups from E2F1 (Marzio et al., 2000), has already been implicated as a factor that is necessary for oligodendrocyte (OL) differentiation (Marin-Husstege et al., 2002; Shen et al., 2008a). The stability of the E2F1 protein, in addition, is modulated by methylation on arginine residues by an enzyme previously shown to modulate OL differentiation *in vitro* (Huang et al., 2011) and called arginine methyltransferase 5 (PRMT5), which is expressed at high levels in progenitors and highly proliferative glioma cells (Cho et al., 2012; Zheng et al., 2013). Finally, it is important to take in consideration the fact that differentiation of NG2 cells is accompanied by E2F1 translocation from the nucleus to the cytoplasm, where it is degraded prior to reaching a late OL differentiation stage (Magri et al., 2014a). Importantly, while the levels of activating E2F family members decreases during the process of differentiation, the levels of repressive family members such as E2F4 remain constant (Magri et al., 2014a; Nygård et al., 2003; Panteleeva et al., 2007). The dynamic pattern of expression and the similarity of the DNA binding sequence for activating and repressive E2F family members in the oligodendrocyte lineage suggested a potential switch from activating to repressive protein complexes at target genes during OL differentiation (Magri et al., 2014a). Chromatin immunoprecipitation studies validated this hypothesis and revealed that E2F1 occupancy of cell cycle gene promoters (e.g. *Ccne, Ccna2, Ccnb1, Cdc20*) and epigenetic regulators (e.g. *Dnmt1, Uhrf1*) in proliferating NG2 progenitors, was replaced by E2F4-containing repressive complexes in OL (Magri et al., 2014a).

The oncogene transcription factor cMyc was also shown to be involved in cell cycle regulation of NG2 cells in response to mitogen stimulation (Dang, 1999; Magri et al., 2014b). In OPC, cMyc targeted several genes involved in cell cycle (e.g. *Cdc2* or *Cdc20),* and it was progressively down-regulated during OL differentiation (Magri et al., 2014b).

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Consistent with the ability of cMyc to recruit histone acetyltransferases and modulate acetylation of histones over large chromatin domains (Guccione et al., 2006; Martinato et al., 2008; McMahon et al., 2000), NG2 cells -characterized by high levels of cMyc – also display global histone acetylation and high levels of gene targets (Magri et al., 2014b; Marin-Husstege et al., 2002). Silencing cMyc in OPC decreased histone acetylation (e.g. H3K9Ac), while increasing repressive histone methylation (e.g. H3K9me3), and favoring the initial compaction of peripheral nuclear chromatin and associated decrease of gene expression. Downregulated genes involved those modulating the cell cycle, such as *Cdc2*, which, in cMyc-silenced OPC was associated with lower H3K9ac and H3K14ac at the promoter (Magri et al., 2014b). Based on these data, we propose that cMyc might have a dual modality of regulation of NG2 cells proliferation by acting as DNA binding transcription factors on genes bearing its consensus sequence and also as a long-range chromatin modifier regulating histone acetylation.

2.2. DNA replication

DNA replication is another critical step of the cell cycle and the fidelity of replication is maintained by checkpoints that guarantee the quality control of DNA integrity, as well as the faithful transmission of the epigenetic marks (Budhavarapu et al., 2013; Probst et al., 2009). Both DNA and epigenetic marks duplication are coordinated by the proliferating cell nuclear antigen (PCNA) which recruits crucial players to the replication fork, including DNA polymerases, histone chaperone chromatin assembly factor 1 (cAF1 or cHAF1), HDACs, lysine methyltransferases, chromatin remodelers and DNA methyltransferases (Estève et al., 2006; Huen et al., 2008; Lu et al., 2013; Milutinovic et al., 2002; Stillman, 1986; Zhang et al., 2000). During cell division, the maintenance DNA methyltransferase DNMT1 is recruited by “Ubiquitin-like, containing PHD and RING Finger domains, 1” (UHRF1) to hemimethylated DNA, where it guarantees the duplication of DNA methylation marks from parents to daughter DNA strands (Bostick et al., 2007, 2007; Jacob et al., 2015; Knox et al., 2000; Milutinovic et al., 2003). The histone K27 methyltransferase “Enhancer of Zeste Homologue 2” (EZH2) has been shown to be necessary for DNA methylation of EZH2-target genes, at least at some genomic loci, like at the promoter of *Myt1*, which is involved in OL lineage cell function (McGarvey et al., 2007; Viré et al., 2006). During replication, EZH2 also binds to methylated H3K27me3 marks on the parent strand, to then replicate this mark on the new daughter strand (Hansen et al., 2008). Thus DNA methylation and histone K27 trimethylation are important epigenetic marks that guarantee the fidelity of transmission of genetic information from mother to daughter cell in highly proliferative populations.

2.3. Glioma proliferation

The disruption of the PCNA/DNMT1/UHRF1 complex is detected in conditions characterized by increased glial progenitor cells proliferation and lack of apoptosis (Hervouet et al., 2010). In the absence of a protein complex ensuring the transmission of correct genetic information and epigenetic marks during replication, the genomic contents and nuclear organization in daughter cells could have serious consequences and result in genomic instability and cancer. Indeed, glioma cells are largely characterized by aberrant DNA methylation and histone modifications and associated changes in chromatin

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organization (Brock et al., 2007; Felsberg et al., 2006; Kim et al., 2012; Long et al., 2013; Nair and Kumar, 2012; Uhlmann et al., 2003; Watanabe and Maekawa, 2010).

