DNA methylation in Schwann Cells and in Oligodendrocytes

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P.A-F and S.M both designed the figures, wrote and edited the paper. Data used for this review have been previously peer-review and are referenced at the end of the manuscript.

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Abstract

DNA methylation is one of many epigenetic marks, which directly modifies base residues, usually cytosines, in a multiple-step cycle. It has been linked to the regulation of gene expression and alternative splicing in several cell types, including during cell lineage specification and differentiation processes. DNA methylation changes have also been observed during aging, and aberrant methylation patterns have been reported in several neurological diseases. We here review the role of DNA methylation in Schwann cells and oligodendrocytes, the myelin-forming glia of the peripheral and central nervous systems, respectively. We first address how methylation and demethylation are regulating myelinating cells' differentiation during development and repair. We then mention how DNA methylation dysregulation in diseases and cancers could explain their pathogenesis by directly influencing myelinating cells' proliferation and differentiation capacities.

Keywords

DNA methylation, Oligodendrocyte, Schwann cell, Demyelination, Glioma, Schwannomas, Aging, Epigenetics

Main points

DNA methylation regulates Schwann cells and oligodendrocytes differentiation.

DNA modifications are necessary for myelination or remyelinating events in the CNS.

DNA methylation is dysregulated in myelinating glia in aging, in neurodegenerative diseases, and in Schwannomas and CNS gliomas.

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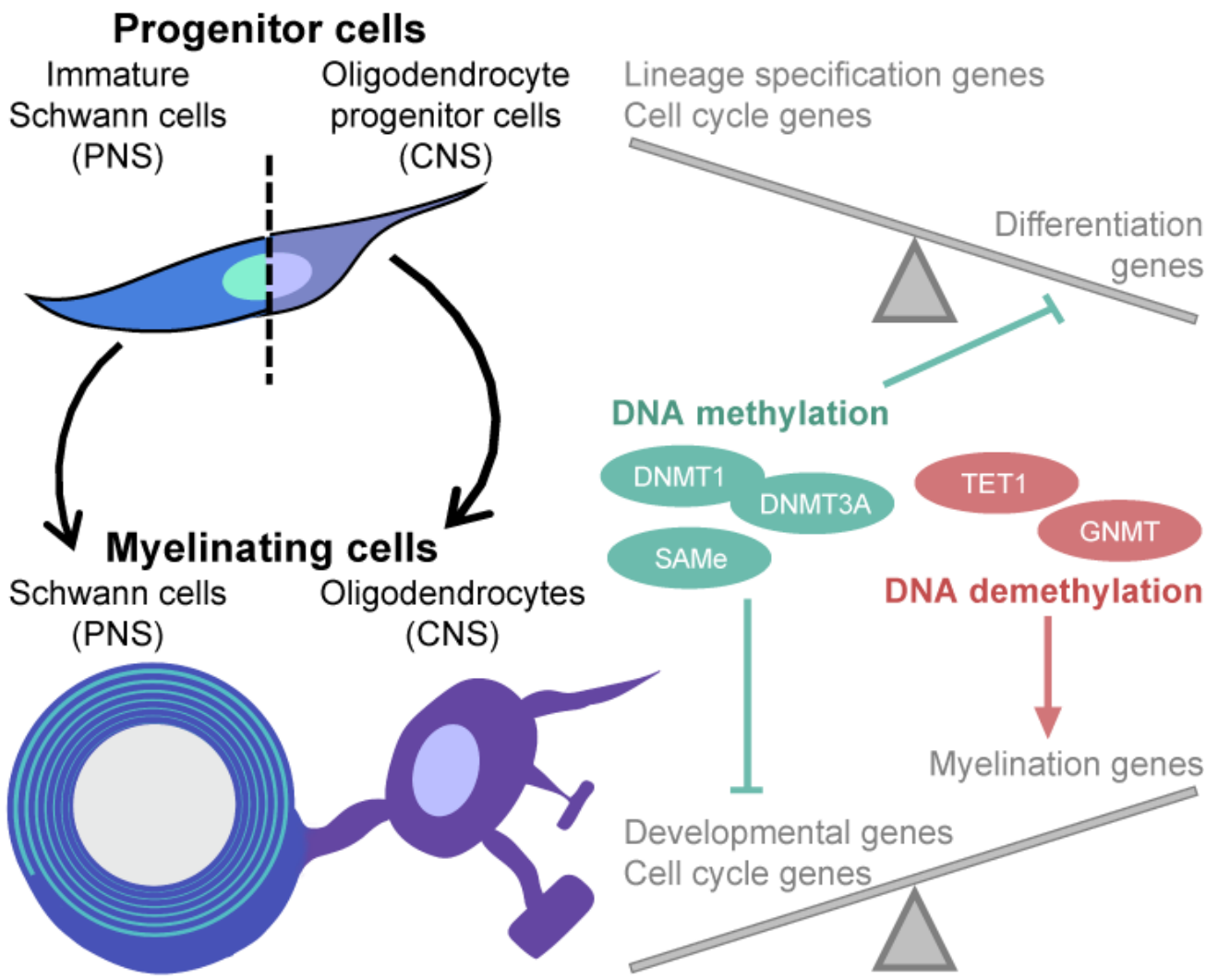
Progenitor cells
Immature Schwann cells (PNS)
Oligodendrocyte progenitor cells (CNS)
Myelinating cells
Schwann cells (PNS)
Oligodendrocytes (CNS)
Lineage specification genes
Cell cycle genes
Differentiation genes
DNA methylation
DNMT1
DNMT3A
SAMe
TET1
GNMT
DNA demethylation
Myelination genes
Developmental genes
Cell cycle genes

1. Introduction

Epigenetic regulation is composed of several layers of modifications, from regionally-restricted marks on DNA and histones, to more global remodeling of chromatin regions. DNA methylation is the first layer of these epigenetic processes, as it directly modifies base residues, on cytosines and to a lower extent on adenines. DNA modifications mainly target the cytosine residues at their C-5 position, essentially at CpG dinucleotides in mammalian genomes (Eden & Cedar, 1994; Lister et al., 2009). DNA methylation itself is a multi-step cycle, in which methylation is first initiated by the addition of a methyl group from S-adenosylmethionine on the C-5 position (5-methylcytosine, 5mC), then demethylation is gradually induced by the oxidation of 5mC to 5-hydroxy-methylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) (Hashimoto, Zhang, & Cheng, 2012; Huang & Rao, 2014; Lister et al., 2013; Meier & Recillas-Targa, 2017; H. Wu & Zhang, 2011) (***Figure 1A***). The first reaction is catalyzed by the DNA methyltransferases (DNMTs): the "maintenance" DNMT1, which is responsible for the faithful copying of DNA methylation from mother to daughter cells during replication, and the *de novo* DNMT3A and DNMT3B, which establish new methylation marks (Goll & Bestor, 2005; Lei et al., 1996; Lyko, 2018, p. 201; Okano, Xie, & Li, 1998). The demethylation reactions can be passive, but they are mainly catalyzed by the Ten-Eleven Translocations (TETs) enzymes, TET1, TET2 and TET3, which are differently expressed depending on the tissue type and also with age (Kriaucionis & Heintz, 2009; Rasmussen & Helin, 2016). The last demethylation step is catalyzed by thymine-DNA glycosylase (TDG), followed by base excision repair (BER) (***Figure 1A***).

