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Defining the chromatin landscape in demyelinating disorders

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Abstract

An intricate network of epigenetic factors regulates cell differentiation by modulating the chromatin structure and ultimately affecting gene expression. This review describes the chromatin landscape defining oligodendrocyte progenitor differentiation during development and remyelination. We shall discuss the current knowledge regarding modifications of chromatin components during the progression of progenitors into myelinating cells and discuss the potential contribution of histone variants, microRNAs, and DNA methylation. We shall also briefly address how changes to this chromatin landscape can disturb this natural progression and alter the capacity to remyelinate.

Keywords

Demyelination; Epigenetics; Multiple sclerosis; Myelin; Oligodendrocyte differentiation

Introduction

One of the first concepts concerning the “chromatin landscape” of a cell was that of a “packaging” system to fit the entire genomic content into a single nucleus (Kornberg and Thomas, 1974). However, this concept has evolved over the years and we are now recognizing the menagerie of chromatin modifications that function as dynamic modulators of gene expression (see Li et al., 2007). Moreover, the topological features of chromatin are not constant but rather are composed of areas of condensation and de-condensation, defining “peaks and valleys” in the chromosomes and affecting the appearance of a specific “chromatin landscape” that changes with the developmental and differentiative state of the cell. The complexity and intricacy of this system becomes vaster by the day as we discover novel modifications and the enzymes facilitating these changes, but the ultimate challenge will be to define how these modifications might contribute to development and disease.

Over the past few years, our understanding of the role of epigenetics during oligodendrocyte development and myelin formation has rapidly progressed. During differentiation, a global increase in histone deacetylation and chromatin compaction is necessary for oligodendrocyte lineage progression (Marin-Husstege et al., 2002; Shen et al., 2005). Specifically, repression of transcriptional inhibitors such as Hes5 (Kondo and Raff, 2000a; Liu et al., 2006), Sox11 and Tcf4 (Fancy et al., 2009; He et al., 2007b; Ye et al., 2009), and Id2 and Id4 (Kondo and Raff, 2000b; Marin-Husstege et al., 2006; Samanta and Kessler, 2004) is a necessary feature of this process (He et al., 2007a). The expression of these inhibitors is modulated by a series of post-translational changes on lysine residues in the tail of nucleosomal histones that allow chromatin de-condensation at the progenitor stage and condensation during maturation.

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In this review, we present an overview of the chromatin landscape in oligodendrocyte lineage cells. We discuss how it potentially may take shape during development and how perturbations to this landscape can affect remyelination capacity. We shall briefly mention changes relative to the acetylation and methylation profiles of histone tails, as these have been discussed extensively in other reviews (see Copray et al., 2009; Shen and Casaccia-Bonnefil, 2008), and turn our focus towards other modifications have yet to be studied extensively in demyelinating disorders.

Normal oligodendrocyte development and maturation

Oligodendrocyte differentiation and myelin formation is a complex developmental process, requiring the coordinated action of transcription factors (Nicolay et al., 2007; Wegner, 2008), the chromatin machinery (Li et al., in press; Liu et al., 2007a; Sher et al., 2008), and additional factors affecting RNA stability and content. To understand how aberrant changes to the chromatin landscape can affect the repair process after demyelination, we must first examine the normal profile of this developmental process.