Extensive global DNA hypomethylation has been observed in several cancers, including gliomas, and often associated with aberrant activation of DNA coding and non-coding regions (Uhlmann et al., 2003; Watanabe and Maekawa, 2010). However, regional DNA hypermethylation at specific sites encoding for cell cycle inhibitors or tumor suppressor genes has also been observed in gliomas, further highlighting the complexity of the role of DNA methylation in tumorigenesis (Felsberg et al., 2006; Sharma et al., 2010).

Histone deacetylation and methylation have also been reported in glial tumors (Long et al., 2013; Zhu et al., 2013). Oligodendroglioma, for instance are characterized by histone hypoacetylation, and high levels of histone deacetylases (i.e. HDAC3). Acetate supplementation or inhibition of HDAC3 using siRNA have both been shown to suppress tumor cell proliferation *in vitro* (Kim et al., 2012). Alterations of repressive methylation marks at lysine residues K9 and K27 in histone H3 have also been detected in gliomas. More precisely, H3K9 and H3K27 methylation levels can be either low or high at different gene loci in glioblastomas, leading to aberrant expression of cell cycle genes or silencing of tumor suppressor genes respectively (Bender et al., 2013; Chan et al., 2013; Venneti et al., 2013a, 2013b). In addition, the loss of H3K9me3 and H3K27me3 repressive marks at DNMT1 promoter, associated with DNMT1 upregulation in gliomas, also suggests the synergistic role of DNA and histone methylation in tumor development (Rajendran et al., 2011).

Finally, miRNAs can function as either oncogenes or tumor suppressors, depending on their target genes. In glioblastomas, miR-10b is highly expressed and can modulate E2F1-mediated transcription, which leads to increased proliferation of NG2 cells (Teplyuk et al., 2015). In fact, E2F family proteins as well as their genes targets (e.g. *Uhrf1, H2afz, Cdc2, Ccnd2*) are up-regulated in gliomas, whereas silencing of *E2f1* in glioma cells decreases also its targets expression (Magri et al., 2014a; Parr et al., 1997). The down-regulation of the oncogenic miR-10b in cells expressing high levels of the cell cycle inhibitor p21 has been shown to down-regulation of numerous E2F1 target genes and stabilization of cell cycle progression (Teplyuk et al., 2015). On the contrary, the tumor suppressors mirR-141, miR-188 and miR-503 have the ability to decrease the levels of cyclins and CDKs and further down-regulate the levels of E2F target genes in cancer cells, thereby promoting a beneficial effect (Cao et al., 2014; Wu et al., 2014; Xiao et al., 2013; Xue et al., 2014). Together these data identify modulation of E2F1 as a valuable therapeutic option to be further explored in proneural gliomas, which share several characteristics of OPCs.

Overall, we have discussed the complex regulation of proliferation in NG2 cells by transcription factors and epigenetic marks that can modulate each other expression or activity (Figure 1). Disruption of this complex regulatory network results in loss of homeostatic control and potentially explain tumorigenic transformation (Figure 2).

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3. Epigenetic mechanisms regulating NG2 cell differentiation

3.1. Necessary epigenetic regulatory machinery for NG2 cell differentiation

It is well-established that differentiation of NG2 cells is triggered by exit from the cell cycle and it is accompanied by dramatic changes of the transcriptional program, which include down-regulation of cell cycle regulatory molecules and differentiation inhibitors, followed by up-regulation of genes enriched in oligodendrocytes (Cahoy et al., 2008; Swiss et al., 2011; Zhang et al., 2014). RNA polymerase II ChIP-Sequencing revealed that start of NG2 cell differentiation is also accompanied by active transcription of genes involved in chromatin remodeling (Yu et al., 2013). Furthermore, chromatin condensation driven by heterochromatin formation can be detected at the periphery of the nucleus (Wu et al., 2012a). In light of these new findings, it is important to provide a new outlook of NG2 cell differentiation. Traditionally, NG2 cell differentiation is considered to be tightly controlled by a hierarchy of transcription factors (TFs) (Emery, 2010). Nevertheless, TFs alone cannot complete the task because genomic DNA is not linear or naked within a cell. Actually, it is compacted by histones into nucleosomes that are further assembled into a higher degree of structure inside the nucleus (Gorkin et al., 2014). Therefore, accessibility of the TFs to the genome is highly regulated and epigenetics is the mechanism that mediates this level of regulation (Chen and Weiss, 2014). In NG2 cells, many epigenetic enzymes are coupled with TFs to regulate the transcriptional program during differentiation. Loss of enzymatic activities results in severe attenuation of differentiation (Table 1). For instance, genetic ablation of *Hdac1/2* in OPC resulted in failure of differentiation in vivo (Cunliffe and Casaccia-Bonnefil, 2006; Ye et al., 2009). *In vitro*, inhibition of HDAC enzymatic activity blocked differentiation in both rodent (Marin-Husstege et al., 2002; Swiss et al., 2011) and human OPCs (Conway et al., 2012). Similarly, the histone lysine methyltransferases "Euchromatic Histone-lysine N-MethylTransferase 2" (EHMT2 or G9a) and "Suppressor of variegation 3-9 homolog 1" (Suv39H1), are required for efficient differentiation (Liu et al., 2015). An important role of a histone arginine modifying enzyme, PRMT5, for OPC differentiation *in vitro* has also been reported (Huang et al., 2011). In addition, genetic deletion of an enzymatic component of the ATP-dependent SWI/SNF chromatin remodeling complex BRG1 in OPC stopped differentiation *in vivo* (Yu et al., 2013), although this finding has been challenged by a more recent report demonstrating that BRG1 is not essential for CNS myelination (Bischof et al., 2015). A detailed discussion of the epigenetic machinery regulating NG2 cell differentiation is presented below (Figure 1).