DNA methylation has been shown to have important roles in X-inactivation, genomic imprinting, transposon silencing, transcription factor binding, cellular differentiation, cancer and aging (Beerman et al., 2013; M. J. Jones, Goodman, & Kobor, 2015; P. A. Jones, 2012; Yin et al., 2017). Generally, the level of methylation is higher in intergenic and repetitive regions of the genome and lower in gene regulatory areas, such as CpG islands (CGIs), transcription start sites, gene bodies and enhancer regions (P. A. Jones, 2012; Lister et al., 2009). At promoter regions and transcription starting sites, 5mC and 5hmC marks have mainly been associated with transcriptional repression and

initiation, respectively (Brenet et al., 2011; Schübeler, 2015; Smith & Meissner, 2013; Suzuki & Bird, 2008) (***Figure 1B***). Yet, while there is strong evidence for 5mC marks at CGIs at transcriptional start sites causing transcriptional repression, 5mC in other regions of the genome, particularly in enhancers and gene bodies, appears to be more dynamic and associated with both gene activation and repression (Deaton & Bird, 2011; P. A. Jones, 2012; Zhu, Wang, & Qian, 2016). Both 5mC and 5hmC marks could directly prevent the access of transcription factors to their binding sequence, especially for those containing a CG in their binding motif, or through binding partners such as methyl-CpG binding domain proteins. It is also worth noting that correlative assumptions between DNA methylation and gene expression have been recently challenged, as some studies have revealed modification of epigenetic marks following transcription. In these cases, DNA methylation and hydroxy-methylation marks would be revelators of ongoing or past gene expression and/or repression (Hodges et al., 2011; Lister et al., 2013; Stadler et al., 2011; Ziller et al., 2013). Specific DNA modifications could also recruit cofactors that modulate the chromatin environment, including histone modifications, which would imply a larger and more integrated role of several epigenetic marks in regulating gene expression (Jian Feng et al., 2015; Yiwei Liu, Zhang, Blumenthal, & Cheng, 2013; Schübeler, 2015; Smith & Meissner, 2013; Szulwach, Li, Li, Song, Han, et al., 2011; Yin et al., 2017). In gene bodies, 5mC and 5hmC marks have also been associated with alternative splicing (Gelfman, Cohen, Yearim, & Ast, 2013; Maunakea, Chepelev, Cui, & Zhao, 2013; Wan et al., 2013; Yearim et al., 2015). Less is known about the gene expression regulation by 5fC and 5caC marks, but the recent development of new sequencing methods and specific antibodies for these marks will certainly lead to a better characterization of their respective biological roles.

Methylation patterns remain reasonably static in terminally differentiated cells, whereas they are dynamically varied across cell types and developmental ages (J. Feng et al., 2010; Lister et al., 2013, 2009; Nestor et al., 2012, p. 201). During early cell lineage choice, in embryonic stem cells, binding sites of pluripotency-associated transcription factors have been shown to be enriched for DNA hydroxy-methylation (Ficz et al., 2011). In the nervous system, DNA methylation has been extensively studied in neurons and

astrocytes, which are both cell types that undergo several steps of lineage specification and cell differentiation (G. Fan et al., 2001; Guo et al., 2014; Hutnick et al., 2009; Kinde, Gabel, Gilbert, Griffith, & Greenberg, 2015; E. Li, Bestor, & Jaenisch, 1992; Milutinovic, Zhuang, Niveleau, & Szyf, 2003; Unterberger, Andrews, Weaver, & Szyf, 2006). During development, DNA methylation has been shown to be essential for determination of the neural lineage (Z. Wu et al., 2012), while demethylation has been reported to be associated with precocious astrogliogenesis, defective survival in proliferating neuroblasts and reduced neuronal plasticity in post-mitotic neurons (Guoping Fan et al., 2005; J. Feng et al., 2010; Hutnick et al., 2009; Z. Wu et al., 2012).

The myelinating cells of the peripheral nervous system (PNS) and the central nervous system (CNS), Schwann cells and oligodendrocytes, also undergo multiple cell lineage specification steps before terminally differentiating. A tight dynamic control of transcription factors is necessary for normal myelination, and their dysregulation, in cancers, diseases and aging, and has been directly linked to glial cell proliferation or differentiation defects. Here, we review the role of DNA methylation in the Schwann cell and oligodendroglial lineages, during the myelination process in development and in the adult, as well as in injury, cancer and aging.

2. DNA methylation in Schwann Cells

2.1. The Schwann cell lineage

Schwann cells are amongst the major glial cell types of the mammalian PNS, alongside enteric glia from the gut and satellite glia from the dorsal root ganglia. Currently, there are four known types of Schwann cells, though this number will likely grow with future studies. Myelinating and Remak (non-myelinating) Schwann cells are found in spinal nerves and are associated with large and small caliber axons, respectively. Whereas terminal Schwann cells and nociceptive Schwann cells are associated with

nerve terminals of motor and nociceptive neurons, respectively (Abdo et al., 2019; Jessen & Mirsky, 2019). Schwann cells are generated from neural crest cells and pass through two well characterized developmental stages before differentiating into myelinating or Remak Schwann cells around birth. These stages are known as the Schwann cell precursor and the immature Schwann cell (Jessen & Mirsky, 2019).

More recently an additional Schwann cell state was identified. After injury to the adult PNS, myelinating and Remak Schwann cells transform into repair Schwann cells to promote nervous system regeneration (Arthur-Farraj et al., 2012; Gomez-Sanchez et al., 2017; Jessen & Arthur-Farraj, 2019). Repair Schwann cells can have subtly different molecular phenotypes depending on their vicinity to the site of injury (Clements et al., 2017). Following axon regeneration, they can re-differentiate into either myelinating or Remak Schwann cells, independent of their original phenotype (Stierli et al., 2018). Importantly, repair Schwann cells appear to be lineage-restricted and incapable of transforming into other cell types or of forming tumors, without further mutation or manipulation of their genome (Parfejevs, Antunes, & Sommer, 2018; Stierli et al., 2018).

2.2. DNA methylation regulates Schwann cell myelination

Both DNMT3A and DNMT3B are important for neural crest specification and the timing of their differentiation (for review see (Hu, Strobl-Mazzulla, & Bronner, 2014)). In the absence of *DNMT3A* in the chick embryo there is a failure to repress neural genes, *Sox 2* and *Sox3* in the prospective neural crest region and a subsequent loss of neural crest specifier genes, *Sox10*, *Foxd3* and *Snail2* (Hu, Strobl-Mazzulla, Sauka-Spengler, & Bronner, 2012). Loss of *DNMT3B* in both human embryonic stem cells and in the chick embryo leads to acceleration of neural crest differentiation and precocious peripheral neuronal differentiation (Hu, Strobl-Mazzulla, Simoes-Costa, Sánchez-Vásquez, & Bronner, 2014; Martins-Taylor, Schroeder, LaSalle, Lalande, & Xu, 2012). In the chick, DNMT3B binds and methylates the *Sox10* promoter, which represses *Sox10* expression, allowing for cessation of neural crest delamination (Hu, Strobl-Mazzulla, Simoes-Costa,

et al., 2014). It is currently unknown whether DNA methylation regulates the generation or behavior of Schwann cell precursors or Immature Schwann cells. Immature Schwann cells begin to myelinate after they select an axon through a process known as radial sorting (Monk, Feltri, & Taveggia, 2015). Schwann cells receive signals to myelinate from their basal lamina, most prominently through interaction of laminin-221 with the G-protein coupled receptor, GPR126, signaling through a cyclic AMP/protein kinase A axis (Mogha et al., 2013; Monk et al., 2009; Petersen et al., 2015). Additionally, Schwann cells also receive signals from the axon that regulate myelination, the most studied of these is Neuregulin 1 type III binding to ErbB receptors (Michailov et al., 2004; Taveggia et al., 2005). These signals coalesce on a number of transcription factors to regulate myelin gene expression, such as *Egr2/Krox-20* and *Yy1* ((Ye He et al., 2010), reviewed in (Herbert & Monk, 2017; Monk et al., 2015)).

