Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Neurobiology

Epigenetic control of oligodendrocyte development: adding new players to old keepers

Jia Liu[1], Sarah Moyon[1], Marylens Hernandez[1] and Patrizia Casaccia[1,2]

Emerging and strengthening evidence suggests an important role of myelin in plasticity and axonal survival. However, the mechanisms regulating progression from oligodendrocyte progenitor cells (OPCs) to myelinating oligodendrocytes remain only partially understood. A series of overlapping yet distinct epigenetic events occur as a proliferating OPC exits the cell cycle, initiates differentiation, and becomes a myelin-forming oligodendrocyte that wraps axons. Here we discuss recent advances towards understanding the epigenetic control of oligodendrocyte development that integrates environmental stimuli. We suggest that OPCs are directly responsive to extrinsic signals due to predominantly euchromatic nuclei, while the heterochromatic nuclei render differentiating and myelinating cells less susceptible to signals modulating the epigenome.

Addresses

[1] Department of Neuroscience, Friedman Brain Institute and Mount Sinai School of Medicine, One Gustave Levy Place, New York, NY 10029, United States

[2] Department of Genetics and Genomics, Friedman Brain Institute and Mount Sinai School of Medicine, One Gustave Levy Place, New York, NY 10029, United States

Corresponding author: Liu, Jia (Jia.Liu@mssm.edu)

Current Opinion in Neurobiology 2016, **39**:133–138

This review comes from a themed issue on **Cellular neuroscience**

Edited by **Bettina Winckler** and **Mikael Simons**

For a complete overview see the Issue and the Editorial

Available online 14th June 2016

http://dx.doi.org/10.1016/j.conb.2016.06.002

Introduction

Oligodendrocytes provide metabolic support and insulation to axons of the CNS, and are responsive to environmental activity [1,2,3••,4–6]. Oligodendrocytes are generated from proliferating oligodendrocyte progenitors cells (OPCs). Upon extracellular signals, OPCs differentiate into post-mitotic premyelinating oligodendrocyte and subsequently myelinate adjacent axons. This process is driven by the interplay of extracellular signals with intrinsic molecular components, in which epigenetic regulation plays a fundamental role in governing the accessibility of transcriptional machinery to DNA sequences, and comprises DNA and histone modifications, histone variants, ATP-dependent chromatin remodeling complexes, microRNAs, and long intergenic noncoding RNAs (lincRNAs). This review focuses on recent advances in understanding epigenetic control leading to both transcriptional repression and activation during oligodendrocyte development. We discuss the potential mechanisms by which environmental signals are transduced into intracellular actions through epigenetic modifications, and how this process is disrupted in neurologic diseases.

Epigenetic changes resulting in transcriptional repression during oligodendrocyte development

OPCs derive from multipotential neuroectodermal derivatives and are characterized by expression of molecules regulating migration and proliferation, and lack expression of myelin [7,8] and pluripotency [9] genes. At the ultrastructural level, OPCs exhibit euchromatic nuclei, defined by a relaxed chromatin structure and easy DNA accessibility. Therefore, OPCs can transduce extracellular signals to transcription factors, which often recruit large protein complexes containing co-activators or co-repressors and histone-modifying enzymes to accessible DNA sequences, allowing for the transcriptional activation or repression of genes regulating lineage determination, proliferation, and migration. The transition from OPC to premyelinating oligodendrocyte is initiated by downregulation of genes involved in proliferation and inhibition of differentiation. This process is characterized by progressive heterochromatin formation [4], starting at the nuclear periphery, where the nuclear lamins are localized, and radially converging towards the nuclear center.

A large body of evidence supports a model where histone deacetylase (HDAC) activity is necessary in the premyelinating stage to remove the inhibitory 'brakes' on myelin gene expression [10–12]. For instance, HDAC1 and HDAC2 were shown to compete with beta-catenin for TCF7L2 interaction to repress Wnt target genes, thereby allowing oligodendrocyte differentiation [12]. During the early differentiation stage, TCF7L2 interacts with a transcriptional corepressor Kaiso/Zbtb33 to block beta-catenin signaling, whereas during maturation, TCF7L2 recruits and cooperates with SOX10 to promote

myelination [13]. Thus, TCF7L2 utilizes coregulators in a stage-specific manner to coordinate the activation or repression of transcriptional events.