3.2. Histone deacetylases (HDACs)

The requirement of HDAC1 (with HDAC2 being functionally redundant to HDAC1, Shen et al., 2008a; Wu et al., 2012a; Ye et al., 2009) for NG2 cell differentiation can be explained by the findings that HDAC1 is actively recruited to chromatin by different key TFs in order to repress gene expression through modulation of histone acetylation. For example, in OPC, it has been shown to interact with NKX2.2 (Ji et al., 2011; Wei et al., 2005) at the promoters of *Mbp* and *Sirt2* genes and inhibits their expression. In addition, it can also interact with SOX10 (Liu et al., 2015). In the differentiated cells, however, HDAC1 no longer binds to SOX10 (Liu et al., 2015). Instead, it becomes an interacting partner of YY1, a TF essential for differentiation (He et al., 2007a). Recruitment of YY1/HDAC1 complex to the promoter

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of genes encoding for differentiation inhibitors (e.g. *Tcf7l2* and *Id4*) resulted in loss of acetylated histone marks and transcriptional repression (He et al., 2007a). Supporting the importance of this mechanism was also the finding that a high percentage of down-regulated genes during OPC differentiation, were also modulated by type-I HDAC activity (Swiss et al., 2011). Global histone deacetylation mediated by HDAC1/2 was detected in OPC treated with extracellular factors promoting lineage progression (i.e. SHH) while increased acetylation was observed in cells treated with factors (i.e.BMP4) blocking oligodendrocyte differentiation (Wu et al., 2012a). Collectively, these findings support a 'de-repression' model where histone deacetylation is required for repressing the expression of differentiation inhibitors during NG2 cell differentiation, hence releasing the transcriptional inhibition from the promoters of myelin genes (Liu and Casaccia, 2010). The recent finding that inhibiting a major acetylated histone binding protein (BRD4) could promote NG2 cell differentiation (Gacias et al., 2014) further underscores the importance of the balance between histone acetylation and deacetylation for NG2 cell differentiation, with acetylation being favored at the progenitor stage and deacetylation required for differentiation.

In addition to modifying histones, HDACs are able to deacetylate also non-histone substrates. Notably, beta-catenin can be modified by acetylation that facilitates its interaction with TCF7L2 (Lévy et al., 2004). Since HDAC1 interacts with beta-catenin in OPC (Ye et al., 2009), it is possible that in this complex HDAC1 keeps beta-catenin in a de-acetylated state in addition to sequestering it from complexing with TCF7L2. Similarly, many other TFs found to be important for oligodendrocyte specification (e.g. GLI2) (Coni et al., 2013) and differentiation (e.g. YY1) (He et al., 2007b; Yao et al., 2001) are also regulated by acetylation/deacetylation. Additional factors which have been shown to be acetylated in other cell types (i.e. E2F1) (Martínez-Balbás et al., 2000) or have lysine residues which could play an important functional role (i.e. MYRF, OLIG1) have also the potential to be acetylated. Given the relevance of post-translational modification of TF in modulating their activity, the study of acetylation of non-histone substrates could be of high interest for future studies. In addition of the several HDAC family members expressed in the oligodendrocyte lineage (Broide et al., 2007; Shen et al., 2005; Tiwari et al., 2014), it is important to take into consideration that, besides HDAC1/2 other family members may play important functional roles including HDAC3 working in synergy with thyroid hormone T3 in promoting differentiation of Oli-neu cells (Castelo-Branco et al., 2014). This finding is actually not surprising considering that HDAC1/2 tend to form complexes with co-repressor proteins (e.g. Sin3a) (Grzenda et al., 2009) and a TF like YY1 (He et al., 2007a), HDAC3 is usually associated with the NCOR/SMRT co-repressor and a nuclear receptor (Perissi et al., 2010). Therefore, it is very likely that they may mediate different mechanisms in the same cells. While the functional significance of the HDAC1-Sin3a-YY1 has been demonstrated in the NG2 cells, further study is still needed to shed new light on the mechanism mediated by the HDAC3- NCOR/SMRT-nuclear receptor complex.