Myelination begins in mouse nerves at birth (Monk et al., 2015). A genome wide CpG methylation study using reduced representation bisulfite sequencing compared mouse newborn nerves to adult mature myelinated postnatal day 60 (P60) nerves. They showed that promoter and regulatory regions for a number of myelin genes, such as *Mbp* and *Pmp22* became globally hypo-methylated by P60 and this broadly correlated with an up-regulation in myelin gene expression between these two time points. Moreover, binding sites for myelin-specific transcription factors, such as *Egr2* and *Yy1* were found to be enriched in the hypo-methylated regions (Varela-Rey et al., 2014) (***Figure 2***). It is important to note that the investigators found that, genome-wide, DNA hypo-methylation was associated with both up- and down-regulation of gene expression, which mirrors findings from other tissues (P. A. Jones, 2012). Although Varela-Rey et al. found that regulatory regions of a number of myelin genes became progressively more hypo-methylated, the relationship of DNA methylation with global myelin gene expression appears more complex. This is because most myelin genes were progressively up-regulated after birth (P10), while myelination proceeded, and then down-regulated again, albeit to levels higher than at newborn, in the adult nerve (P60) (Varela-Rey et al., 2014). Additionally, there are two further considerations to take into account with the interpretation of these findings. Firstly, Schwann cells are actively proliferating in the early

postnatal nerve and this could certainly contribute to some of the reduction in global CpG methylation observed in the adult nerve. Secondly, genome wide hypo-methylation is a phenomenon that is observed in many tissues with aging and it is possible that some of the hypo-methylation seen between newborn and P60 sciatic nerve could be related to the aging process (M. J. Jones et al., 2015). Despite this, genetically increasing the global level of DNA methylation in the mouse sciatic nerve through knockout of *Gnmt*, an enzyme that regulates the level of S-adenosylmethionine, the major methyl donor, led to thinner myelin sheaths and a reduction in expression of a number of lipid metabolism genes important in the myelination process (Varela-Rey et al., 2014) (***Figure 2***). This does demonstrate that altering methylation levels can regulate Schwann cell myelination *in vivo*, however it remains uncertain what the relative contribution of methylation of DNA versus histones contributes to this phenotype and whether it occurs through a Schwann cell autonomous mechanism.

Cyclic AMP has been identified as a signal that could regulate the level of DNA methylation in Schwann cells during myelination. Firstly, treating cultured Schwann cells with cyclic AMP analogues, an *in vitro* assay for myelin differentiation, induces global CpG hypo-methylation of the Schwann cell methylome (Varela-Rey et al., 2014). Additionally, it has been shown that elevation of cyclic AMP levels in Schwann cells, *in vitro*, can increase 5hmC in promoters and gene bodies of up-regulated myelin genes (e.g. *Prx* and *Mbp*), likely through increasing the bioavailability of TETs cofactor Fe^{2+}, in a process that is independent of protein kinase A activation (Camarena et al., 2017) (***Figure 2***). In support of this, the activity of TETs in the sciatic nerve significantly increases as myelination proceeds (Varela-Rey et al., 2014). Genome-wide profiling of 5hmC has yet to be performed in peripheral nerve but in the CNS, it has been shown that hydroxy-methylation is a relatively abundant epigenetic mark compared to other tissues and is enriched in enhancers and gene bodies while largely absent from transcriptional start sites (Szulwach, Li, Li, Song, Wu, et al., 2011).

While these studies implicate CpG methylation and potentially hydroxy-methylation in regulating myelination in the PNS, we still do not know the relative roles of the DNMTs and TETs enzymes in the Schwann cell lineage. Furthermore, it is likely that

global DNA hypo-methylation is not the principal molecular mechanism driving myelination but works in concert with histone modifications, transcription factor binding and microRNA mediated post-transcriptional processing, which all have substantial roles in initiating myelination (reviewed in this issue by N. Tapinos and C. Jacob, and by M. Wegner). Finally, single-cell methylome studies will be required to further clarify the methylome signature in the Schwann cell lineage and, in particular, how the methylome of Remak Schwann cells differs from that of myelinating Schwann cells in adult peripheral nerves.

2.3. Schwann cell methylome changes after nerve injury

Whole genome shotgun bisulfite sequencing of sciatic nerve seven days after nerve transection demonstrated relatively few methylation changes (853 differentially methylated CpGs out of over 4 million identified) compared to uninjured nerves (Arthur-Farraj et al., 2017). At this time point post-nerve injury, all Schwann cells are either in the process of or are already transformed into repair Schwann cells (Arthur-Farraj et al., 2012; Gomez-Sanchez et al., 2017). One caveat to this kind of analysis is that Schwann cells compose 80% of the uninjured and between 50-70% of the injured peripheral nerve, raising the possibility that other cell types could contribute to the methylation signatures. While this cannot be completely excluded without performing single cell methylation analysis, the *in vivo* methylation profile of the injured nerve was strongly correlated with the methylation profile of cultured Schwann cells (which have similar morphology and gene expression to repair Schwann cells) but not macrophages, cultured endoneurial fibroblasts or perineurial cells (Arthur-Farraj et al., 2017). Often, global methylation changes are the hallmark of loss of lineage restriction and tumorigenesis (Baylin & Jones, 2016). The fact that we detected relatively few methylation changes after injury might reflect the observation that myelinating and Remak Schwann cells remain lineage restricted after conversion to repair Schwann cells and are not multipotent (Stierli et al., 2018).

Schwann cells react to injury by down-regulating myelin genes and up-regulating developmental genes, alongside expression of a new program of genes specialized for repair (Jessen & Arthur-Farraj, 2019). Furthermore, repair Schwann cell morphology is radically different to that of immature Schwann cells (Gomez-Sanchez et al., 2017). In line with this, the DNA methylation changes occurring during myelination in development are not reversed upon injury, as one might expect if this was simply de-differentiation (Arthur-Farraj et al., 2017; Varela-Rey et al., 2014). Together, this shows that the Schwann cell reaction to injury cannot be classified solely as 'de-differentiation', which it is often referred to as, but instead as an adaptive change of cellular state, which is required to promote effective nerve repair (Jessen & Arthur-Farraj, 2019; Jessen, Mirsky, & Arthur-Farraj, 2015) (***Figure 2***).

Among the limited methylation changes observed in the injured nerve, the majority of differentially methylated regions (DMRs) were localized in regulatory regions of the genome, including putative enhancer regions. DMRs in these regions showed enrichment of genes associated with ErbB, TGFβ and neurotrophin signaling, and occurred in the vicinity of binding sites for AP1 family, BACH2, MAFK and BATF transcription factors (Arthur-Farraj et al., 2017). Working in concert with other epigenetic modifications during nerve injury, DNA methylation changes may regulate expression of certain sets of genes through differential enhancer methylation and subsequent alteration of transcription factor binding. Conversely, altered methylation may occur as a result of transcription factor binding (Schübeler, 2015). The DNA demethylase, TET2 has been identified as having an important role in regulating enhancer methylation (Lister et al., 2013). In light of this, it would be particularly interesting to investigate whether TET2 and have a role in regulating demethylation/hydroxy-methylation at enhancers in Schwann cells.

