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The epigenetic landscape of oligodendrocyte lineage cells

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Abstract

The epigenetic landscape of oligodendrocyte lineage cells refers to the cell-specific modifications of DNA, chromatin, and RNA that define a unique gene expression pattern of functionally specialized cells. Here, we focus on the epigenetic changes occurring as progenitors differentiate into myelin-forming cells and respond to the local environment. First, modifications of DNA, RNA, nucleosomal histones, key principles of chromatin organization, topologically associating domains, and local remodeling will be reviewed. Then, the relationship between epigenetic modulators and RNA processing will be explored. Finally, the reciprocal relationship between the epigenome as a determinant of the mechanical properties of cell nuclei and the target of mechanotransduction will be discussed. The overall goal is to provide an interpretative key on how epigenetic changes may account for the heterogeneity of the transcriptional profiles identified in this lineage.

Keywords

brain; chromatin; development; histone; myelin; transcription

INTRODUCTION

While all the cells of an organism share the same genetic information, functional specialization is achieved by the establishment of a cell-specific transcriptional program. The spatial organization of the genome within nuclear territories, its relationship with the nuclear lamina, together with modifications of nucleic acids and histone proteins, and the state of compaction of chromatin, collectively define the epigenomic landscape of a

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I.S. prepared the first draft and wrote the section on RNA processing as well as prepared Figures 1 and 2. E.P. wrote the section on mechanotransduction and prepared Figure 3. P.C. edited and revised the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

cell. Parts of the genome containing genes not compatible with specialized cell functions are rendered inaccessible, while other regions regulating functional specificity are made accessible and become either poised for transcription or transcriptionally competent.

In the nuclei of eukaryotic cells, the DNA is wrapped around protein octamers called histones, which define the nucleosome, the basic unit of chromatin. The amino acids in the N terminal tails of these proteins undergo several post-translational modifications, including lysine acetylation, methylation or ubiquitination, serine phosphorylation, and arginine methylation or citrullination. These histone marks result from the concerted actions of enzymatic histone writers (responsible for the deposition of the modification) and erasers (responsible for the removal of the modification). The modified amino acids are recognized by specialized reader proteins via specific recognition domains, including bromodomains that recognize lysine acetylation or chromo-domains that recognize methylated residues. DNA can also be modified by the addition of a methyl group at the 5′ cytosine residue (5mC), resulting in transcriptional repression, or by the oxidation of the methyl group (5hmC), leading to hydroxymethylation, associated with transcriptional activation. The dynamic regulation of histone and DNA modifications is associated with distinct transcriptional states allowing for transcriptionally competent euchromatin or repressed heterochromatin. Eukaryotic cell nuclei also possess higher-order organization in large domains of repressed or active chromatin within specific topological domains.

DNA methylation masking transcription factor recognition sites, repressive histone modifications, chromatin compaction, and recruitment to the nuclear lamina act by hindering the access of transcription factors to DNA, reducing or diminishing the ability of cells to respond to external cues (Figure 1). Gene-poor or -silenced genomic regions are recruited to the nuclear periphery where they interact within the nuclear lamina, forming lamina-associated domains (LADs),[1,2] while gene-rich transcriptionally active regions tend to arrange around transcription factors to form transcriptional “factories” and cluster into topologically associating domains (TADs)[3–5] (Figure 2). While these domains and associated modifications are generally stable, they also have the potential to be reversed, and this implies that the epigenetic landscape is not static, but allows for adaptation to external conditions.

Here, we will first discuss some generalities on mechanisms of repression and activation, then address the role of histone and DNA modifications during oligodendrocyte lineage progression, followed by a discussion of their crosstalk with mechanisms of RNA processing and we conclude with a review of the role of nuclear chromatin and lamina in determining the mechanical properties of the nuclei and also as a point of convergence of physical forces in the regulation of gene expression.

General concepts of epigenetic regulation of gene expression

Acetylation of lysine residues in the histone tails is considered a modification permissive for transcription, as it neutralizes the positive charge of the amino acid, loosens the interaction with negatively charged DNA, and facilitates the access of transcription factors. This modification is modulated by the opposing actions of writer histone acetyltransferases (HATs) and eraser histone deacetylases (HDACs) and is, therefore, suitable for the dynamic

regulation of genes.[6,7] Histone methylation is a more complex event, catalyzed by enzymes that transfer one or more methyl groups on specific lysine or arginine residues.[8] The transcriptional outcome is dependent on the number of methyl groups added to lysine residues (mono-, di-, or tri-methylation), as well as the position of a given lysine residue within the histone tails. For instance, lysine K4 in histone H3 is associated with transcriptional activation. In its monomethylated state (H3K4me1), this modification is found in active enhancers, while its trimethylated state (H3K4me3) marks transcriptionally active promoters.[9,10] This modification is placed by the enzymatic writers MLL1/KMT2A and MLL4/KMT2B and reversed by the enzymatic erasers KDM5A/JARID1B and KDM5B/JARID1A. Dimethylation of arginine residues, catalyzed by protein methyl transferases PRMTs, has been shown to play an important role in transcriptional activation or repression, depending on the position of the arginine residue and whether the deposition of the methyl groups is symmetrically or asymmetrically placed.[11] While specific erasers for arginine methylated marks have not been identified, the activity of deiminase enzymes (PADI) responsible for the conversion of arginine into citrulline has been proposed to reverse the transcriptional consequences of arginine methylation on histones.[12]

The trimethylation of K9 and K27 residues in histone H3 results in transcriptional repression. The enzymes responsible for H3K27me3 deposition are part of the Polycomb group PRC2 (e.g., EZH1 and EZH2), which deposit the mark at transcriptionally inactive promoters.[13] Recognition of the H3K27me3 mark by distinct chromo-domain binding proteins can lead to poised expression or stable repression, depending on whether the recruited PRC1 complexes (RING1A and B) induce ubiquitination of specific lysine residues in histone H2A (and result in poised expression of genes) or recruit NURD repressive complexes and lead to heterochromatin formation.[14] Thus, even though erasers for the H3K27me3 mark exist (i.e., UTX/KDM6A and JMJD3/KDM6B), the activity of the PRC2 complex results in long-term repression due to chromatin compaction.

H3K9me3 marks are deposited by specific histone writers (e.g., SUV39H1/2) and removed by erasers, such as KDM3A/JMJD1 and KDM4/JMJD2. Both writers and erasers are highly expressed in the oligodendrocyte lineage,[15–17] thereby suggesting that this modification may play an essential role in regulating transient repression. In addition, H3K9me3 marks have been shown to be recognized by specific readers (such as HP1-α)[18] and contribute to chromatin compaction and recruitment to the nuclear periphery.

DNA methylation catalyzed by methyltransferases (DNMTs) plays an essential role in many biological processes, including transcription and cellular differentiation. DNA methylation preferentially occurs at exon-boundaries, characterized by high CpG density.[19,20] It has been shown that DNA methylation cooperates with other histone modifications to further stabilize repression. For instance, the 5mC mark is recognized by a family of proteins carrying conserved methyl-CpG binding domains (e.g., MECP2), which recruits other histone modifiers and further alters the local chromatin conformation.[21–23] Importantly, MECP2 was reported to also regulate alternative exon splicing by recruiting HDACs and altering the kinetics of RNA pol II elongation.[24] A relationship between DNA methylation and splicing was also reported in the oligodendrocyte lineage,[25] as cell-specific deletion of

Dnmt1 in progenitors impaired the alternative splicing of several transcripts regulating lipid metabolism, myelination, and cell cycle.[25]

While DNA methylation at promoters has been associated with transcriptional repression, and a true demethylase has not been identified, it has been shown that methylated cytosines are targeted by enzymes called *ten-eleven translocases* (TETs) and converted to hydroxymethyl cytosines which can be oxidized to formyl cytosine and then carboxyl cytosine, which is eventually excised by the DNA repair complex.[26]