Nuclear architecture

Regulation of the chromatin landscape is not limited to changes within pockets of genes but occurs on a nuclear level, where spatial organization plays a role. The nuclear architecture has long been studied in oligodendrocyte cells. Ultrastructural studies on the developing corpus callosum of neonatal rats described the progressive increase of chromatin compaction in the nuclei of oligodendrocyte progenitors during differentiation (Kozik, 1976; Mori and Leblond, 1970; Sturrock, 1976). According to these studies, at postnatal day 1 the nuclei of glial precursors were identified by the presence of dispersed chromatin (i.e., euchromatin) and abundant cytoplasm. At postnatal day 8 the appearance of the differentiating cells, called “oligodendroblasts,” was characterized by a slightly higher electron density and by the presence of large conglomerates of nuclear chromatin (i.e., heterochromatin) in the inner part of the nuclear membrane (Kozik, 1976). Finally, around the third week of postnatal development, the nucleus of myelinating oligodendrocytes was characterized by the presence of very large chromatin aggregates and smaller granules scattered throughout (Kozik, 1976; Mori and Leblond, 1970; Sturrock, 1976). A more recent study (Menn et al., 2006) using ultrastructural characterization of myelinating and non myelinating oligodendrocytes in the corpus callosum and the white matter tracks in the striatum and fimbria fornix confirmed these findings and reported clear differences in the appearance of the chromatin in the nucleus of these two cell populations, thereby confirming earlier reports (Peters et al., 1991). Non-myelinating oligodendrocytes were characterized by a relatively large electron-lucent nucleus with more dispersed chromatin, while myelinating cells were characterized by an electron-dense nucleus with large clumps of chromatin and a prominent layer of heterochromatin underlying the nuclear envelope. These data suggested that the degree of chromatin compaction correlates with the functional status of the cell.

Besides the general appearance of hetero and euchromatin within the cell, it is important to discuss the existence of individual chromosomal territories which include the localization of gene-poor and silenced regions at the periphery of the nucleus and that of gene-rich areas towards the interior (Schneider and Grosschedl, 2007). This topological organization of chromosomal domain is not static. Rather it resembles an organic interface, shifting with the proliferative state of the cell and its differentiation. An example of this dynamic topological shift is the localization of pro-neural genes during neural induction of ES cells (Williams et al., 2006). Uncommitted and proliferating ES cells, for instance, are characterized by preferential peripheral positioning of the pro-neural bHLH Mash1, whose promoter has low levels of histone acetylation and high levels of H3K27 methylation. Upon commitment to the neural lineage, but not during commitment to other non-neural lineages, Mash1 positioning

shifted towards the inside of the nucleus and was associated with increased levels of gene expression (Williams et al., 2006). Together these data suggest the importance of positional information within nuclear domains that are associated with the developmental stage of the cell and its specific fate choice.

Critical determinants for the localization of heterochromatin proteins at the nuclear periphery are the nuclear lamins (Cohen et al., 2001). It is interesting that mutations in lamin A, which result in aberrant hererochromatin localization, altered histone modifications, and mislocalization of the nuclear pores (Scaffidi and Misteli, 2006), have been associated with peripheral neuropathies, such as the Charcot–Marie–Tooth disease (De Sandre-Giovannoli et al., 2002). Mutations in lamin B1, in contrast, have been associated with demyelination and altered mitotic spindle organization and adult onset autosomal dominant leukodystrophy (Padiath et al., 2006.). Thus, maintenance of appropriate nuclear domains and proper localization of heterochromatin is essential for the integrity of myelin and proper oligodendrocyte function.

An initial study on the nuclear organization of the oligodendrocytes was performed by Nielsen et al. (2002), who addressed the localization of the myelin gene encoding for proteolipid protein (PLP) during the progression of progenitors to mature cells. Interestingly, and in contrast with previous reports for the Mash1 locus in ES cell, PLP was localized at the nuclear periphery in both progenitors and differentiated oligodendrocytes, although a functionally related gene, myelin basic protein (MBP), was not spatially associated with PLP in either case. It will be important to determine whether the chromosomal territories (with PLP being localized on the X chromosome and MBP on chromosome 18 in the mouse and human genome) or potential differences in the histone codes for these two genes might account for the spatial differences.

Histones

The first unit of chromatin organization is the formation of 10 nm fibers that are composed of “beads on a string” structures, whose simplest unit, the globular nucleosome, is composed of four pairs of constituent core histones: H2A, H2B, H3, and H4 (Davey et al., 2002). An additional layer of complexity is provided by a fifth histone, the so called “linker” histone H1, which stabilizes the position of the nucleosomes and is critical for the formation of 30 nm chromatin fibers (Robinsin and Rhodes, 2006). Distinct differentiation stages are associated with different ratios of H1/core nucleosomes for specific cell types, thereby suggesting that the type of compaction might be different among distinct lineages (Woodcock et al., 2006).