3. DNA methylation in oligodendrocytes

3.1. The oligodendroglial cell lineage

Oligodendrocytes (OLs), the myelinating cells of the CNS, emerge from oligodendrocyte progenitor cells (OPCs), themselves deriving from neural stem cells. The switch from highly proliferative and migrative cells, characteristic of OPCs, to differentiating and ensheathing cells, specific to OLs, is regulated by the dynamic and orchestrated expression of specific transcription factors, from early specification (e.g. *Ascl1*, *Olig1/Olig2*, *Sox10*) to late maturation (e.g. *Yy1*, *Myrf*, *Zfp191*) (Emery et al., 2009; Y. He et al., 2007; Howng et al., 2010; Küspert & Wegner, 2016; Q. R. Lu et al., 2002; Nakatani et al., 2013). These processes are also regulated by epigenetic modifications, including chromatin remodeling (reviewed in this issue by C. Parras and QR. Lu), histones modifications (reviewed in this issue by J. Liu and G. Castelo-Branco) and DNA methylation.

3.2. DNA methylation in oligodendroglial cells during developmental myelination

DNA modification enzymes, DNMTs and TETs, are highly enriched in brain, liver and reproductive tissues, which correlate with high DNA methylation and hydroxy-methylation levels in the CNS, compared to other tissues (Globisch et al., 2010; W. Li & Liu, 2011; Ono, Uehara, Kurishita, Tawa, & Sakurai, 1993; Szulwach, Li, Li, Song, Wu, et al., 2011; Tawa, Ono, Kurishita, Okada, & Hirose, 1990). However, their levels at specific genomic regions dynamically vary during oligodendroglial cell development, from their specification to their differentiation.

In early developmental stages, specification of cortical neural stem cells into the glial lineage has been shown to be regulated by two successive DNA methylation waves, first global demethylation, followed by specific methylation and silencing of neuronal genes (Guo et al., 2014; Oswald et al., 2000; Sanosaka et al., 2017; Z. Wu et al., 2012). Low-methylated regions at promoters of astrocyte- and oligodendrocyte-specific genes are also enriched for gliogenic transcription factors, such as the nuclear factor I-binding motif, which are necessary to drive glial specification (Guoping Fan et al., 2005; Namihira et al., 2009; Sanosaka et al., 2017; Shu, Butz, Plachez, Gronostajski, & Richards, 2003).

Finally, acquisition of *de novo* methylation and hydroxy-methylation at specific astroglial (e.g. *Gfap*, genes involved in the JAK-STAT pathway) and oligodendroglial (e.g. *Olig1*, *Sox10*, *Id2/4*) genes distinguishes between these two glial lineages (Guoping Fan et al., 2005; Hatada et al., 2008; Takizawa et al., 2001; Teter et al., 1996; H. Wu et al., 2010; M. Zhang et al., 2019) (***Figure 3***).

The dynamic levels of DNA methylation and hydroxy-methylation in the oligodendroglial lineage, as well as their respective catalytic enzymes, DNMTs and TETs, suggest that these epigenetic marks are also essential for oligodendrocyte differentiation (Moyon et al., 2016; Y. Zhang et al., 2014; Zhao et al., 2014). An initial descriptive study detected a specific demethylation of the myelin gene, *Mag*, during OPC differentiation (Grubinska, Laszkiewicz, Royland, Wiggins, & Konat, 1994). Indeed, TET1, TET2 and TET3 have been shown to be necessary for OPC differentiation *in vitro* (Zhao et al., 2014). On the contrary, the blockade of the DNA methylation enzymes, *in vivo*, during rat CNS development, has been shown to delay myelination (Ransom, Yamate, Black, & Waxman, 1985). However, this study was using a non-specific demethylating drug, which also affected RNA metabolism and post-transcriptional processes. More detailed whole-genome methylome analysis comparing sorted neonatal OPCs and OLs has shown that OPC differentiation is associated with the same extent of hypo- as hyper-methylation. DNA methylation marks, identified by bisulfite-conversion sequencing, are mainly inversely correlated with gene expression during developmental myelination: genes with hypermethylated promoters and decreased expression in OLs compared to OPCs are associated with “neuronal lineage”, “cell cycle regulation” and “proliferation”, while genes with hypomethylated promoters and increased expression in OLs compared to OPCs are associated with “lipid processes” and “myelin components”. Decreasing methylation of differentiation genes after genetic ablation of *Dnmt1* in OPCs was not sufficient to induce their differentiation, as it was also associated with reduced methylation and hence defective repression, of cell cycle genes and activation of genotoxic stress and the ER stress response. Conversely, RNA-Sequencing of *in vitro* OPCs lacking *Tet1* revealed that downregulated genes were enriched for differentiation and cell cycle regulation genes. However, loss of *Tet1* in neonatal OPC was not sufficient to block their proliferation

and differentiation *in vitro* and *in vivo* (Moyon et al., 2019; M. Zhang et al., 2019). This highlights a more complex role for DNA methylation in the oligodendroglial lineage, requiring both methylation and demethylation of specific genomic regions (***Figure 3***). Further analysis of the RNA-Sequencing of sorted control and *Dnmt1*-mutant OPCs also identified different alternative splicing events, correlated with massive hypo-methylation at the exon-intron boundaries (Moyon et al., 2016). On one hand, alternative splicing events have been shown to be necessary for oligodendrocyte differentiation during normal myelination (de Ferra et al., 1985; Jordan et al., 1990; Kevelam et al., 2015; Nave, Lai, Bloom, & Milner, 1987; Y. Zhang et al., 2014), and on the other hand, to be correlated with DNA methylation marks (Gelfman et al., 2013; Lev Maor, Yearim, & Ast, 2015; Wan et al., 2013; Yearim et al., 2015). In OPCs, the gene ontology of the alternative spliced transcripts is enriched for genes involved in the cell cycle process and myelination (Moyon et al., 2016). This shows that DNA methylation and demethylation directly affect gene expression and alternative splicing in OPCs, and are both required for normal myelination.