Gene silencing is further stabilized by establishing contacts between heterochromatin and the nuclear lamina. These genomic regions forming stable interactions with the nuclear lamina have been identified as LADs.[27,28] The nuclear lamina in oligodendrocyte lineage cells consists of intermediate filaments called lamins. Lamin A and lamin C are expressed in mature oligodendrocytes, and lamin B1 is expressed in oligodendrocyte progenitor cells (OPCs). These proteins can directly bind to chromatin via specific interactors and also associate with the cytoskeleton through the linker of nucleoskeleton and cytoskeleton (LINC) protein complex (see below), thereby enabling the direct transduction of physical forces from the exterior of the cell to its genome.[29]

HISTONE AND DNA MODIFICATIONS RESPONSIBLE FOR THE ACQUISITION OF THE OLIGODENDROCYTE LINEAGE IDENTITY

Although neural stem cells (NSCs) are multipotential and able to generate neurons and glia within the developing nervous system, they are neurogenic at mid-gestation and gliogenic at late gestation. This section aims to review the mechanisms regulating the switch from neurogenic to gliogenic transcriptional competence of NSCs and then delve into the transcriptional and epigenetic mechanisms responsible for the transition from oligodendrocyte progenitors to oligodendrocytes.

Epigenetic landscape of NSCs during the neurogenic to gliogenic transition

The neurogenic to gliogenic switch of NSC during embryonic development, despite the exposure to the same external factors, implies the involvement of epigenetic mechanisms regulating their responsiveness to these external cues. At least two mechanisms have been described: DNA methylation and histone post-translational modifications (Figure 1A). DNA methylation has been shown to prevent the binding of transcription factors to astrocytic genes during the neurogenic phase by altering their recognition site and keeping astrocytic genes repressed.[30,31] At the same time, neurogenic genes are poised for transcription due to the coexistence of the transcriptionally competent histone H3K27 acetylation and repressive H2AK119 ubiquitination, mediated by the recruitment of the PRC1 complex (RING1B) to H3K27me3 marks at specific genomic sites.[32]

The switch to the gliogenic phase is characterized by the activation of astrocytic genes and stable ubiquitin-independent repression of neurogenic genes (Figure 1A). Late gestation is characterized by the expression of the transcription factor NFIA,[33] previously identified as a critical astrogliogenic factor,[34,35] which releases the DNA methylation block by dislodging the DNA methyltransferase DNMT1 and allows transcription factors like STATs and

SMADs to recruit HATs and activate astrocytic genes.[36] Consistent with this mechanism, mice with genetic ablation of *Dnmt1* in NSC[30,31] and those with forced expression of NFIA[37] are characterized by precocious astrogenesis. Neurogenic genes lose the H3K27 acetylation and become stably repressed due to the concerted activity of the PRC2 complex, which imposes the repressive H3K27me3 mark and the PRC1 complex, containing PHC2, which promotes clustering and further recruits repressive NURD complexes containing HDAC1 and other repressors, ultimately effecting heterochromatin formation.[32] In support of the importance of the PRC2 complex in lineage commitment, oligodendrocyte-lineage cells lacking PRC2 components, such as EZH2 or EED, were characterized by a gene expression pattern reminiscent of the astrocytic phenotype and severe hypomyelination.[38,39] The decision of NSC and glial-restricted precursors to become either astrocytes or oligodendrocytes occurs in late embryogenesis when the epigenomic landscape organizes the cell-specific pattern of gene expression in response to external cues. The presence of Notch or BMP, for instance, promotes an astrocytic pattern of gene expression, whereas noggin or Sonic hedgehog favors the establishment of the oligodendrocytic transcriptome.[40] Therefore, late embryonic NSCs are characterized by a remarkable susceptibility to external signals due to a receptive epigenomic configuration, underlying the importance of both extracellular and intracellular contexts for attaining specific developmental outcomes.[41–43]

Epigenetic landscape of OPCs: Repression of neurogenic genes

OPCs are electrically active cells[44–47] that receive direct synaptic inputs from excitatory and inhibitory neurons[48–51] and respond to neuronal activity with proliferation[52–54] or differentiation.[55,56] It is, therefore, not surprising that they retain the expression of several neurotransmitter receptors and ion channels, characteristically defined as neuronal genes. Despite the expression of these neuronal genes and initial reports that neurons can be generated from OPC in specific conditions[57] and in selective brain regions,[58] it is now clear that oligodendrocyte progenitors are not neurogenic[59] as neurogenic genes are silenced in these cells, as described above (Figure 1B). The concept that OPCs behave as multipotential cells with the ability to generate neurons was suggested by initial *in vitro* studies, with cells cultured in the presence of growth factors[60] or HDAC inhibitors.[57] However, with the exception of a few reports in selected brain regions,[58] *in vivo* fate mapping studies did not support OPCs as neurogenic cells.[61–63] Consistent with the inability of OPCs to form neurons *in vivo*, their epigenomic landscape is characterized by the presence of widespread PRC2-dependent repressive H3K27me3 marks on neurogenic genes, which remain unaltered throughout the process of differentiation.[64] The presence of these marks on neurogenic genes is also in agreement with the previously reported presence of the PRC2 enzymatic complex EZH2 on genes promoting neuronal fate, during the transition from embryonic stem cells to OPCs.[65,66] Nevertheless, a more recent study showed that OLIG2$^+$ cells lacking *Ezh2* expression can still generate oligodendrocyte precursors, indicating that the absence of PRC2 activity per se is not sufficient to transition into a neuronal fate.[38] Thus, the loss of neurogenic potential of OPCs is consistent with the silencing of neurogenic genes during embryonic development, using a mechanism of repression involving both PRC2-dependent histone methylation and PRC1-dependent recruitment of HDACs.[67] In specific regions of the central nervous system (e.g., ventral areas of the neural tube), however, OPCs share the same precursors with interneurons.[68] Due to this common origin, it is not

surprising that their epigenome reflects this shared origin of interneuron-specific genes in OPCs that are mostly characterized by unmodified histones, which render them responsive to direct reprogramming into neuronal cells upon transfection of neurogenic transcription factors.[69]

As OPCs differentiate into oligodendrocytes, they progressively lose synaptic contacts and become electrically inert,[49] a process which is accompanied by the downregulation of a large number of broadly defined neuronal genes, including neurotransmitter receptors and ion channels[25,64] (Figure 1B).

Epigenetic landscape of OPCs: Repression of astrocytic genes

The prolonged exposure of cultured OPCs to morphogenic factors and mitogens[70] or HDAC inhibitors[60] favored the expression of astrocytic and neuronal genes in these cells. However, *in vivo*, only some OPCs in the ventral gray matter can generate astrocytes during the embryonic period.[63] This suggests that the epigenomic landscape of cultured OPCs is different from that of brain OPCs, whose lineage becomes progressively more restricted over time. DNA methylation is not used as one of the mechanisms for lineage restriction, as the ablation of *Dnmt1* in OPCs does not result in lineage switch or even misexpression of astrocytic or neuronal genes.[25] Rather, it is accompanied by dysregulation of genes regulating cell division, subsequent defective proliferation, downregulation of transcription factors important for oligodendrogliogenesis (e.g., *Ascl1*, *Sox10*, and *Myrf*), and defective RNA splicing events (related to exon skipping) ultimately leading to decreased survival.[25] In contrast, ablation of the enzymes responsible for PRC2-dependent repression in OPCs resulted in the upregulation of Notch pathway-related genes, including the astrogliogenic factor NFIA,[38] and increased astrogliogenesis. Since the astrogliogenic function of NFIA in OPCs is antagonized by OLIG2,[34,71] it is not surprising that increased generation of protoplasmic astrocytes in the dorsal forebrain during embryonic development could also be detected after deletion of *Olig2* in OPCs. Importantly, the ability of OPCs to form astrocytes was not stable over time, but rather it became less effective with aging.[72] NFIA astrogliogenic function in OPCs is also antagonized by SOX10[35,71] and HDAC3 activity.[73] In glial progenitor cells, NFIA cooperates with SOX9 to generate astrocytes.[71,73,74] As OPCs become committed to the oligodendrocyte lineage, the increasing levels of SOX10 can act by directly antagonizing NFIA (Figure 1B) and indirectly upregulating the levels of the microRNA miR-338 reduces SOX9 levels.[75] The genetic deletion of *Sox10* also increases the generation of astrocytes at the expense of oligodendrocytes.[71] Ablation of *Hdac3* induces a very similar phenotype to that of *Olig2* deletion,[73] thereby suggesting the cooperation between transcription factors and epigenomic modulators in regulating the oligodendrocytic/astrocytic switch.