Histone modifications

The structural determinants of chromatin compaction and the topological interaction within nuclear compartment provide the landscape for genomic organization within each cell. Post-translational modifications of core histones, however, provide the dynamic modulation of gene expression at distinct stages of differentiation. Acetylation and deacetylation oppose each other, as acetylation is functionally associated with active and open chromatin, while deacetylation is functionally correlated with inactive and often closed chromatin (Bartova et al., 2008). Methylation, on the other hand, is location-dependent in terms of its activity: trimethylation of histone H3 lysine 4 is associated with transcriptionally active genes, while trimethylation of histone H3 lysine 9 or 27 is associated with transcriptionally inactive genes (Shukla et al., 2009; Sims and Reinberg, 2008). Trimethylation of lysine residue 27 on histone H3 by the enzyme EZH2 has been associated with oligodendrocytic differentiation from stem cells (Sher et al., 2008), while global changes in histone deacetylation (Marin-Husstege et al., 2002) and methylation of lysine 9 on histone H3 (Shen et al., 2005) have been associated with the maturation of oligodendrocyte progenitors to mature cells. Of importance to oligodendrocyte development are the repressive modifications, including deacetylation and

repressive methylation of specific lysine residues within the tail of histone H3, as these allow the progression of oligodendrocyte progenitor cells to differentiated oligodendrocytes (Liu et al., 2007a). Specifically, these modifications suppress the choice of an alternative lineage and repress the expression of transcriptional inhibitors of oligodendrocyte differentiation. Intriguingly, new evidence has proposed that histone deacetylation in myelin genes is associated with myelin gene expression during oligodendrocyte maturation (Liu et al., 2009). A thorough understanding of the dynamic global changes in gene expression during the progression of progenitors to myelinating oligodendrocytes remains to be provided.

Histone variants

Besides the post-translational modifications occurring in the core histones, the existence of several variants for core nucleosomes or linker histones contributes to the level of complexity (Bernstein and Hake, 2006; Kamakaka and Biggins, 2005; Sarma and Reinberg, 2005). Individual histone variants have distinct roles, ranging from gene activation to chromosomal segregation (Bernstein and Hake, 2006). H2AX, for instance, has been associated with a number of cancers (Kokandakar et al., 2007; Liu et al., 2007b; Srivastava et al., 2008), as per its role in DNA repair and genomic integrity. Studies of H2AX-deficient mice have confirmed its role as a tumor suppressor (Dickey et al., 2009). Another example is H2AZ, which has been shown to occupy a distinct set of genes in neural precursors and in embryonic stem cells (Creyghton et al., 2008). This histone variant has been proposed as biomarker for breast cancer, since its levels increase during breast cancer development and metastasis (Hua et al., 2008). The specific histone variants in oligodendrocyte development have not yet been identified, although the last notable histone variant discovered to play a role in oligodendrocyte development was H1(0), which increases during differentiation (Di Liegro and Cestelli, 1990). More recent studies in other cell types, including dendritic cells and fibroblasts, have correlated the presence of the histone H1(0) variant to terminal differentiation in lineages associated with heterochromatization (Izzo et al., 2008; Sekeri-Pataryas and Sourlingas, 2007). Thus the presence of this linker histone variant during oligodendrocyte differentiation is consistent with the progressive nuclear condensation associated with maturation.

DNA methylation

Biologically related yet separate from histone modifications is DNA methylation, a modification to DNA primarily located on the cytosine of the dinucleotide CpG (Cedar and Bergman, 2009). The hierarchy between histone modification and DNA methylation is still debated, as some evidence indicates that DNA methylation marks gene silencing with specific histone marks (Eden et al., 1998; Hashimshony et al., 2003), while others show that an inactive chromatin state must first be established before being followed by DNA methylation to establish transcriptional silencing (Ooi et al., 2007). DNA methylation is normally synonymous with transcriptional silencing; however, the story is more complex than a simple on and off switch. An unmethylated state does not necessarily mean active gene expression, but rather marks an open state that is capable of transcription. Similarly, methylation adjacent to a gene does not necessarily silence it, as it is usually a specific core region of the promoter that must be hypermethylated to turn off gene expression (Ushijima, 2005). During oligodendrocyte development, as noted above, the activity of histone deacetylases plays a critical role in turning off transcriptional inhibitors of oligodendrocyte development. Coinciding with this process is an increase in the activity of myelin-specific genes, including myelin-associated glycoprotein (MAG). Concomitant with this increased activity is a notable demethylation of specific methyl cytosines 5′ of the *MAG* gene (Grubinska et al., 1994). Similar demethylation patterns may occur with other coordinately expressed myelin-specific genes but they have yet to be identified.