Functional studies suggest specific roles for each DNMTs and TETs in the oligodendroglial lineage during development. Recently, *in vitro* loss-of-function experiments have shown that DNMT3A may participate in OPC survival and proliferation, while DNMT1 might be necessary for OPC differentiation (Egawa et al., 2019). DNMT1 could also affect oligodendroglial cells survival *in vitro*, as it has already been observed in embryonic stem cell, but these results were not duplicated *in vivo* (Egawa et al., 2019; Liao et al., 2015). Indeed, the genetic ablation of *Dnmt1* only – and not *Dnmt3a* – *in vivo* in OPCs (using *Olig1-cre* line) resulted in a severe hypo-myelination of the CNS, associated with tremors and decreased survival. In OPCs lacking *Dnmt1*, neither cell lineage specification nor survival were affected but, despite the hypomethylation of myelin genes, OPCs did not precociously proliferate or differentiate. Genetic ablation of *Dnmt1* or *Dnmt3a*, *in vivo*, in later stages of OL development (using *Cnp-cre* line) did not show any phenotype, which suggested that DNA methylation might only be required in the early steps of OPC differentiation *in vivo* (Moyon et al., 2016). This discrepancy suggests that *in vitro* and *in vivo* DNA methylation mechanisms might be slightly different, since epigenetic modifications can reflect extra-cellular and environmental cues. To better

correlate and understand the role of DNA methylation on gene expression and alternative splicing, it would also be necessary to analyze the different DNA methylation marks at the single-cell level in these knock-out mouse lines. Concerning DNA hydroxy-methylation, loss of *Tet2* or *Tet3* in the oligodendroglial lineage during developmental myelination did not show any phenotypes (Moyon et al., 2019; M. Zhang et al., 2019). While *in vivo* ablation of *Tet1* in OPCs (using *Olig1-cre* line) appears to result in a lower number of embryonic OPCs and slightly delayed OL differentiation at early stages (post-natal day 14), only in brain regions, the extent of the myelination and its ultra-structure in adult animals are comparable to controls (post-natal day 60) (M. Zhang et al., 2019). This would suggest that DNA hydroxy-methylation and its respective enzymes are not required for neonatal OPC differentiation during developmental myelination.

3.3. DNA methylation in oligodendroglial cells, in adult and aging

During development, a pool of undifferentiated adult OPCs is maintained and uniformly distributed in the grey and white matter of the adult CNS (Chang, Nishiyama, Peterson, Prineas, & Trapp, 2000; Dawson, Polito, Levine, & Reynolds, 2003; Pringle, Mudhar, Collarini, & Richardson, 1992; Wolswijk & Noble, 1989). Adult OPCs are not only immature and on-standby cells, as once thought. More and more evidence has confirmed their essential roles in the adult CNS, which includes directly regulating neuronal, glial and vascular systems (Frühbeis et al., 2013; Gautier et al., 2015; Hayakawa et al., 2011; Pham et al., 2012). They are also the main myelinating cells of the adult CNS, necessary for myelin remodelling, plasticity, learning and for remyelination (Bengtsson et al., 2005; Fancy et al., 2011; I. A. McKenzie et al., 2014; Young et al., 2013). However, adult OPCs have different proliferation, migration and differentiation capacities than neonatal OPCs, which result from their different transcriptomic profiles (Chari, Crang, & Blakemore, 2003; Clarke et al., 2012; Lin, Mela, Guilfoyle, & Goldman, 2009; Marques et al., 2016; Moyon et al., 2015; Spitzer et al., 2019). Many epigenetic marks have been demonstrated to

change with aging, but DNA methylation, especially, has been identified as the prominent epigenetic clock or age predictor (Bell et al., 2012; Hernandez et al., 2011; Horvath, 2013; Horvath & Raj, 2018; Masser et al., 2018; Shen et al., 2008; Stubbs et al., 2017; Szulwach, Li, Li, Song, Wu, et al., 2011; Unnikrishnan et al., 2019). This suggests that phenotypic differences observed between adult OPCs and neonatal OPCs could also reflect age-related methylomic changes.

The role of DNA methylation and DNMTs has recently been reported *in vivo* in adult OPCs during remyelination. Genetic ablation of *Dnmt1* and/or *Dnmt3a* in the oligodendroglial lineage impairs OPC differentiation into mature OLs, leading to thinner and delayed remyelination, following lysolecithin-induced focal demyelination in ventral spinal cords (Moyon et al., 2017). Interestingly, loss of a single *Dnmt* is less dramatic than loss of both *Dnmt1* and *Dnmt3a*, suggesting compensatory or redundant roles for DNMTs in adult OPCs, an observation not seen in neonatal OPCs. The lack of *Dnmt1* reduced differentiation in both neonatal and adult OPCs, but only proliferation in neonatal OPCs (Moyon et al., 2016, 2017) (***Figure 3***). This suggests an age-dependent role for DNA methylation in OPC differentiation. One caveat with this conclusion is that the neonatal and adult studies used slightly different genetic strategies (i.e. *Olig1-cre* line targeting early progenitors in developmental brain and *Plp-cre* line targeting newly formed oligodendrocytes in adult brain), so the effects observed on the cell cycle may simply reflect the distinct proliferative potential of these two targeted cell populations, and not only their age-related differences (Moyon et al., 2016, 2017). Future parallel studies comparing the contribution of DNA methylation to neonatal and adult progenitor function are needed to fully address these issues.

In adult human tissues, TET genes have been shown to be enriched in the oligodendroglial lineage compared to neuronal subtypes. DNA methylation and hydroxy-methylation levels appear to be cell type-specific in the adult CNS, which might suggest an interesting specification role in each cell lineage, including oligodendrocytes (Kozlenkov et al., 2018). Recent studies have functionally shown that TET1 – and not TET2 or TET3 – is the main DNA hydroxy-methylation enzyme regulating adult OPC differentiation (Moyon et al., 2019; M. Zhang et al., 2019). Following lysolecithin-induced

lesion in young adult ventral spinal cords, efficient remyelination appears to be correlated with high TET1 expression and increased DNA hydroxy-methylation in the oligodendroglial population. Moreover, ablation of *Tet1* in the oligodendroglial lineages impaired OL differentiation and delayed remyelination. In aging mice, defective remyelination was also associated with lower TET1 expression and no increased DNA hydroxy-methylation in the oligodendroglial cells. Interestingly, impaired remyelination observed in young mice lacking *Tet1* seems to recapitulate the hallmarks of an aging phenotype, such as delayed repair and ultra-structural peri-axonal swellings, which would eventually lead to defective neuronal functions (Moyon et al., 2019). Altogether, these new evidences highlight the essential role of TET1-mediated DNA hydroxy-methylation in adult OPC, especially after injury, and its potentially deleterious role during aging repair.

3.4. DNA methylation in oligodendroglial cells in diseases

Epigenetic mechanisms, including DNA methylation, have particular relevance for human neurodegenerative and psychiatric disease. The development of genome-wide DNA methylation studies of human post-mortem brain tissues has highlighted methylation and demethylation changes in Alzheimer's disease, Parkinson disease, amyotrophic lateral sclerosis and schizophrenia (Chestnut et al., 2011; Desplats et al., 2011; Jaffe et al., 2015; P. Li et al., 2019; Semick et al., 2019). These datasets have mainly been performed on whole-tissue, and their analysis have followed an historically neuro-centric hypothesis. Though previously overlooked, the role of oligodendroglial cells in neurological disorders has recently been the focus of a number of studies (Chen, Huang, Michael, & Xiao, 2015; A. T. McKenzie et al., 2017; Nasrabady, Rizvi, Goldman, & Brickman, 2018; Nguyen et al., 2013). New single-nucleus isolation and sequencing technology have now noted specific DNA methylation changes in oligodendroglial populations in Alzheimer's disease and in schizophrenia. In these studies, DNA methylation changes appeared to be as frequently represented in the oligodendroglial

population as in the neuronal population, but occurring at different genomic regions between the two cell populations (Gasparoni et al., 2018; Mendizabal et al., 2019). DNA methylation dysregulation in OPCs and OLs could be associated with several pathologies, as patients with deficiency in S-adenosylhomocysteine hydrolase have been observed to also present correlative CNS hypomyelination (Barić et al., 2004).