From NSC to oligodendrocyte lineage cells and back: The role of pioneer transcription factors

It is important to clarify here that progressive lineage restriction occurs during normal development and requires the establishment of repressive DNA methylation and chromatin compaction, as delineated above. However, although the transcriptional program defining cell identity is stable, it is possible, in specific circumstances, to reactivate silent genes by

altering the epigenomic landscape. The discovery that somatic cells could be reprogrammed into pluripotent stem cells by the transfection of four transcription factors (e.g., OCT4, SOX2, KLF4, and MYC) suggested that their expression was sufficient to erase the epigenetic landscape responsible for cell specialization.[76] A deeperunderstanding of this mechanism of action led to the concept of *pioneer* transcription factors. These proteins are characterized by the ability to bind only to partial transcription factor recognition motifs displayed on the surface of nucleosomes, and either alone or in tandem, they are capable of affecting the epigenetic landscape by inducing nucleosomal remodeling independent of ATP or affecting DNA methylation.[77] Thus, specific transcription factors have the dual ability to both establish or dismantle the epigenetic landscape.

In an attempt to define the key transcription factors responsible for the transition from NSCs to OPCs, an elegant study[78] focused on three transcription factors, differentially expressed between human NSCs (already expressing OLIG2) and OPCs (e.g., ASCL1, SOX10, and NKX2.2) and analyzed the transcriptional profile induced in NSCs by overexpressing each of them separately and in combination. While the combined expression led to oligodendrocyte lineage cell generation, the expression of ASCL1 induced both oligodendrocyte and neuronal genes.[78] This result is consistent with the role of ASCL1 as a pioneering transcription factor with the ability to reactivate neuronal genes even within the context of a repressive chromatin state, and also explains previous studies on its role as both neurogenic and oligodendrogliogenic factors.[79–81]

Intriguingly, the expression of SOX10 alone was sufficient to induce a gene expression pattern that resembled that of primary human OPCs, in terms of repressed and activated genes.[78] Since SOX10 is an HMG transcription factor and a member of the SOX family, it is conceivable that, like SOX2, it may play the role of “pioneer” in opening genes required for myelin production within the heterochromatic nuclei of differentiating OPCs. Consistent with its role as a pioneer transcription factor, a recent study reported that expression of OLIG2, ASCL1, SOX10, and NKX2.2 is sufficient to reprogram human dermal fibroblasts into oligodendrocyte lineage cells.[82]

Epigenetic landscape of differentiating oligodendrocyte progenitors: Repressive events regulating cell cycle, electrical properties, and transcriptional inhibitors of myelin genes

The transition from OPCs to mature oligodendrocytes is characterized by a series of functional changes. This section will summarize the current knowledge of the changes in the epigenetic landscape occurring during this transition (Figure 1B,C). They include (1) exit from the cell cycle; (2) loss of migratory capacity associated with morphological changes (from bipolar to multiprocess bearing cell); (3) loss of electrical responsiveness to neuronal stimulation; and (4) generation of large quantities of lipid and specialized proteins to be assembled into a membrane structure called myelin. These processes are not concurrent but rather sequential, with the early repressive events referring to regulatory RNA processes and downregulation of genes encoding for positive regulators of proliferation and negative regulators of myelin gene expression.[83]

We have previously discussed how OPCs are electrically active cells with the ability to respond to neurotransmitters by activating ionotropic receptors and voltage-gated

ion channels.[44,49,84,85] They receive synaptic neuronal contacts and are proliferative, migratory, electrically active cells whose genomic distribution of the repressive methylation mark H3K27me3 is localized on neurogenic genes and not present on genes regulating the expression of neurotransmitter receptors, ion channels, and synaptic transmission.[64] However, as the OPCs start to differentiate into oligodendrocytes, eventually forming myelin to provide axonal insulation, it is of paramount importance that genes regulating their electrical properties are silenced.[25,49] This occurs by the deposition of the repressive histone mark H3K9me3 at genomic loci responsible for the expression of ion channels and pathways related to synaptic transmission.[64] Downregulation of the enzymatic writer for H3K9me3 (e.g., SUV39H1) during the differentiation process prevents the changes in the excitability of these cells.[64] Thus, the OPCs adopt two distinct mechanisms of neuronal gene silencing: an early PRC2-dependent mechanism of repression of neurogenic genes and a later SUV39H1-dependent mechanism of inactivation of the electrical properties of the cells. H3K9me3 is also found on GABAergic genes as OPCs differentiate.[64] The H3K9me3 mark is recognized by specific chromodomain binding proteins, such as HP1-α, a protein that we previously reported to be enriched in white matter tracts during developmental myelination.[86] In nuclear domains characterized by transcriptionally silent chromatin, HP1-α has the ability to recruit genes to the nuclear periphery that are repressed due to this histone mark.

At the same time, additional mechanisms of transcriptional repression are in place to prevent the premature differentiation of OPCs into myelin-forming oligodendrocytes, as initially shown by our group first in cultured OPCs[87] and then in developing and aging rodents[86,88,89] and subsequently validated by several other groups.[90–92] The initial discoveries identified reversible histone acetylation of specific lysine residues as histone marks in the nuclei of OPCs,[86,87,89] which are favored by the presence of mitogens[87] and differentially affected by astrogliogenic and oligodendrogliogenic signals.[70] Additional crosstalk between epigenetic modifications, such as PRMT5-mediated symmetric arginine methylation and histone acetylation,[93] and regulation of chromatin accessibility by arginine citrullination,[94] further contribute to tighter regulation of this transcriptional network. The histone deacetylase HDAC1 was identified as the major enzyme responsible for the transcriptional repression occurring during the transition from OPCs to oligodendrocytes,[86,95] and genetic approaches further validated this observation in mice and cultured cells.[70,96]

Repression occurs at genomic loci encoding for transcriptional repression of inhibitory bHLH transcription factors class V (e.g., ID2 and ID4) and class VI (e.g., HES5), which were shown to play a major role as inhibitors of myelin gene expression.[97–100] Importantly, besides acetylation/deacetylation regulated by the opposing activity of HATs and HDACs, these genes were also shown to be regulated by PRMT5[101] and complexes regulating the chromatin accessibility at their promoter region.[102]

It is worth noting that several of these genes, such as transcriptional inhibitors[103] and cell cycle regulatory genes,[25] are further silenced by additional mechanisms, including histone and DNA methylation and also recruitment to the nuclear lamina after being repressed by initial histone deacetylation.[104]

The relationship between cell cycle exit and differentiation in OPCs was shown to be tightly connected to the major transition in the epigenomic landscape, as transcription factors involved in cell cycle regulation, such as members of the E2F and MYC family, act as major transcriptional switches. For instance, E2F1 and MYC were shown to modulate the recruitment of HATs to genomic locations encoding for chromatin components and regulatory enzymes, as well as transcriptional inhibitors of differentiation.[105,106]

Conditions favoring histone acetylation at the expense of deacetylation prevent the differentiation of OPCs. Those conditions include treatment of OPCs with HDAC inhibitors,[86,87] exposure to BMPs[70] and genetic ablation of the histone arginine methyltransferase PRMT5,[93] the histone deacetylase HDAC1,[96] or one of the transcription factors responsible for their recruitment, such as YY1.[98] Conversely, silencing E2F1[106] or MYC,[105] or blocking the activity of histone acetylation readers,[107] are capable of inducing the progression of OPCs toward the first stages of oligodendrocyte differentiation but not sufficient to induce the myelinating terminally differentiated phenotype.