microRNA

A feature of the chromatin landscape that has gained momentum in the past few years is microRNAs (miRNAs). A small non-coding RNA molecule that regulates gene expression at the post-transcriptional level (Kim et al., 2009), miRNAs have been shown to be critical for neural development (Mehler, 2008; Stefani and Slack, 2008). These single-stranded RNAs are approximately 22 nt in length and are functionally associated with the silencing of mRNA transcripts, but they have also been linked with heterochromatin formation and several other functions (Kim et al., 2008). Arising from endogenous hairpin-shaped transcripts, mature miRNAs are generated by the coordinated and consecutive actions of RNase III-type proteins Drosha and Dicer (Kim et al., 2009). Once processed into their mature form, miRNAs are loaded onto argonaute proteins to form the silencing complex, which ultimately functions as a post-transcriptional regulator through imperfect binding at the 3′ untranslated region of target mRNA transcripts. This subsequently catalyzes mRNA degradation or mediates translational repression. As of now, only a few definitive mRNA targets are known, while others are primarily identified through bioinformatic analyses of conserved base-pairing between miRNAs and their targets.

Systematic characterization of miRNAs reveals their presence in a multitude of systems and tissues, especially localized within the brain (Mehler, 2008; Sempere et al., 2004). One of the first miRNA expression profiles in developing oligodendrocytes isolated from postnatal rat brains identified 98 miRNAs, with a subset showing dynamic expression during differentiation from progenitor cells to premyelinating oligodendrocytes (Lau et al., 2008). Among those miRNAs, miR-9 was shown to be down-regulated during oligoden-drocyte differentiation and to regulate peripheral myelin protein (PMP) 22. Interestingly, PMP22 mRNA, but not protein, is present in oligodendrocytes, while Schwann cells produce PMP22 protein and lack miR-9. Another example of a miRNA crucial for oligodendrocyte development and maturation is miR-23, a regulator of the nuclear structural protein lamin B1 (Lin and Fu, 2009). Studies conducted by Lin and Fu (2009) showed that overexpression of lamin B1 can inhibit oligodendrocyte maturation, while overexpression of miR-23 could rescue this maturation defect in a dosage-dependent manner.

The chromatin landscape shifts in demyelinating disorders

The chromatin landscape that takes shape during normal oligodendrocyte development and myelin formation is a complex network requiring the coordinated action of multiple epigenetic pathways. And with this idea in mind, we can begin to see how perturbations to any one of these processes can affect oligodendroglial maturation and myelination. Specifically, we examine this landscape in terms of the changes that affect remyelination capacity, as this process utilizes a similar developmental program to normal development in order to lay down new myelin (Miller and Mi, 2007). We focus on remyelination capacity, as many of the changes associated with demyelinating disorders affect the capacity of oligodendrocyte progenitor cells to differentiate into mature myelin forming cells.

Histone modifications

As noted above, post-translational modifications to histones are required for proper development of oligodendrocytes and myelin. However, the appearance of modifications unnecessary for this developmental process, such as histone citrullination, can alter the ability of oligodendrocytes to form myelin. Mediated by human peptidylarginine deiminase 4 (PAD4), citrullination is an irreversible structural modification that is used to remove arginine methylation (Wang et al., 2004). Methylation of arginine 17 on histone H3 (H3R17) has been correlated with gene activation (Bauer et al., 2002; Chen et al., 1999; Strahl et al., 2001; Wang et al., 2001), while methylation of arginine 8 (H3R8) and arginine 2 on histone H3 (H3R2; Pal

et al., 2004; Wysocka et al., 2006) is mutually exclusive with trimethyl K4 and linked to repression. The methylation mark on these arginine residues can be removed by specific deiminases, such as PAD4 (Wang et al., 2004). High levels of PAD4 and the byproduct, citrullinated histone H3, have been detected in the brain of multiple sclerosis (MS) patients (Mastronardi et al., 2006). Because the functional significance of increased global histone citrullination in oligodendrocyte lineage cells remains to be clearly defined, the biological significance of this modification remains to be elucidated.