3.3 Histone methyltransferases (HMTs)

Two types of amino acid residues can be modified by methylation on the core histones-lysine and arginine-by two different groups of methyltransferases. Regarding lysine methylation, EZH2, the enzyme responsible for the repressive histone mark H3 lysine 27

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trimethylation (H3K27me3), was the first one to be characterized in neural stem cells differentiated along the oligodendrocyte lineage, while its expression was decreased in neurons and astrocytes (Sher et al., 2008). It was described that EZH2 overexpression favored, while silencing it blunted, oligodendrocyte differentiation. This was consistent with the relatively unchanged genomic occupancy of EZH2 on the neuronal (e.g. *Phox2b, Six1, Neurod2, Tlx3* and *Otp*) and astrocytic genes (e.g. *Tal1*) from neural stem cell differentiation into oligodendrocyte (Sher et al., 2012) and with the decreased EZH2 occupancy of oligodendrocyte lineage specific genes such as *Olig2, Pdgfra, Nkx6.2* and *Nkx 2.2*, thereby suggesting that EZH2 is required for the early stages of oligodendrocyte differentiation from neural stem cells and may modulate cell fate decision of progenitors. A recent study confirmed these findings and identified another group of HMTs, the ones that are responsible for generating H3 lysine 9 trimethylation (H3K9me3), catalyzed by EHMT1 (also known as Glp) and EHMT2 (also known as G9a) and by Suv39H1, to be important for the subsequent stages of differentiation from NG2 cells to oligodendrocytes (Liu et al., 2015). In this study, the authors performed ChIP-Sequencing analysis for H3K9me3 and H3K27me3 in proliferating progenitors and their differentiated progeny and detected a global increase of H3K9me3 but not H3K27me3. At the progenitor stage 920 genes were shown to be uniquely repressed by H3K9me3 marks and more than 600 genes were uniquely repressed by H3K27me3 mark (Liu et al., 2015). Interestingly, as OPCs differentiated into OLs, the number of genes with H3K9me3 marks increased, in parallel with an up-regulation of EHMT2. The number of genes with H3K27me3 marks decreased, in parallel with the down-regulation of EZH2 in myelinating OL, compared to NG2 cells (Liu et al., 2015; Sher et al., 2008; Zhang et al., 2014). These data suggest that distinct repressive marks characterize diverse functional states. Repressed genes with unique H3K9me3 marks included those regulating membrane excitability in NG2 cells, such as clusters of potassium channel subunits (e.g. *Kcnb1, Kcnb2, Kcnk1* and *Kcnmb4*). Accordingly, silencing the enzymes *Ehmt2* and *Suv39h1*, responsible for generating this mark in NG2 cells altered the electrical properties of the cells. Additional genes regulated by both marks were transcription factors modulating neuronal fate, including *Lhx1, Pax6, Grip1* and *Dcx* (Liu et al., 2015). In agreement, silencing *Ehmt2* and *Suv39h1* rather than *Ezh2* impaired oligodendrocyte differentiation and altered expression of neuronal genes. Taken together, these results suggest that H3K27 HMT is required for oligodendrocyte lineage specification from neural progenitors to OPC, while the H3K9 HMT is critical for NG2 cell differentiation into OL.

Arginine residues in the tails of nucleosomal histones are also methylated by protein arginine methyltransferases (PRMTs) (Di Lorenzo and Bedford, 2011). In NG2 cells, a role of PRMT5 in regulating the transcriptional program during differentiation has been suggested (Huang et al., 2011). Considering its critical role in modulating E2F1-dependent gene expression in gliomas and as gatekeeper of “stemness” and survival in neural stem cells mediated by regulation of the mRNA splicing machinery (Bezzi et al., 2013), it would be interesting to determine whether it plays a similar role in NG2 cells and OLs, where alternative splicing events are known to occur in abundance (e.g. *DM20/Plp1*, immature/mature MBP transcripts, long/short MAG transcripts) (Zhang et al., 2014).

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3.4. DNA methylation

In addition to histone deacetylation and H3 lysine 9 trimethylation, DNA methylation is another important epigenetic mechanism for gene repression, which might be important for developmental myelination. While DNA methylation has been studied extensively in neurons and astrocytes (Fan et al., 2001; Hutnick et al., 2009; Li et al., 1992; Milutinovic et al., 2003; Unterberger et al., 2006), it still remains poorly characterized in the oligodendrocyte lineage. During development, DNA methylation has been shown to be essential for stem cell differentiation into the neural lineage (Wu et al., 2012b), while demethylation has been reported to be associated with precocious astrogliogenesis (Fan et al., 2005; Wu et al., 2012b). Genetic ablation of *Dnmts* in the neuronal lineage has been linked either to defective survival in proliferating neuroblasts or defective neuronal plasticity in post-mitotic neurons (Feng et al., 2010; Hutnick et al., 2009). The concept of demethylation-associated expression of mature genes has been proposed for neuronal, astrocytic, and Schwann cell differentiation (Fan et al., 2001; Takizawa et al., 2001; Varela-Rey et al., 2014). A similar model could be envisioned for OLs as the TET proteins appear to be necessary for OPC differentiation and since the myelin gene *Mag* is specifically demethylated during differentiation (Grubinska et al., 1994; Zhao et al., 2014). However, a previous study performed in neonatal rats during developmental myelination, showed that injection of 5-azacytidine, a nucleoside inhibitor of DNMTs, resulted in an almost complete absence of myelin in the optic nerve (Ransom et al., 1985). When rats were allowed to recover from the chemical perturbation, myelinated fibers began to reappear, indicating that an oligodendrocyte population persisted but could not differentiate into myelin-forming cells. Taken together, these data suggest that, in the oligodendroglial lineage, DNA methylation is a complex mechanism, requiring both methylation and demethylation of specific genomic regions.