An additional mechanism preventing premature differentiation of OPCs into myelinating oligodendrocytes is the association of lipid metabolism genes to the nuclear lamina.[104] Downregulation of *LmnB1* as OPCs differentiate is guaranteed by miR23, and the inability to decrease the levels of this nuclear lamina protein results in nuclear structural defects, including the formation of atypical intranuclear membrane and decreased expression of myelin genes.[108,109] Indeed, failure to decrease LMNB1 levels results in reduced *Plp1* expression[110] and overall decreased transcription of myelin genes.[108,111] From a mechanistic perspective, the progressive decrease of LMNB1 during differentiation results in increased expression levels of genes encoding for key lipid enzymes, resulting from the release from the nuclear periphery.[104] This also explained the dramatic dysmyelinating phenotype that was reported in transgenic mice overexpressing *Lmnb1*.[112]

Epigenetic landscape of oligodendrocyte progenitors differentiating into oligodendrocytes: Transcriptional activation of genes regulating cytoskeleton, lipids, and myelin proteins

The transcriptional signature of differentiated oligodendrocytes includes the activation of several genes necessary for the synthesis of myelin lipids and proteins as well as cytoskeletal remodelers necessary for axon wrapping, membrane extension, and transporters of ions and metabolites, which allow for the exchange of solutes at the neuro–glial interface. While the mechanisms of derepression defined above address the timing of myelin protein gene expression, a number of additional gene activation mechanisms need to occur to achieve the identity of myelinating oligodendrocytes. The program of activation includes the recruitment of ATP chromatin remodelers (such as BRG1) to enhancer regions containing SOX10 and OLIG2 binding sites in OPCs and to OLIG2 binding sites near the transcriptional start site for early differentiation genes (e.g., *Cnp*, *Mbp*, and *Sirt2*) and genes encoding for cytoskeletal elements in newly formed oligodendrocytes.[113] The role of chromatin remodeling complexes at later stages of differentiation, however, appears less prominent, as indicated by the modest phenotype in mice with genetic ablation of *Brg1* in differentiating oligodendrocytes.[114] The binding of SOX10 to enhancer regions of genes

related to the actin cytoskeleton and metabolic regulation[115] is essential for the progression of OPCs to oligodendrocytes, and SOX10 acts as an orchestrator of both repressive[64] and activating marks characterizing the epigenomic landscape as well as to aid in the recruitment of the chromodomain helicase DNA-binding (CHD) family of ATP-dependent chromatin remodelers. Among those, CHD8 was shown to open chromatin at promoter regions around the transcriptional start site and allow either for repression or activation of gene expression, the latter favored by the recruitment of the histone methyltransferase KMT2[102] and responsible for the deposition of the activating H3K4me3 histone mark at the promoters of genes associated with oligodendrocyte differentiation (e.g., *Olig1*, *Sox10*, *Nkx2.2*, *Tcf7l2*, *Myrf*, *Mbp*, and *Ugt8*). CHD7, in contrast, was identified at later stages of differentiation to be recruited at SOX10 binding sites of genes modulating lipid homeostasis, cytoskeletal reorganization, myelin, and axonal ensheathment (e.g., *Olig1*, *Nkx2.2*, *Myrf*, and *Sip1*).[116] An additional mechanism regulating chromatin accessibility in differentiated oligodendrocytes involves the removal of repressive arginine methylation mediated by PADI2, the enzyme responsible for converting arginine residues into citrulline at loci encoding for oligodendrocyte differentiation genes.[94]

Finally, DNA hydroxymethylation, mediated by TET enzymes, has been shown to induce the activation of genes regulating the crosstalk between myelinating oligodendrocytes and neurons. The global levels of brain hydroxymethylation increase during development and decline with age. This pattern correlates with decreased levels of the TET1, but not of the TET2 isoform in oligodendrocytes, thereby suggesting TET1 as the main enzyme responsible for DNA hydroxymethylation in the oligodendroglial lineage.[117] The functional significance of TET1 was inferred by characterizing the phenotype of mice with lineage-specific ablation of this gene,[117,118] which revealed important phenotypic similarities but also significant differences, possibly due to the different regions of targeted ablation. While mice with lineage-specific ablation of *Tet1* catalytic domain (encoded by exons 11–13, *Tet1Δ11–13*) showed defects in developmental myelination, cell-cycle progression, OPC differentiation, and adult myelin repair,[118] mice with cell-specific ablation of exon 4 (*Tet1Δ4*) did not display defective differentiation but were characterized by impaired adult repair of demyelinated lesions due to misexpression of genes regulating axo–glial interaction.[117] These findings are intriguing, as they suggest that the N-terminal domain of TET1 might exert a role which is independent of the enzymatic activity. In this regard, it is noted that in other cell types, the N-terminal domain of TET1 has been shown to modulate the levels of repressive histone mark H3K27me3 and repress the expression of developmental genes.[119,120] Future studies are needed to provide a better understanding of the role of the distinct TET family members at the distinct stages of the oligodendrocyte lineage.

EPIGENETIC REGULATION OF GENE EXPRESSION MEDIATED BY RNAs

As OPCs differentiate into mature oligodendrocytes, their functional specialization is guaranteed by the presence of a set of diverse proteins encoded by the same gene due to alternative splicing of the pre-mRNA, which allows for exons and introns to be either retained or skipped[121] and thereby allowing the developmental stage-specific expression of the same protein with different functional domains.[122,123] These RNAs can also be

reversibly modified by specific enzymes (e.g., METTL3 and METTL14) and transported to distal sides of the cell to allow for local translation in response to external stimuli. It is clear that RNA processing plays a prominent role in the oligodendrocytes,[83] and the detection of RNA splicing defects in mice with lineage-specific ablation of histone or DNA modifiers[25,93] further highlights the existence of crosstalk between epigenetics and RNA processing. Additional modalities of epigenetic regulation of gene expression by RNAs include the study of methylation of adenosine residues in RNA, regulatory microRNAs (miRNA) (responsible for fine-tuning of transcript levels in response to external conditions), long noncoding RNAs (lncRNAs) (which may bind to chromatin reorganize genomic architecture), and circular RNAs (circRNAs)[124] (Figure 2).

mRNA methylation

N^6-Methyladenosine (m^6A) mRNA methylation has recently been identified as a post-transcriptional reversible chemical modification affecting gene expression.[125] This mark is deposited by a multiprotein methyltransferase complex composed of METTL3 and METTL14 enzymes.[126,127] While METTL14 acts as a scaffold for RNA-binding, the biochemical reaction is catalyzed by METTL3.