Indeed, alterations in DNA methylation have been reported in diseases that affect the oligodendroglial lineage, such as Multiple Sclerosis (MS). MS is a common immune-mediated CNS disease, characterized by oligodendroglial loss and focal attacks of demyelination, which are frequently associated with neurodegeneration (Ghosh et al., 2011; International Multiple Sclerosis Genetics Consortium*†, 2019; Oluich et al., 2012). A recent study has shown that *DNMTs* are up-regulated and *TETs* down-regulated in demyelinated areas of the hippocampus from MS patients, which would suggest that one would expect an increase in methylation in MS tissues (Chomyk et al., 2017). However, DNA methylation sequencing of MS-affected brain tissues revealed a variety of methylomic changes in MS-affected normal appearing white matter (NAWM) and hippocampus compared to controls. For example, genes known to regulate oligodendroglial survival and differentiation (i.e. *BCL2L2*, *NDRG1, NFASC*) are hyper-methylated and down-regulated in MS NAWM samples, which could affect the OPCs' response capacities and overall remyelination in patients (Chomyk et al., 2017; Huynh et al., 2014). In contrast, genes implicated in proteolytic processing (i.e. *LGMN*, *CTSZ, PAD2*) are hypo-methylated and up-regulated in MS NAWM samples, which could even have the capacity to trigger the disease (Chomyk et al., 2017; Huynh et al., 2014; Mastronardi, Noor, Wood, Paton, & Moscarello, 2007). Indeed, PAD2 can citrullinate myelin basic protein (MBP), which results in the breakdown of myelin, the release of myelin protein fragments and a subsequent immune response (Mastronardi & Moscarello, 2005; Mastronardi et al., 2006). Citrullination of MBP has been shown to be elevated in MS tissues compared to controls, which directly correlates with hypo-methylation and up-regulation of *PAD2*, and with increased levels of PAD2 enzyme (Mastronardi et al., 2007; Moscarello, Wood, Ackerley, & Boulias, 1994). These findings suggest that complex DNA methylation changes in OPCs and OLs could contribute to MS pathology, possibly by

affecting both demyelination and remyelination. Knowing the predominant incidence of MS in women compared to men, it is also worth noting that a recent study has shown that DNA methylation changes observed during aging in mouse hippocampus were sex-specific. DNA methylation did not differ between males and females in young tissues but more than 95% of age-related changes occurred in methylation at specific sites in one sex but not the other (Masser et al., 2017). Further oligodendroglial-specific and sex-specific analysis would be interesting to address the potential role of DNA methylation in MS incidence and pathology.

4. The role of DNA methylation in Schwann cell and oligodendroglial tumors

4.1. Glial origin of some PNS and CNS tumors

The main Schwann cell tumors are benign Schwannomas and neurofibromas, and malignant peripheral nerve sheath tumors (MPNST) (for reviews see (Evans et al., 2002; Hilton & Hanemann, 2014; Ratner & Miller, 2015)). The commonest genetic abnormality found in sporadic Schwannomas is mutation in the *NF2* gene, which codes for the protein, Merlin (Hilton & Hanemann, 2014). Patients with neurofibromatosis type 1 (NF1), develop amongst other neoplasms, cutaneous and plexiform neurofibromas, which are thought to be predominantly Schwann cell tumors but which also contain other cell types. All neurofibromas are associated with bi-allelic inactivation of the *NF1* gene, which codes for the tumor suppressor protein, neurofibromin, an inhibitor of RAS signaling (Ratner & Miller, 2015). In a proportion of NF1 patients, plexiform neurofibromas will transform into MPNSTs, however 50% of MPNST do occur sporadically. These tumors are highly aggressive and generally have a poor prognosis (Farid et al., 2014).

Gliomas are the most common type of primary brain tumors in adults and they are usually characterized by poor prognoses (Ohgaki & Kleihues, 2005). Molecular characterization of gliomas suggest that they originate from proliferative cells, such as neural stem cells, astrocytes and OPCs (for review see (Zong, Parada, & Baker, 2015)). Histopathological analysis of human glioma samples (e.g. expression of OPC-specific markers, such as NG2 and Olig2) and analysis of the molecular signature of proneural glioblastomas (e.g. expression of *PDGFRα*, *NKX2-2*, *OLIG2*) strongly suggest an oligodendroglial origin (Ligon et al., 2004; Q. Richard Lu et al., 2001; Shoshan et al., 1999; Verhaak et al., 2010). Proneural gliomas present alterations of *PDGFRα*, such as mutations and/or amplifications, often associated with point mutations in tumor protein gene *TP53* and in isocitrate dehydrogenase (IDH) 1 (Verhaak et al., 2010). Interestingly, three recent studies even highlighted the synaptic interaction of OPC-like cells with neural circuits in gliomas, which might promote their progression (Venkataramani et al., 2019; Venkatesh et al., 2019; Zeng et al., 2019).

4.2. Aberrant DNA modifications in Schwannomas and glioblastomas

Aberrant DNA methylation is strongly implicated in tumorigenesis. There are three ways DNA methylation can contribute to an oncogenic phenotype: firstly by enabling somatic and germline mutation through deamination of 5mC to thymine within gene bodies, following exposure to UV irradiation or carcinogens; secondly by global hypo-methylation; and thirdly by hyper-methylation of CGI promoters of tumor suppressor genes (Baylin & Jones, 2016).

In some gliomas, OPC proliferation and apoptosis dysregulation has been directly linked to mutation of genes involved in the DNA methylation/demethylation cycle. IDH1/2 mutation, which is frequently detected in these types of cancers, has been shown to induce the accumulation of 2-Hydroxyglutarate, inhibiting Alpha-Ketoglutarate-dependent deoxygenase and the metabolic-epigenetic interplay, leading to alteration of both histone and DNA methylation patterns (Christensen et al., 2011; Ohba & Hirose, 2018; Unruh et al., 2019; Yan et al., 2009).

Many tumors, and especially gliomas, have been characterized by extensive global DNA hypo-methylation, associated with aberrant activation of genes and non-coding regions (Chou et al., 2012; Chu et al., 2011; Felsberg et al., 2006; Jia et al., 2019; Sharma, Kelly, & Jones, 2010; Uhlmann et al., 2003; Watanabe & Maekawa, 2010; J. Zhang et al., 2016). Inversely, 5hmC enrichment, potentially allowing gene expression activation, has also been detected in enhancers implicated in glioma pathogenesis (Glowacka et al., 2018; Johnson et al., 2016). A number of studies have also shown that the significant DNA methylation changes observed in Schwann cell tumors are likely to contribute to their pathogenesis, as well as aid in their classification. Firstly, the global methylation profiles of Schwannomas differ based on their anatomical location, as cranial Schwannomas show different methylation patterns to spinal Schwannomas (Agnihotri et al., 2016). Genome-wide methylation mapping using MeDIP-Seq, which immunoprecipitates methylated DNA prior to whole genome sequencing, compared the methylome of benign Schwannomas, MPNSTs and cultured human Schwann cells. This study found over 100,000 DMRs between samples, including hyper-methylation of tumor suppressor genes, hypo-methylation of oncogenes and differential methylation of CGI shores. Yet, the most common methylation change was hypo-methylation of non-intronic satellite regions, particularly SATR1 and ARLalpha satellite repeat regions (Feber et al., 2011). Microsatellite instability does not appear to be a frequent aberration in MPNSTs suggesting that hypo-methylation of these regions may have a more complex role, possibly in the regulation of nearby genes, though this remains to be tested (Serra et al., 1997). A genome-wide methylation microarray of vestibular Schwannomas demonstrated a trend towards hypo-methylation with more differential methylation identified away from CGIs, similar to the findings in MPNSTs (Feber et al., 2011). Significant hypo-methylation of the *Hox* gene cluster was identified as a commonly occurring alteration but this study did not identify any *NF2* promoter hypermethylation, unlike previously (Feber et al., 2011; Gonzalez-Gomez, Bello, Arjona, et al., 2003; Torres-Martín et al., 2015).