3.5. Nucleosome remodeling

Since genomic DNAs including coding and regulatory regions are packed into nucleosomes inside the nucleus, fully activating a gene requires sliding of the nucleosomes to expose the DNA regions that TFs or other transcriptional machineries can land on. It has been demonstrated that this process is energy-consuming (requiring the use of ATP) and mediated by a set of large protein complexes that are collectively termed as ATP-dependent chromatin remodeling complexes (Hargreaves and Crabtree, 2011). It has been shown that activation of genes by TF during NG2 cell differentiation depends on one of such mechanisms. Upon differentiation, the ATP-dependent SWI/SNF chromatin-remodeling enzyme BRG1 was recruited by OLIG2 to the active enhancer regions (defined by enrichment of H3 lysine 27 acetylation, H3K27ac) and this correlated with the expression of genes characteristic of the differentiated state (Yu et al., 2013). However, further studies are required to examine the genome-wide distribution of OLIG2 binding and whether it is changed upon loss of BRG1. This is of great importance considering a more recent finding from another group that demonstrated that ablation of *Brg1* using *NG2-cre* and *Cnp-cre* is not essential for oligodendrocyte differentiation (Bischof et al., 2015). In addition, it would be of relevance to define whether the OLIG2/BRG1 complex contributes to the formation of a novel type of regulatory hubs (‘super-enhancers’) at clusters of enhancer regions that are cell type specific and developmentally regulated, as initially described in embryonic stem cells (Whyte et al.,

2013). It is also conceivable that such a role could be played by SOX10 through its interaction with MED12 (Vogl et al., 2013), a component of the Mediator complex that functions by bridging enhancer regions with the basal transcription machinery at proximal promoter regions. In addition, given the current debate on the plastic and multipotential nature of NG2 cells, it would be of great relevance to map all the enhancer regions that retain the potential for transcriptional activation in these cells, by defining the 'poised' enhancers - which are enriched in H3K4me1, H3K4me2 and H3K27me3 marks and depleted of H3K4me3 and H3K27ac histone marks (Heinz et al., 2010). This would address a different question that mapping the active enhancers defined by the H3K27ac mark, as in the previous study (Yu et al., 2013), by uncovering the "multipotentiality" of the cells at a molecular level and provide novel insights into the controversial "multipotency" of NG2 cells (Richardson et al., 2011).

3.6. MicroRNAs play an additional role

An additional layer that adds to the complexity of epigenetic modulation of OL differentiation is the presence of microRNAs. The necessity of these molecules for differentiation was firstly revealed by the phenotype of mice with ablation of the gene encoding a key enzyme for microRNA maturation (DICER), which revealed microRNAs were not required for the specification of the oligodendrocyte lineage but are necessary for differentiation and myelination (Dugas et al., 2010; Shin et al., 2009; Zhao et al., 2010). Several microRNAs have been characterized in detail along with their mRNA targets. Specifically, miR-7a has been shown to safeguard from aberrant gene expression of *Pax6* and *Neurod4* and pro-oligodendrocytic genes during the specification of NG2 cells from neural stem cells (Shin et al., 2009). Similarly, miR-9 has been shown to prevent expression of Schwann cell specific transcripts, such as *Pmp22* (Lau et al., 2008). On the other hand, miR-219, miR-338, miR-23 and miR-32 are much more abundant in differentiated cells and facilitate lineage progression towards myelinating oligodendrocytes. Specifically, miR-219 has been identified to be the most dramatically up-regulated microRNA during NG2 cell differentiation. It targets a wide range of mRNAs whose protein products constitute major obstacles to differentiation, including the mitogen receptor (*Pdgfra*) and multiple TFs (*Sox6, Foxj3, Zfp238* and *Hes5*) (Dugas et al., 2010; Zhao et al., 2010). At later stages of differentiation, miR-219 targets the transcripts of a gene encoding a lipid metabolizing enzyme (*Elovl7*) whose overexpression would result in abnormal lipid accumulation in myelin (Shin et al., 2009). Similarly, miR-32 has also been shown to regulate the expression of an enzyme (Slc45a3) important for lipid metabolism in oligodendrocytes and myelin (Shin et al., 2012). Among other microRNAs enriched in differentiated NG2 cells, miR-338 seems to be functionally redundant to miR-219 (Zhao et al., 2010) while miR-23 is likely to play a different yet critical role in mature oligodendrocytes by suppressing the expression of a nuclear lamina component Lamin-B1, whose overdosing is the genetic cause of the an adult-onset demyelinating disease (Lin and Fu, 2009). Besides, it has been revealed more recently that over-expression of miR-23a in mice led to increased thickness of myelin in CNS, further supporting the importance of this microRNA for myelination (Lin et al., 2013).