The m6A methyl RNA mark can be recognized by several reader proteins, including members of the YT521-B homology (YTH) domain family (such as YTHDC1), IGF2 binding proteins (IGF2BPs), eukaryotic elongation factor (eIF3), HNRNPA2/B1,[128,129] and PRRC2A.[130] The latter is of special interest, as gene ontology enrichment analysis of PRRC2A targeting m^6A-methylated mRNAs revealed transcripts regulating various biological functions related to brain development, gliogenesis, oligodendrocyte differentiation, and myelination. Among the transcripts bearing the m^6A modification and bound by PRRC2A is the *Olig2* transcript, suggesting that the m^6A RNA/PRCC2A pathway may play an important role in the regulation of this important transcription factor for the OL. Consistently, neural-cell-specific deletion of *Prrc2a* resulted in downregulation of gliogenesis and myelination-related genes, as well as hypomyelination and cognitive dysfunction.[130] In addition, the PRRC2A paralogue, PRRC2C, has also been identified as an oligodendrocyte-specific substrate of the protein arginine methyltransferase PRMT5.[131]

Erasers of the m^6A mark on RNA are specific m^6A demethylases, such as ALKBH5 (the ALKB homolog H5) and FTO (Fat mass and obesity-associated),[132,133] the latter with the ability to recognize and remove the m^6A mark from the *Olig2* mRNA, leading to its degradation.[130] Thus, m^6A mRNA methylation can affect the mRNA stability and favor the interaction with RNA-binding proteins resulting in the formation of condensates or membrane-less compartments regulated by phase separation, such as stress granules.[134–138]m^6A mRNA profiling in the oligodendrocyte lineage identified thousands of differentially modified mRNAs between OPCs and mature oligodendrocytes,[137] with only 23 transcripts showing the same pattern of m^6A methylation at both stages. Oligodendrocyte lineage-specific ablation of *Mettl14* did not affect the progenitor state, or the translation or subcellular distribution of *Mbp* transcripts.[137] However, it impaired their differentiation of OPC into oligodendrocytes with consequent hypomyelination accompanied by aberrant

splicing of numerous transcripts, including *Ptprz1* (protein tyrosine phosphate receptor type Z1) and *Nfasc* (neurofascin).[137]

MicroRNAs

MiRNAs are short, small noncoding RNAs (ncRNA) that negatively regulate their targets in a sequence-specific manner. miRNAs are derived from primary miRNAs (pri-miRNAs) cleaved by the nuclear Drosha complex into shorter precursor miRNAs (pre-miRNAs). Then, these molecules are translocated into the cytoplasm, where they are further processed into mature miRNAs by the endoribonuclease Dicer and incorporated into the RNA-induced silencing complex (RISC), which regulates their interactions with the mRNA targets.[139] The RISC–miRNA complex recognizes a complementary sequence in the 3'UTR of mRNA, inhibiting its translation with or without mRNA degradation.[140]

Ablation of *Dicer* in mice—generated by *in vivo* recombination—demonstrated the critical role of miRNAs in mouse development. Lineage-specific deletion of *Dicer1* in the oligodendrocyte lineage resulted in delayed oligodendrocyte differentiation and myelin production *in vivo* and *in vitro* and late neurodegeneration.[106,107,141–143]

Several miRNAs were identified as differentially regulated at distinct stages of oligodendrocyte development.[141,143–147] The levels of miR-219, miR-338, miR-138, miR-29, and miR-23, for instance, were shown to increase during the differentiation of OPCs and into oligodendrocytes.[141,143,144,148,149] These miRNAs were found to decrease the differentiation inhibitors' levels further, thereby resulting in a prodifferentiative effect.[142] For instance, miR-219 mRNA targets included mitogen receptors and transcriptional inhibitors (e.g., *Pdgfra*, *Sox6*, and *Hes5*) as well as inhibitors of myelination (e.g., *Lingo1* and *Etv5*).[150] The overexpression of miR-219 and miR-338 in cultured primary OPCs lacking *Dicer1* partially rescued oligodendrocyte differentiation by inducing myelin gene expression, including *Mbp*, *Cnp*, and *Mog*,[141,143,150] and reducing the levels of *Sox9*.[75] In contrast, miR-145–5p was shown to be downregulated during oligodendrocyte differentiation and exert an overall proliferative effect[150]. Downregulation of miR-145–5p (anti-145) promoted differentiation of cultured OPCs,[151] possibly due to the release of the brake on the levels of *Myrf* (Figure 2), a critical transcription factor regulating oligodendrocyte maturation, and also a downstream target of miR-145–5p.[151] Additional miRNAs of functional relevance to the oligodendrocyte lineage include miR-23a, a prodifferentiation factor, which acts as a negative regulator of *LmnB1*[108,146] while also favoring the expression of lncRNA (*2700046G09Rik*), and together with the lncRNA decrease *PTEN* levels.[111]

Long noncoding RNAs

LncRNAs are nonprotein-coding RNAs that are spliced, mostly polyadenylated, and longer than 200 nucleotides in length and are generally characterized by low expression levels and nuclear localization. Many lncRNAs exhibit cell type-specific expression and are primarily associated with distinct developmental stages.[152] They modulate gene expression by binding to chromatin and changing the epigenetic landscape by modifying the genomic architecture.

Although both human and mouse genomes encode thousands of lncRNAs, only a few lncRNAs have been functionally characterized.

Recent transcriptomic studies identified cell type-specific lncRNAs in eight mouse brain cell types,[121,153,154] including 355 lncRNAs as differentially expressed between NSCs and OPCs. Of those transcripts, 254 were upregulated during oligodendrogenesis, and 88 of them were characterized by the presence of OLIG2 binding sites within 10 kb of their transcription start site. Among them, *lnc-OPC* levels increased during the transition from NSCs to OPCs,[155] and its ablation in NSC impaired the generation of OPCs.[153] Additional lncRNAs were identified at later stages of oligodendrocyte lineage progression.[155]

Another study analyzing lncRNAs differentially expressed in cultured primary mouse OPCs, immature oligodendrocytes, and mature oligodendrocytes identified 1342 unique gene loci named *lncOLs* characterized by the presence of SOX10 binding sites and activating H3K27ac and H3K4me3 histone marks and exhibiting conservation across species.[154] A total of 301 lncRNAs were identified as differentially expressed in differentiating oligodendrocytes compared to OPCs. Of those, *lncOL1* and *lncOL4* were associated with neurogenesis and gliogenesis and their function was strongly linked with the expression of oligodendrocyte and myelin-specific genes, such as *Nkx2-2*, *Mbp*, *Mog*, and *Plp1*. Their expression was not detected in NSC at birth but peaked at postnatal day P14 as OPCs differentiated and then sharply declined. Targeted siRNA knockdown was sufficient to decrease *Mbp*, *Plp1*, and *Cnp* expression in cultured OPCs, while their overexpression increased the levels of *Mbp*, *Mag*, and *Myrf*.[154] Consistent with the *in vitro* data, *lncOL1*-deficient mice were also characterized by a low number of mature oligodendrocytes in the spinal cord and exhibited severely impaired myelination at postnatal day 21.[154] *lncOL1* was detected both in cytoplasmic and nuclear compartments with the nuclear *lncOL1* detected in discrete puncta in association with chromatin.[154] This was of interest as the RNA–protein prediction algorithm identified SUZ12, a subunit of the PRC2 complex, as a potential interactor with *lncOL1*.[154] The functional consequence of the interaction between *lncOL1* and SUZ12, as shown by immunoprecipitation, was further validated by the detection of increased transcript levels of target genes in *lncOL1* knockout mice.[154] Collectively, these results suggest that lncRNAs modulate the epigenome by modifying chromatin transcriptional states in oligodendrocytes (Figure 2).

Circular RNAs

CircRNAs are single-stranded, stable, functional RNAs that have a closed-loop structure. They are produced by noncanonical splicing events known as *back-splicing*, where a downstream 5′ splice site is joined to an upstream 3′ splice site forming an exon-containing lariat precursor. CircRNAs are predominantly found in the cytoplasm, and the lack of a 5′ cap and 3′ tail makes these molecules escape degradation and have a longer half-life than linear RNAs. They play important roles in regulating miRNA activity, alternative splicing, RNA binding protein sequestration, and transcription through interactions with RNA polymerase II.[156–159] Unlike miRNAs and lncRNAs, a subset of circRNAs is reported to be translated into proteins.