In parallel, tumors, such as gliomas, have been characterized by regional DNA hyper-methylation at specific loci, correlated with silencing of tumor suppressor genes (Chou et al., 2012; Chu et al., 2011; Felsberg et al., 2006; Jia et al., 2019; Sharma et al.,

2010; Uhlmann et al., 2003; Watanabe & Maekawa, 2010; J. Zhang et al., 2016). In Schwannomas and MPNSTs, a number of early and targeted studies have also identified promoter hyper-methylation of tumor suppressor genes and their subsequent inactivation, which appeared as potential mechanism for how aberrant DNA methylation contributes to tumorigenesis (Gonzalez-Gomez, Bello, Alonso, et al., 2003; Gonzalez-Gomez, Bello, Arjona, et al., 2003; Kawaguchi et al., 2006; Kino et al., 2001; Oh et al., 2015). Promoter hyper-methylation of the downstream effectors of Merlin/NF2, *Lats1* or *Lats2*, has been described in Schwannomas and it was recently shown in mice that specific deletion of both *Lats1* and *Lats2* in Schwann cells can lead to MPNST generation (Oh et al., 2015; L. M. N. Wu et al., 2018). In contrast to *Nf2*, hyper-methylation of the *Nf1* promoter does not seem to occur in Schwann cell tumors (Feber et al., 2011; Fishbein, Eady, Sanek, Muir, & Wallace, 2005; Harder et al., 2004; Luijten et al., 2000). However, site specific methylation of discrete CpGs in *SP1*, *AP2* and *CRE* binding sites in the *Nf1* promoter may affect transcription factor binding and *NF1* expression in neurofibromas and MPNSTs (Harder et al., 2004; Kino et al., 2001; Mancini, Singh, Archer, & Rodenhiser, 1999).

DNA methylation modifications have been highly correlated with tumorigenesis and prognosis of Schwannomas, MPNSTs, and gliomas, which suggests that specific methylating and demethylating agents could be potential therapies to prevent cancer cell progression in these tumours (Aoki & Natsume, 2019; de Souza et al., 2018; Heiland et al., 2016; Yanwei Liu et al., 2015; Ohba & Hirose, 2018). Certainly epigenetic therapies targeting the polycomb repressive complex 2 (PRC2) are a promising current avenue of research for MPNSTs and high grade gliomas given genetic studies strongly implicate PRC2 and loss of Histone H3K27 methylation in their progressions (De Raedt et al., 2014; Filbin et al., 2018; Lee et al., 2014; Nagaraja et al., 2017; Natalie Wu & Lu, 2019; M. Zhang et al., 2014). Presently, the main challenges facing the field are to discern whether the differential methylation observed in tumors are more cause or consequence of the oncogenic process. Furthermore, what role does the DNA methylation machinery have in the development of Schwannomas, MPNSTs and gliomas? Finally, we still don't understand the hierarchical interaction between DNA methylation, histone modifications

and chromatin states within individual tumor cells and this needs to be addressed to develop better future treatments (Baylin & Jones, 2016).

4. Concluding remarks

A growing body of evidence supports a prominent role for both DNA methylation and potentially DNA hydroxy-methylation in Schwann cells and oligodendroglial cells lineages, during development and in a number of neurological diseases, including tumors. A better integration of these specific 5mC and 5hmC marks with other epigenetic layers, such as histone modifications, chromatin remodeling or microRNA post-transcriptional processing, would be essential to clearly map their respective roles on gene regulation during myelinating cells proliferation and differentiation processes. New tools, including specific 5fC and 5caC antibodies and sequencing techniques, should also now allow a better comprehension of these DNA modifications marks. Single-cell sequencing coupled with methylome analysis would be essential to precisely address the functional role of epigenetic marks, which are highly specific between each cell type and within each cellular lineage, between developmental times and within aging, injury and disease.

Figures

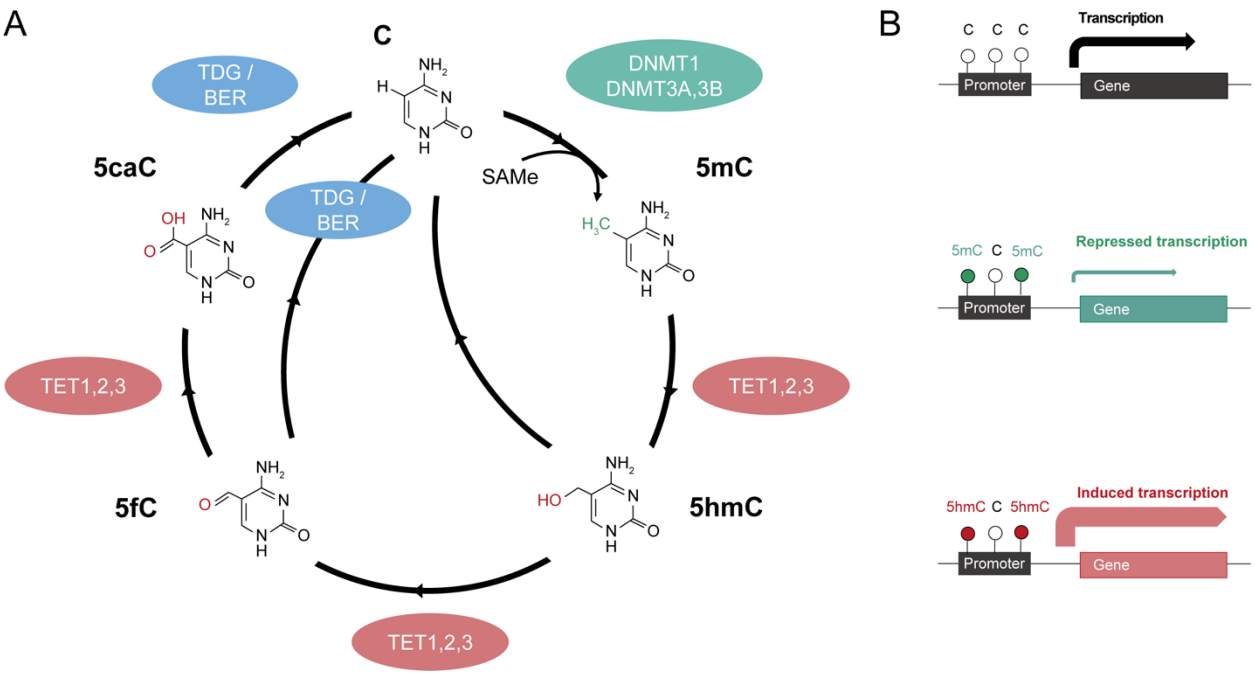

Figure 1. DNA methylation/demethylation cycle

(**A**) A class of enzymes called DNA methyltransferases (DNMT1, DNMT3A, 3B) methylate cytosines (C) by transferring a methyl group from S-adenosylmethionine (SAMe). 5-methylcytosine (5mC) can be oxidized by ten eleven translocation (TET) enzymes (TET1, TET2, TET3) to 5-hydroxy-methylcytosine (5hmC), to 5-formylcytosine (5fC), then 5-carboxylcytosine (5caC). The last demethylation step is catalyzed by thymine-DNA glycosylase (TDG), followed by base excision repair (BER). (**B**) Generally, DNA methylation (5mC) marks are associated with gene repression, while DNA hydroxy-methylation (5hmC) marks are correlated with gene expression.