Additional changes in the chromatin landscape of oligodendrocyte lineage cells have been reported in physiological conditions associated with decreased capacity to remyelinate (Shen et al., 2008a,b), such as aging (Shields et al., 1999), which has been proposed to recapitulate the process of inefficient oligodendrocyte differentiation (Sim et al., 2002). It has been proposed that part of the mechanism behind inefficient repair of demyelinating lesions is dependent on perturbation of the normal chromatin landscape of developing oligodendrocytes. Aging was shown to be associated with decreased levels of repressive methylation and increased acetylation of lysine residues on histone H3 (Shen et al., 2008a), leading to increased expression levels of oligodendrocyte differentiation inhibitors (Shen et al., 2008b). It would be of interest to determine whether similar modifications occur also in human brains of healthy old subjects and in patients with a definite diagnosis of multiple sclerosis.

DNA methylation

Many of the shifts seen in the chromatin landscape of demyelinating disorders are linked together, and such is the case for PAD2. In contrast to PAD4, whose substrates are arginine within histones, PAD2 is a cytoplasmic enzyme with the ability to convert methylation of arginine residues within MBP into citrulline, thereby inducing structural changes in the molecule and leading to developmentally immature myelin (Moscarello et al., 1994). High levels of citrullinated MBP, with 18 out of 19 arginines converted to citrulline, were detected in the brain of patients with a rare acute Marburg's form of multiple sclerosis (Wood et al., 1996). These changes correlated with high levels and activity of PAD2 enzyme (Mastronardi et al., 2006; Wood et al., 2008) and resulted in changes in the charge of MBP and altered interaction with other myelin components (Wood et al., 1996).

But what mechanism underlies the increase in PAD2 levels? Sequence analysis of the *PAD2* promoter shows that 74% of the DNA content is represented by CpG dinucleotides, and bisulfite sequencing reveals that this region is hypomethylated in MS brains compared to controls (Mastronardi et al., 2007). Such decreased regulation of *PAD2* could explain its enhanced expression in MS brains (Casaccia-Bonnefil et al., 2008).

Disease models provide a glimpse of changes that are poorly understood in demyelinating disorders

Great strides have been made with classifying the epigenetic mechanisms that contribute to changes seen in demyelinating disorders. However, most of these findings are limited to features that have been studied extensively in oligodendrocytes, such as histone modifications. For other aspects of the chromatin landscape, such as DNA methylation and miRNAs, we can turn to other systems to help us understand their role in disease.

DNA methylation

Oligodendrocyte dysfunction is linked to a number of disorders, including schizophrenia. Immunohistochemical analysis of patients with schizophrenia showed decreased levels of oligodendrocyte proteins (Flynn et al., 2003; Honer et al., 1999), while DNA microarray studies support the finding of oligodendrocyte alterations (Haroutunian et al., 2007). The mechanism

accounting for the downregulation of the numerous oligodendrocyte genes varies, depending on the gene. Iwamoto et al. focused on *SOX10*, a transcription factor necessary for the terminal differentiation of oligodendrocytes (Stolt et al., 2002). Using bisulfite modification of the CpG island of *SOX10*, Iwamoto et al. (2005) determined that patients with schizophrenia showed a tendency for higher methylated alleles as compared to controls. This finding correlated with the lower expression levels of *SOX10*. Iwamoto et al. (2005) also showed that DNA methylation did not account for the downregulation of *OLIG2* or myelin-associated oligodendrocyte basic protein, both coordinately activated genes during myelination. Once again, using bisulfite analysis, they determined that the methylation status of these genes did not change much in schizophrenia brains compared to controls. Such data suggest that aberrant DNA methylation of oligodendrocyte-specific genes may lead to subtle changes resulting in functional impairment, such as in patients with schizophrenia.