Similar to linear isoforms, multiple circRNAs variants can be generated from a single gene by alternative splicing, containing different combinations of exons and/or introns.[160] For instance, *circCFAP299* has two isoforms in human oligodendroglioma cells; the short isoform is favored during differentiation, suggesting a distinct functional role for the unique exon in the long isoform, including interactions with RNA-binding proteins.[161] In addition to the isoform switch, the circular transcriptome profile also changes at different stages of differentiation in oligodendroglioma cells.[161] For instance, *circVPS13C*, whose mutation results in mitochondrial dysfunction, is upregulated in differentiated cells.

MECHANOTRANSDUCTION ALLOWS CHROMATIN AND NUCLEAR LAMINA TO ADJUST IN RESPONSE TO PHYSICAL FORCES

Over the last decade, it is becoming well-accepted that mechanotransduction is very important for the epigenetic regulation of gene expression because cells respond to the stiffness or elasticity of substrates they come in contact with as well as strain and compression forces. Mechanotransduction can, therefore, modify histone marks and change the association of chromatin with the nuclear lamina.[162] Several reports have highlighted the biological response of oligodendrocyte lineage cells exposed to distinct mechanical stimuli.[163–167] In addition, the dynamic state of chromatin condensation has been related to changes in the mechanical properties of the nuclei of OPC as they differentiate into mature oligodendrocytes.[168] The nuclei of OPCs are relatively elastic and oscillating,[169] characterized by the presence of loose euchromatin and by a nuclear lamina predominantly formed by LMNB1, conferring a level of softness and elasticity, which is compatible with the migratory and proliferative ability of these cells. The nuclei of differentiated oligodendrocytes, in contrast, are much more rigid, characterized by high levels of heterochromatin especially distributed along the nuclear periphery, where the nuclear lamina is now characterized by the presence of LMNA. These features allow the protection of the genetic material of highly specialized cells and are compatible with the highly branched morphology of the mature oligodendrocytes that make contact with several axons and wrap them with their membrane, providing both insulation and metabolic support.[168] In this section, we will first discuss general mechanisms of mechanotransduction and then provide an outlook of potential pathways connecting mechanosensing to the regulation of gene expression in oligodendrocyte lineage cells (Figure 3).

Chromatin remodeling complexes and HDACs respond to actomyosin contractility

Studies on the differentiation properties of stem cells plated on substrates with diverse ranges of softness and stiffness suggested that the mechanical properties of the substrate were capable of inducing specialized patterns of gene expression. For instance, very rigid surfaces induced expression of bone and ossification genes, soft surfaces induced brain-specific genes, and substrates of intermediate stiffness induced muscle-specific genes.[170] Within the normal brain parenchyma, however, more subtle regional and temporal differences in stiffness between gray (softer) and white matter could be correlated to the amount of myelin in distinct regions.[171–173] Gray matter stiffness increased from prenatal to postnatal periods (from 0.3 to 0.7 kPa), and white matter stiffness remained substantially higher (up to 10 kPa)[174] and increased with aging.[166,175] Fine-tuning of substrate elasticity

using hydrogels allowed to define the range of stiffness promoting neuronal (0.1–0.5 kPa) versus glial (1–10 kPa) specification.[176] Among the glial cells, OPCs were studied by several groups and were shown to respond by increasing proliferation and migration on stiffer substrates and differentiation on softer ones, suggesting that these cells respond to external mechanical stimuli.[165–168]

There is evidence that the growth of OPC on softer substrates reduced actomyosin contractility and led to myosin-dependent translocation of HDAC3 from the cytoplasm to the nucleus, leading to increased deacetylation and compaction of the chromatin[177] and differentiation. Reduced actomyosin contractility also resulted in a reduction of polymerized actin and a shift from F to G actin, which is critical for the process of myelination.[178,179] The role of deploy-merized nuclear actin as a modulator of chromatin in response to mechanical cues has been reported in HeLa cells since nuclear actin can bind to all three RNA polymerases,[180] interact with transcription factors, and suppress class I HDAC activity.[181] Globular actin in the nucleus also has the ability to bind to specific components of the BRG1 chromatin–remodeling complexes,[182] thereby suggesting a direct link between cytoskeletal remodeling and transcriptional competence of chromatin.[183] BRG1, in the SWI/SNF complex, has been shown to have spatiotemporal relevance to the development of oligodendrocytes in the early brain by regulating the expression of the key transcription factor, OLIG2,[184] remodeling chromatin,[113] and modulating differentiation.[114]

Mechanotransduction in response to tension: Piezo1, YAP, and regulation of nuclear pores

As the brain develops, oligodendrocyte lineage cells are also exposed to different types of tensile forces, including those created on migratory OPCs by blood pulsation, cerebrospinal fluid flow, axonal growth, and those affecting the several branches of newly differentiated oligodendrocytes—each contacting axons in all directions. The tensile strain was reported to decrease nuclear oscillations in OPCs and increase their rigidity.[169] This was consistent with the increased deacetylation of histone H3K14[185] and also with the results of studies supporting increased H3K9me3 and the formation of heterochromatin.[164] The molecular players responsible for the relationship between tensile strain and epigenome modulators remain to be defined, but several potential mechanisms have been proposed, including the induction of transient calcium waves via the membrane protein Piezo1 and the nuclear accumulation of the coactivator Yes associated protein1 (YAP) and transcription factors, which are due to stretching of the nuclear pores. Piezo1 is a propeller-shaped trans-membrane protein that responds to changes in membrane tension by opening a cation channel that causes an influx of calcium ions into the cell.[186–188] It is expressed in neurons, astrocytes, and microglial cells at low levels. In the oligodendrocyte lineage cells, Piezo1 is highly expressed in OPCs, where its activation decreases both proliferation and migration.[166,189]

The transcriptional coactivators YAP and TAZ with the PDZ domain encoded by the gene *WWTR1* are part of the Hippo (named after the Hpo/MTS1/2 kinase) pathway cascade, which regulates organ size by modulating cell proliferation and apoptosis (Figure 3). In the unphosphorylated state, the coactivators YAP and TAZ are nuclear and favor proliferation due to the transcription of cell cycle genes. In conditions that favor low

actomyosin contractility (such as softer substrates), YAP is phosphorylated by nuclear kinases LATS1/2 and becomes cytosolic and unable to activate transcription of proliferative genes, thereby contributing to cell cycle exit.[190] Mechanical stimulation, including shear stress, or cytoskeletal tension results in the transmission of physical forces to the nuclear envelope and stretching of the nuclear pores[191,192] to allow for YAP nuclear localization and accumulation and activation of proliferation genes.[190,193]

Chromatin at the nuclear envelope

A major hallmark of differentiation is the accumulation of constitutive and facultative heterochromatin at the nuclear periphery, which confers rigidity to the nucleus of differentiated oligodendrocytes. An intricate array of proteins play a major role in organizing the epigenome. These proteins include those that span the nuclear envelope (e.g., SYNE/nesprins and SUN proteins), a mesh of intermediate filaments called lamins (e.g., lamin B1 and lamin A/C) at the inner nuclear membrane, and proteins involved in regulating the organization of chromatin and its association with the nuclear envelope. Indeed, a large number of proteins containing lamina association domains, as well as readers of acetylated and methylated histone marks (e.g., LAP2A, LBR, and emerin) serve as bridge and anchor chromatin to the nuclear lamina. This recruitment allows the creation of lamin-associated domains consisting of heterochromatic regions characterized by low rates of gene expression and silenced genes.[1] The transition from OPC to mature oligodendrocytes shows clear changes in the mechanical properties of the nucleus, from a softer nucleus to one that is more rigid,[168] and this coincides with the progressive accumulation of peripheral heterochromatin. The mechanical properties of the nucleus also respond to changes in substrate rigidity by changes in the composition of the nuclear lamina via upregulation of specific lamins and phosphorylation of emerin.[194,195] Oligodendrocyte progenitors, for instance, express LMNB1 and progressively upregulate the levels of LMNA during differentiation and when cultured on stiffer substrates, thereby differentially affecting heterochromatin recruitment to the nuclear envelope.[104,194]