Silencing of pluripotency and neuronal-lineage genes remains constant throughout differentiation, and has been attributed to the activity of the histone methyltransferases [14,15•], including EZH2, a polycomb protein family member, which deposits triple methyl groups on lysine residue K27 of histone H3 (H3K27me3), and other histone methyltransferases that target K9 (H3K9me3). Genome-wide studies using neonatal OPCs found EZH2 occupancy at pluripotency gene loci and certain genes determining neuronal and astrocytic lineage [16], which was further confirmed by a recent study characterizing the presence of H3K27me3 and H3K9me3 at these loci [15•]. Interestingly, there are very few genes that share H3K27me3 and H3K9me3 marks in OPCs and premyelinating oligodendrocytes [15•], suggesting they play overlapping yet unique repressive roles. While the initial loss of neurogenic ability as neural stem cells transition into OPCs is likely established via repression mediated by H3K27me3 [14,16], H3K9me3 serves as the predominant repressive mechanism for subsequent transition into premyelinating oligodendrocytes [15•]. An exception to this is observed with myelin genes, which can be found in a 'bivalent' state with coexisting H3K27me3 and H3K4me3 marks. This dual code defines a state of transcriptional competence that prevents myelin genes from being inappropriately expressed, but allows them to remain 'poised' for subsequent activation upon differentiation [8].

DNA methylation is a traditional yet new epigenetic player in oligodendrocyte development. Dynamic expressions of DNA methyltransferases and ten-eleven translocation enzymes (TETs) in the oligodendroglial lineage suggested that DNA methylation and hydroxymethylation are essential for oligodendrocyte differentiation [17,18]. Indeed, TET1, TET2, and TET3 have been shown to be necessary for oligodendrocyte differentiation *in vitro* [18]. Recently, a whole-genome transcriptome and methylome analysis comparing OPCs and oligodendrocytes revealed that DNA methylation is inversely correlated with gene expression during developmental myelination. However, new data show that reduction of DNA methylation via genetic ablation of *Dnmt1* in OPCs is not sufficient to induce differentiation, but rather results in severe hypomyelination of the CNS associated with aberrant alternative splicing events and activation of an ER stress response [19•]. This suggests that DNA methylation acts as a regulator of the OPC state and subsequent transition into differentiating oligodendrocytes.

Regulation from non-coding RNAs, including microRNAs and lincRNAs, is more discrete, targeting expression at the transcript level. miR-23 was recently found to enhance oligodendrocyte differentiation by negatively regulating phosphatase and tensin homolog on chromosome 10 (*Pten*) via the activation of a lincRNA *2700046G09Rik* [20]. In addition, miR-23 suppresses expression of the nuclear envelope protein lamin B1, the overexpression of which leads to perturbation of nuclear membrane structure, chromatin organization, and oligodendrocyte differentiation and myelination [21–24]. *OLMALINC* (oligodendrocyte maturation-associated long intervening non-coding RNA) is a recently identified primate-specific lincRNA that is highly expressed in the white matter of the human frontal cortex [25]. Knockdown of *OLMALINC* in human oligodendrocyte cell lines upregulates inhibitors of oligodendrocyte differentiation, including genes regulating maintenance of cytoskeleton structure, cellular adhesion, and membrane signaling. These recent studies suggest the importance of coordination of protein and non-coding RNAs in oligodendrocyte maturation, particularly in the myelin maintenance stage. However, the *in vivo* relevance of non-coding RNAs in oligodendrocyte development remains to be further determined.

Epigenetic changes resulting in transcriptional activation during oligodendrocyte development

Much less is known about epigenetic regulation that leads to transcriptional activation during oligodendrocyte differentiation. OPCs are characterized by their competence of generating multi-lineage cells in addition to oligodendrocyte. A recent study using genome-wide analysis combined with fate mapping revealed that HDAC3 competes with STAT3 for p300, a histone acetyltransferase, to activate expression of oligodendrocyte lineage-specific genes, such as *Olig2*, while repressing astrocyte lineage-specific genes, such as *Nfia* [26].

The limited accessibility of DNA sequences to transcription factors within the nuclei of differentiating oligodendrocytes restricts their responsiveness to extracellular signals. However, access to specific binding sites can be provided via displacement of nucleosomes by ATP-dependent chromatin remodeling complexes. Chromatin immunoprecipitation-sequencing (ChIP-seq) analysis with RNA polymerase II identified *Smarca4*/*Brg1*, which encodes the central catalytic ATPase subunit of the SWI/SNF chromatin-remodeling complex, as the most significant target during the initiation of oligodendrocyte differentiation [27••]. Furthermore, BRG1 chromatin remodeler is prepatterned with OLIG2 to facilitate expression of oligodendrocyte lineage-specific genes [27••], functioning as a feed-forward loop, as the OLIG2/BRG1 complex further targets another chromatin remodeling enzyme, the ATP-dependent chromodomain helicase DNA-binding protein 7(*Chd7*). Genome-wide mapping of CHD7 target sites revealed that CHD7 forms complexes with SOX10 to activate positive regulatory oligodendrocyte genes, thereby initiating the myelination