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3.7. Coordination between extrinsic signaling mechanisms and epigenetics

It should be noted that one of the most important reasons why epigenetic changes are considered as critical modulators of gene expression is because they are dynamic and with varying degrees of reversibility and with a longer lasting effect on transcription than TF alone. Some regulatory mechanisms are associated with turning on or off transcription in a cell, in response to the signals it receives. For example, it is well established that neurons utilize many of the epigenetic enzymes such as the histone acetyltransferase CBP to mediate their transcriptional response to synaptic activity and depolarizing stimuli (Riccio, 2010). In contrast, not enough studies have been performed in the NG2 cells to illustrate unambiguously how extrinsic signals can affect the epigenetic machinery. However, some findings are emerging to suggest such coordination may exist. Wu *et al.* showed that two important morphogens for oligodendrocyte development (SHH and BMP4) converge on regulating the histone state in oligodendrocyte progenitors. While SHH promoted oligodendrocyte differentiation and heterochromatin formation by decreasing global histone acetylation, BMP4 blocked this process by increasing histone acetylation globally and at astrocytic genes (Wu et al., 2012a). Interestingly, downstream of SHH signaling in the developing telencephalon, gene repression and activation has been reported to be modulated by BRG1, whose pleiotropic function is influenced by the developmental stage and brain region (Zhan et al., 2011). It would be of interest to see whether similar mechanisms exist in the NG2 cell lineage and such insight may be able to reconcile the findings that deletion of the BRG1 gene in different populations of the lineage results in different phenotypes on myelination (Bischof et al., 2015; Yu et al., 2013).

Further, many of the other aforementioned epigenetic mechanisms that are important for NG2 cells can be potentially regulated by hormonal ligands. It is well established that members of the nuclear receptor family (including the thyroid hormone receptor, Vitamin D receptor and Retinoid acid receptor) enter the cells and bind to their cognate receptor, thereby inducing an exchange of binding partners, from HDACs to HATs that would result in functional switch of the complex from repressive – in the absence of the ligand- to activating, in the presence of the hormone (Kato et al., 2011). The current finding that silencing the HMTs responsible for H3K9 methylation resulted in block of lineage maturation only in OPCs maintained in a proliferating condition (with the mitogens PDGFaa and bFGF) but not in the cells already induced to differentiate (with the thyroid hormone T3) suggests that in the NG2 cells also, the HMTs functions are likely linked to extracellular signals of the nuclear receptor superfamily (Liu et al., 2015).

Finally, recent studies have highlighted the importance of neuronal activity (Gibson et al., 2014) and social behavior (Liu et al., 2012) in modulating post-translational modifications of histones in NG2 cells in the adult brain. Using optogenetic stimulation of NG2 cells in the adult motor cortex in order to induce a motor behavior, Gibson and colleagues reported the subsequent occurrence of histone deacetylation and increased H3K9me3 methylation in response to neuronal stimulation. They further reported that pharmacological inhibition of histone deacetylation with the inhibitor trichostatin, prevented the occurrence of these histone marks and prevented the acquisition of the motor behavior (Gibson et al., 2014). Conversely, studies on mice subject to social isolation revealed decreased repressive

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H3K9me3 marks and the persistence of an immature chromatin state, which correlated with behavioral changes (i.e. a decrease in the social interaction time) and fewer myelinated fibers in the prefrontal cortex (Liu et al., 2012). Together these studies support the concept of modulation of epigenetic machinery by external stimuli.

4. Therapeutic approaches based on epigenomic modulators

4.1. Epigenomic approaches to remyelination failure

Consistent with their role in development, NG2 cells and the oligodendrocytes that they generate are extensively involved in the pathology of many CNS demyelinating disorders including multiple sclerosis (MS). Despite the many immunomodulatory treatments, a cure is still not available to repair the damage (Ransohoff et al., 2015). As a consequence, even when the immune attack or inflammation has receded, the demyelinated axons may not be properly remyelinated and therefore they remain exposed to axonal damage. In addition, a portion of progenitor cells, despite their presence around MS lesions, show a declining propensity to differentiate as the disease progresses and fail to generate enough OLs capable to remyelinate axons (Fancy et al., 2010). However, remyelination is a robust regenerative process in the mammalian CNS and NG2 cells are responsible for this process. In response to injury, NG2 cells are not only capable to proliferate and migrate to the lesions but also to differentiate into OLs and form new compact myelin sheaths wrapping around the demyelinated axons and leading to functional recovery. Repair can be promoted either by resident NG2 cells within the brain, or by cells from the subventricular zone. These cells may undergo similar steps as during postnatal development and produce oligodendrocytes (Huang and Franklin, 2012; Vidaurre et al., 2012). This suggests that endogenous myelin repair in MS patients is achievable. At the cellular level, it is known that many key mechanisms for remyelination, including the ones composed of epigenetic modulation, recapitulate those in development for regulating NG2 cell proliferation and differentiation (Fancy et al., 2011). For example, the type-I HDAC activities are required for both efficient developmental myelination and remyelination (Shen et al., 2008b). In agreement with this, increased immunoreactivity for acetylated histone H3 accompanied by high levels of transcriptional inhibitors of NG2 cell differentiation (i.e., TCF7L2, ID2, and SOX2) and HAT transcript levels (i.e., CBP, P300) have been observed in oligodendrocytes localized to the normal-appearing white matter (NAWM) of chronic MS lesions where remyelination is not sufficient in contrast to a low level of histone H3 acetylation in early MS lesions where remyelination is still efficient (Pedre et al., 2011). This implies that the status of H3 acetylation correlates with the differentiation state of the cells, similar to what happens during development. In addition, similar to the situation in MS, the ability of NG2 cells to regenerate myelinating oligodendrocyte also seems to decline with aging. This phenomenon can be at least partially explained by inefficient recruitment of HDACs in the aged but not young brains during remyelination (Shen et al., 2008b) (Figure 3). Therefore, it may be feasible to provide therapeutic interference in the NG2 cells to promote remyelination by modulating the epigenome. For instance, in light of a recent report that a small molecule inhibitor to one of the acetylated lysine binding domain of BRD4 is capable to tilt the balance of histone acetylation in NG2 cells to favor differentiation (Gacias et al., 2014), the acetylated histone binding protein BRD4 may become a druggable target for remyelination,