As the brain grows and the skull sutures close, the oligodendrocyte lineage cells undergo rapid expansion to adjust to the extensive requirement for myelination across distinct brain regions. These events lead to an overall increased cell density, which is sensed by the cells via a complex that connects the plasma membrane through the nucleus via the LINC complex (Figure 3). In the adult brain, in inflammatory conditions characterized by increased blood–brain barrier permeability, immune cells can enter into the parenchyma creating local crowding conditions. These physical constraints exert physical forces on the cells, which can be studied by culturing cells in the presence of inert microspheres[196] or using a compression device.[164] Both conditions were shown to induce changes in histone repressive marks and heterochromatin recruitment to the nuclear envelope.[164] These nuclear changes and the effect on differentiation have been shown to be mediated by the SYNE–SUN–actin complex, as silencing of the KASH-domain containing LINC complex component SYNE1 prevented the mechanisms of differentiation of OPCs induced by mechanotransduction, without altering biochemical-induced differentiation.[164]

Tethering of heterochromatin to the periphery of the nucleus has been shown in retinal cells, keratinocytes, and fibroblasts to depend upon both LBR and lamin A.[197] Future studies will be needed to further clarify the role of nuclear lamins in regulating chromatin organization in oligodendrocyte lineage cells.

CONCLUDING REMARKS

This review highlights the complexity and current understanding of the epigenomic landscape in oligodendrocyte lineage cells, providing a perspective on the multiplicity of events that regulate gene expression and underlie the transcriptional heterogeneity of OPCs as described by many labs. Importantly, stable modifications of gene expression allow for the expression of genes responsible for the functional specialization of cells. However, chronic conditions and pathological states may allow for a reorganization of the landscape and allow for the expression of genes that are silenced in physiological conditions (e.g., immune genes). While some of the key eraser enzymes and pioneer transcription factors have been identified, it will be important to understand how distinct pathological conditions lead to pathological transcriptional states.

In addition, it is important to realize that we have just started to identify responsible histone, DNA, and RNA modifications, and much remains to be explored. Our current models are biased by the use of experimental genetic approaches using conditional mouse lines and developmental myelination as readout. This approach has been successful in the definition of enzymatic activities and transcriptional networks involved in the process. However, it has possibly led to over-generalization, and future work will need to take into consideration the functional role of time and stage of differentiation on topological domains. Novel approaches need to be considered in order to explore the relative role of protein readers of epigenetic marks and the relative contribution of the biophysical state of chromatin and membrane-less organelles at each stage of lineage progression.

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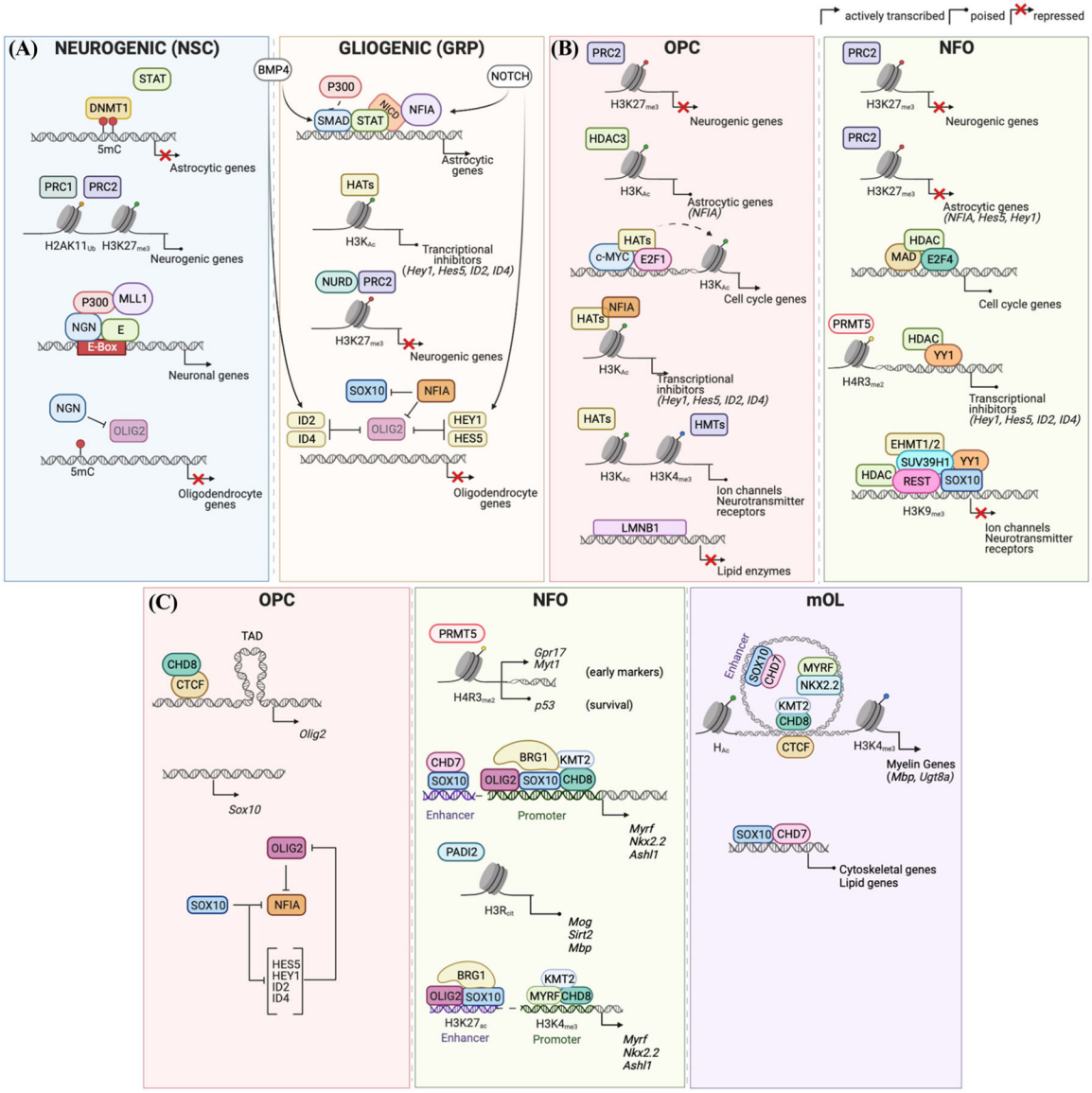

FIGURE 1.

Regulation of gene expression during the major transitions from neural stem cell to oligodendrocyte. Histone and DNA modifications and relative enzymatic activities regulating the expression of the indicated gene categories during the transition from neurogenic to gliogenic stem cell (panel A). Repressive histone modifications and transcriptional inhibitors responsible for the maintenance of the undifferentiated, proliferative, and electrically active state of oligodendrocyte progenitor cells (OPCs) and for the transition to newly formed oligodendrocyte (NFO) (panel B). Schematic representation of the histone modifications and chromatin remodeling events regulating the differentiation from progenitor (OPC) to newly formed oligodendrocyte (NFO) to mature oligodendrocyte (mOL) (panel C). Created with BioRender.