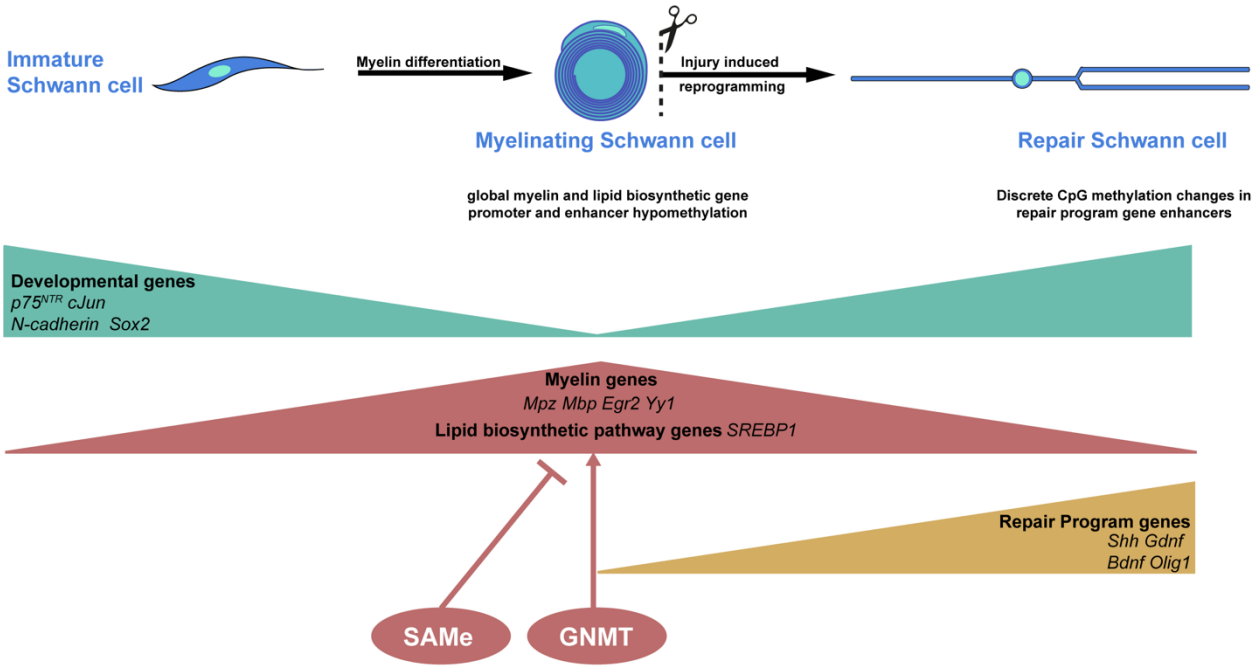

Figure 2. DNA methylation in Schwann cells during myelination and after nerve injury.

The transition from immature Schwann cell to myelinating Schwann cell is accompanied by hypomethylation of promoters and enhancers of myelin and lipid biosynthetic pathway genes. The DNA methyltransferase, Glycine N-methyltransferase (GNMT), which metabolizes S-Adenosylmethionine (SAMe), positively regulates the myelination process, whereas increases in the levels of SAMe negatively regulate myelination (Varela-Rey et al., 2014). The transformation of myelinating Schwann cells to Repair Schwann cells after nerve injury is accompanied by down-regulation of myelin genes, up-regulation of developmental genes and also of repair program genes (Jessen & Arthur-Farraj, 2019). There are no global methylome changes in Schwann cells upon nerve injury but discrete differential methylation in putative repair program gene enhancers (Arthur-Farraj et al., 2017).

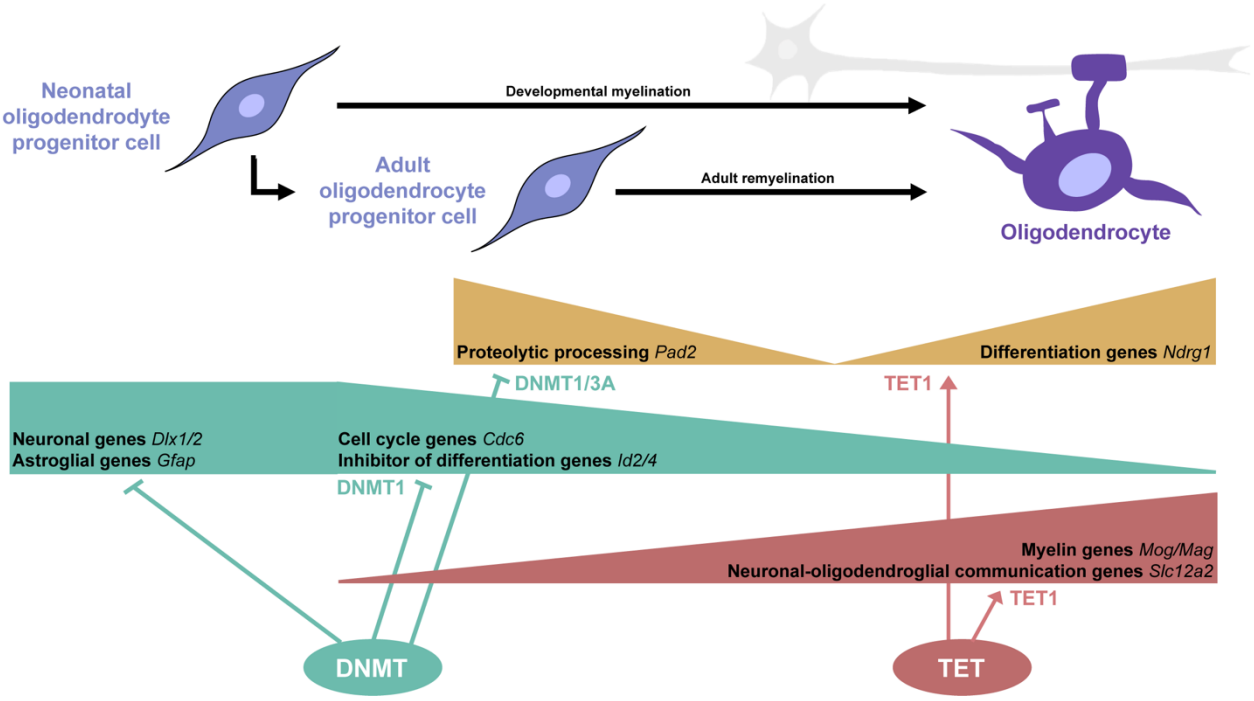

Figure 3. DNA methylation in oligodendroglial cell differentiation during myelination and remyelination.

Oligodendroglial cell lineage differentiation is regulated by both DNA methylation and demethylation. Early DNA methylation of neuronal and astroglial lineage genes induce oligodendroglial specification. During oligodendrocyte progenitor cell differentiation, DNA methylation – mediated by DNMT1 during development and mainly DNMT3A in adult - has been associated with transcriptional repression of proliferation genes and of inhibitor of differentiation genes. In contrary, DNA demethylation has been observed on differentiation and myelin genes, resulting from TET activity that induces the OPC differentiation program, during developmental myelination and repair.

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