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considering a panel of different chemical inhibitors have been developed lately for this protein (Gacias et al., 2014; Shi and Vakoc, 2014).

4.2. Epigenomic approaches to program/reprogram the NG2 cells

It has been proven that transplantation of human NG2 cells has significant beneficial effects in several rodent models that mimic human neurological pathologies, including spinal cord injury (Volarevic et al., 2013) and the side effects of radiation therapy to brain tumors (Piao et al., 2015). Therefore, it is desirable to obtain human NG2 cells. A practical and feasible way to do so is the generation of human pluripotent stem cells (hPSCs). Although differentiation of hPSCs into NG2 cells (Douvaras et al., 2014; Stacpoole et al., 2013; Wang et al., 2013) is achievable, the process is still time-consuming (it takes from 95 days to 150 days). Human NG2 cells have the potential also to be obtained by direct reprogramming from other lineages (e.g. skin fibroblasts) and the pioneering results in murine cells are quite encouraging (Najm et al., 2013; Yang et al., 2013). However, the molecular identity of these cells is not entirely equivalent to the one of the native counterpart, since these reprogrammed cells express some Schwann cell markers and myelinate single axons as Schwann cells do (Najm et al., 2013; Yang et al., 2013), thereby suggesting insufficient epigenetic reprogramming. Therefore, derivation of NG2 cells *in vitro* still needs to be improved and it is predictable that the process could be enhanced by epigenetic manipulations, considering the many successful cases made in other lineage of cells (Zhang et al., 2012).

5. Concluding remarks

Several epigenetic mechanisms underlie the functions of NG2 cells by interacting with transcription factors and regulating both their proliferation and differentiation properties. It is foreseeable that with accumulating knowledge regarding the epigenetic landscape of OPC and its regulation, we will be able to answer many of the open questions regarding NG2 cells, especially their heterogeneity and plasticity. Recently, zinc-finger proteins or transcription activator-like effectors fused with chromatin-modifying enzymes or nanofiber-mediated microRNA have been used to modulate epigenetic modifications *in vitro* or *in vivo* (Diao et al., 2015; Heller et al., 2014; Mendenhall et al., 2013; Sanjana et al., 2012; Snowden et al., 2002). Such new tools could be used as strong therapeutic strategies in NG2 glial cells to specifically promote their remyelination capacities or unlock their multipotentiality *in vivo*.

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Highlights

- Epigenetic regulation includes DNA methylation, chromatin and non-coding RNA changes

- It affects the transcriptional landscape of NG2 glial cell

- Epigenetic changes of nuclear structural components define transitions in NG2 cells

- Epigenetic dysregulation can result in defective myelin repair or gliomas formation

- Modulation of epigenetic marks can be explored as therapeutic strategy for NG2 cells

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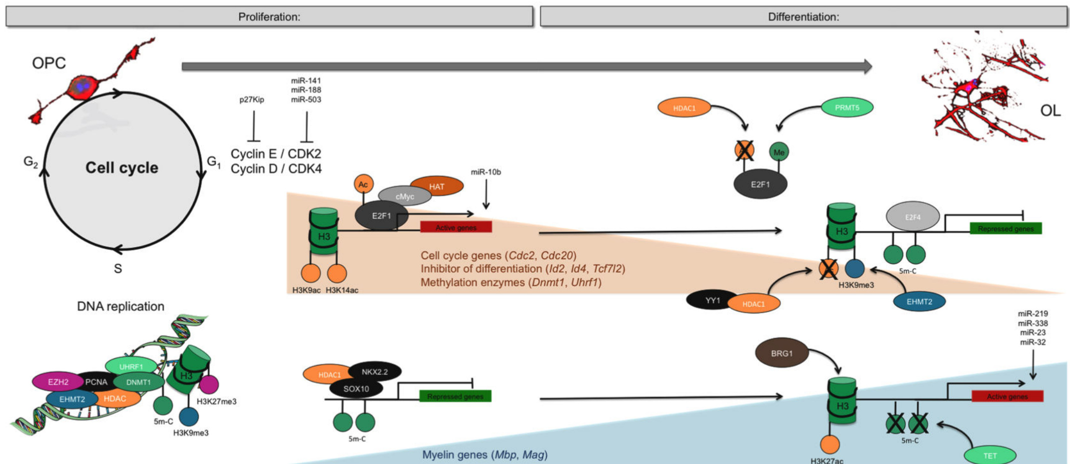

Figure 1.