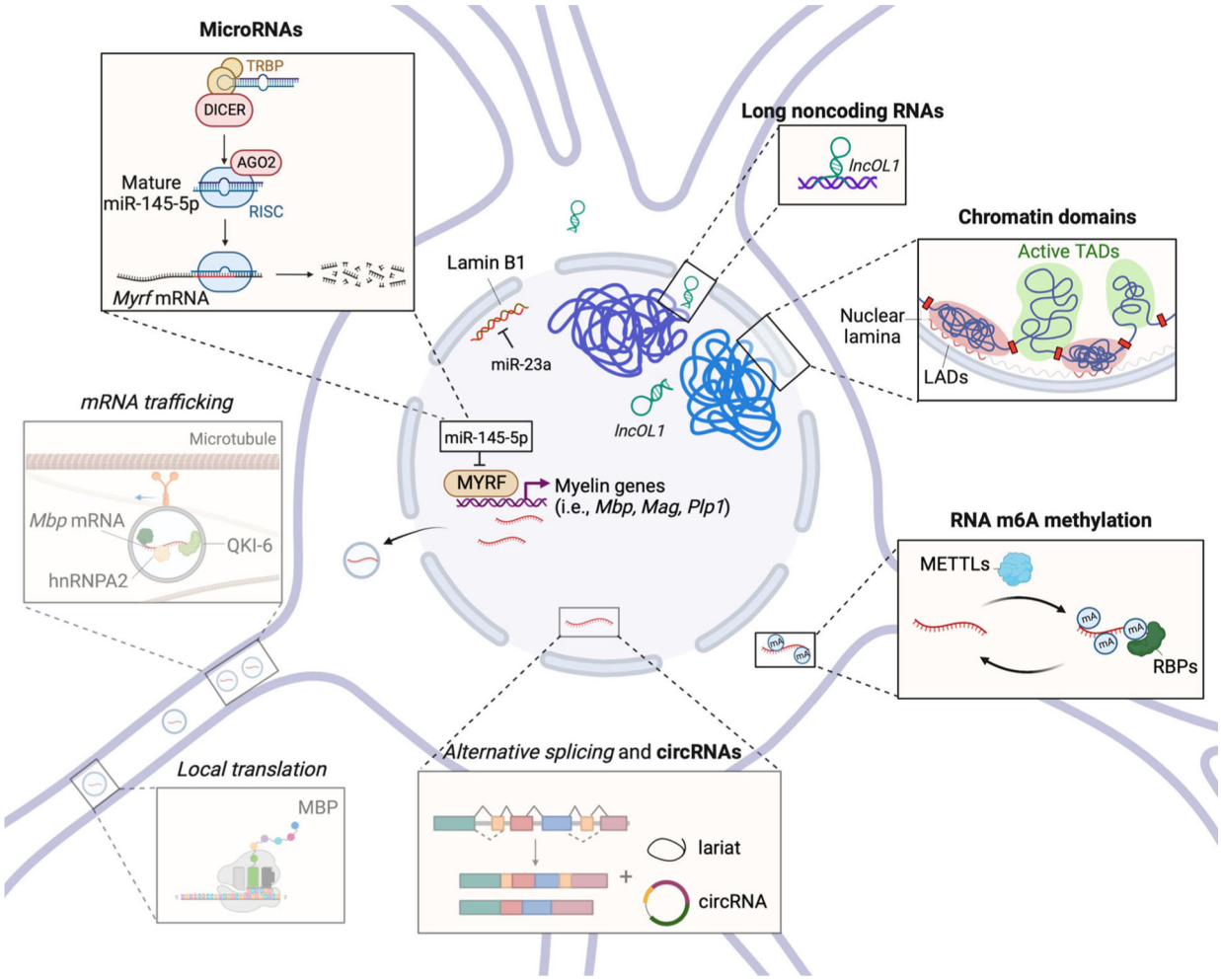

FIGURE 2.

The epigenomic landscape of an oligodendrocyte. Depicted here is a schematic representation of the 3D nuclear organization of the genome, including lamina-associated domain (LAD) and topologically associating domain (TAD), which together with histone and DNA modifications and chromatin remodelers, define the cell-specific unique epigenomic landscape. RNA processing, modification, and trafficking are shown in shaded gray boxes. Epigenetic regulation of gene expression by microRNA, long noncoding RNA, and circRNAs is shown in separate boxes. Created with BioRender. Abbreviations: circRNA, circular RNA; mRNA, messenger RNA.

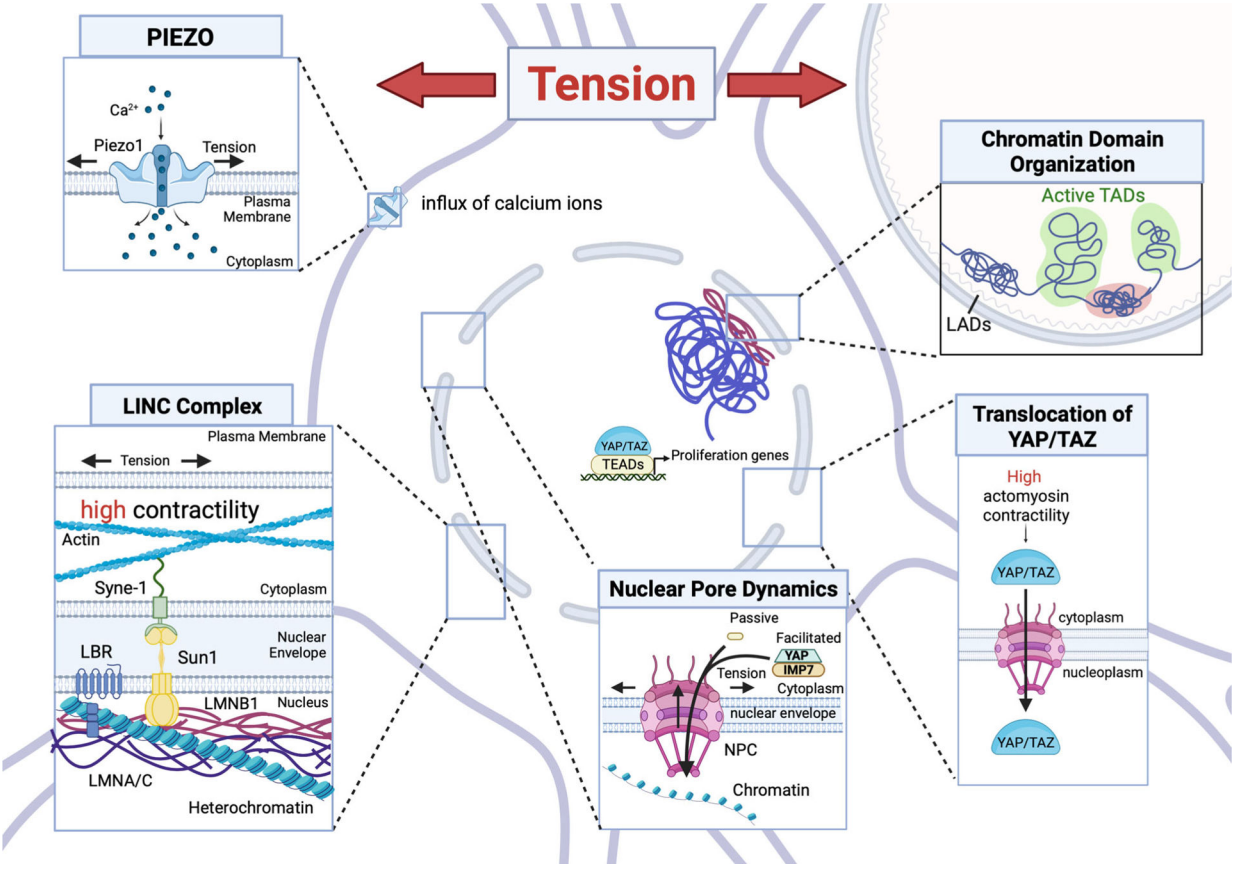

FIGURE 3.

Major pathways of mechanotransduction signal epigenetic changes in response to tension. The figure shows the main pathways responsible for the transmission of the signal from the outside of the cell to the nucleus. Boxes represent modalities of response to tensile stretches. Created with BioRender. Abbreviations: LAD, lamina-associated domain; LINC, linker of nucleoskeleton and cytoskeleton; NPC, nuclear pore complex; TAD, topologicallly associating domain.