Epigenetic mechanisms regulating NG2 cell proliferation and differentiation during development.

OPC proliferation is controlled by epigenetic marks that activate cell cycle genes expression and repress mature genes expression. During the S phase, genetic and epigenetic marks are also tightly duplicated. Combined epigenetic marks, especially deacetylation and methylation, lead to cell cycle genes and inhibitor of differentiation genes repression during OL differentiation, while acetylation and hypomethylation induce expression of myelin genes like *Mag*.

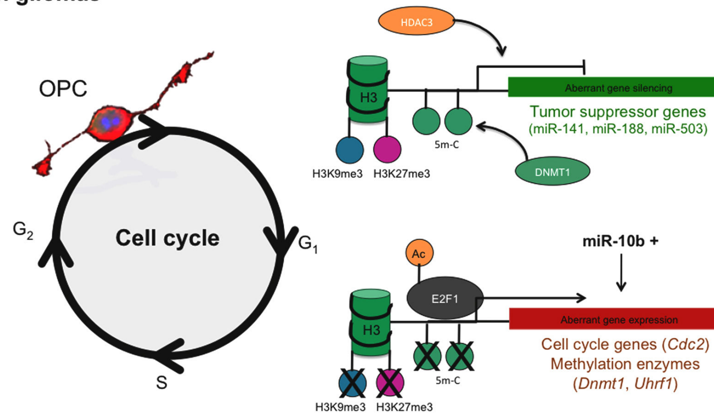

Figure 2.

Epigenetic mechanisms regulating NG2 cell proliferation in gliomas.

Increased levels of DNMT1 and HDAC3 result in aberrant gene silencing, such as tumor suppressor genes. In parallel, hypomethylation and overexpression of miR-10b maintain the expression of cell cycle genes, which keep the OPC in a proliferative stage.

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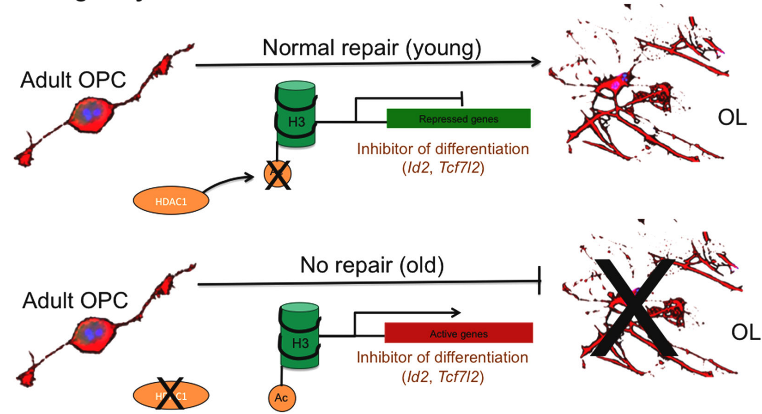

Figure 3.

Epigenetic mechanisms regulating NG2 cell differentiation during repair.

Epigenetic modifications identified during development can be recapitulated, like the histone deacetylation, leading to gene repression (of inhibitor of differentiation). In chronic disease or in old animals, the lack of remyelination can be partially explained by the downregulation of HDAC1, thus the expression of inhibitors of differentiation.

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Table 1

Epigenetic enzymes required for normal oligodendrocyte development.

Enzyme	Modification	Required for	Experimental system
HDAC1/2	Histone de-acetylation	Specification, differentiation and myelination	Primary rodent OPC cultures (Marin-Husstege et al., 2002; Wu et al., 2012a), human OPC culture (Conway et al., 2012), zebrafish (Cunliffe and Casaccia-Bonnefil, 2006) and conditional knockout mice (*Olig1-Cre*) (Ye et al., 2009)
HDAC11	Histone de-acetylation	Differentiation	OPC cell line (Liu et al., 2009)
EZH2	H3K27 methylation	Specification	Neural stem cell culture (Sher et al., 2008)
G9a/SUV39h1	H3K9 methylation	Differentiation	Primary rodent OPC culture (Liu et al., 2015)
PRMT5	Histone arginine symmetric methylation	Differentiation	Primary rodent OPC culture and glioma cell line (Huang et al., 2011)
BRG1	Nucleosome remodeling	Differentiation and myelination	Primary rodent OPC culture and conditional knockout mice (*Olig1-Cre*) (Yu et al., 2013)
DICER	Process pre-microRNAs	Differentiation and myelination	Primary OPC cultures and conditional knockout mice (*Plp-CreERT* (Shin et al., 2009); *Olig2-Cre* and *Cnp-Cre* (Dugas et al., 2010); *Olig1-Cre* (Zhao et al., 2010))