microRNA

MicroRNAs are involved in a myriad of biological processes, and with all those systems, it is found associated with a number of diseases, including diabetes (Lovis et al., 2008; Tang et al., 2008), cardiovascular disease (Sayed et al., 2007; Thum et al., 2008), and neurological disorders (Hébert et al., 2008). The mRNA target of the specific miRNA will determine if overexpression or downregulation will lead to disease. Using gliomas as a disease system, we can find examples of both changes. A miRNA exhibiting oncogenic features in glioblastomas is miR-21, which is expressed at high levels in glioblastoma cells (Chan et al., 2005). Furthermore, miR-21 is associated with essential mechanisms that regulate apoptosis, as inhibition of this molecule leads to increased caspase-dependent apoptosis (Chan et al., 2005). Specific targets of miR-21, both directly and indirectly, include p53, TGF-β, and mitochondrial apoptosis (Papagiannakopoulos et al., 2008). Up-regulation of this oncogenic molecule leads to impairment of DNA damage responses, giving way to cancer mutations. Opposed to miR-21 are miRNAs with tumor suppressor activity, which require down-regulation in order to contribute to tumor formation. miRNAs with such characteristics are miR-181a and miR-181b, which are found at abundant levels in normal brain tissue but are down-regulated in human glioma cells (Shi et al., 2008). Concordant with their role as a tumor suppressor, over-expression of miR-181a and miR-181b in glioma cell lines triggered growth inhibition, reduced invasion capacity, and induced apoptosis of glioma cells (Shi et al., 2008). The direct targets of these miRNAs have yet to be identified. It would be of interest to determine how microRNAs affect repair or disease progression in MS.

Summary

Our view of the chromatin landscape that takes shape during oligodendrocyte development, myelination, and remyelination is only at the cusp of what is still to be found. The interplay of so many epigenetic factors makes it a difficult process to characterize this landscape but we have slowly begun to unravel it. And with each discover, unknown factors of normal developmental are revealed and the possibilities for therapies are expanded with each new target.

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References

Bartova E, Krejci J, Harnicarova A, Galiova G, Kozubek S. Histone modifications and nuclear architecture: a review. J Histochem Cytochem 2008;56:711–721. [PubMed: 18474937]

Bauer UM, Daujat S, Nielsen SJ, Nightingale K, Kouzarides T. Methylation at arginine 17 of histone H3 is linked to gene activation. EMBO Rep 2002;3:39–44. [PubMed: 11751582]

Bernstein E, Hake SB. The nucleosome: a little variation goes a long way. Biochem Cell Biol 2006;84:505–517. [PubMed: 16936823]

Casaccia-Bonnefil P, Pandozy G, Mastronardi F. Evaluating epigenetic landmarks in the brain of multiple sclerosis patients: a contribution to the current debate on disease pathogenesis. Prog Neurobiol 2008;86:368–378. [PubMed: 18930111]

Cedar H, Bergman Y. Linking DNA methylation and histone modification: patterns and paradigms. Nat Rev Genet 2009;10:295–304. [PubMed: 19308066]

Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. Cancer Res 2005;65:6029–6033. [PubMed: 16024602]

Chen D, Ma H, Hong H, Koh SS, Huang SM, Schurter BT, Aswad DW, Stallcup MR. Regulation of transcription by a protein methyltransferase. Science 1999;284:2174–2177. [PubMed: 10381882]

Cohen M, Lee KK, Wilson KL, Gruenbaum Y. Transcriptional repression, apoptosis, human disease and the functional evolution of the nuclear lamina. Trends Biochem Sci 2001;26:41–47. [PubMed: 11165516]

Copray S, Huynh JL, Sher F, Casaccia-Bonnefil P, Boddeke E. Epigenetic mechanisms facilitating oligodendrocyte development, maturation, and aging. Glia 2009;57:1579–1587. [PubMed: 19373939]

Creyghton MP, Markoulaki S, Levine SS, Hanna J, Lodato MA, Sha K, Young RA, Jaenisch R, Boyer LA. H2AZ is enriched at polycomb complex target genes in ES cells and is necessary for lineage commitment. Cell 2008;135:649–661. [PubMed: 18992931]

Davey CA, Sargent DF, Luger K, Maeder AW, Richmond TJ. Solvent mediated interactions in the structure of the nucleosome core particle at 1.9 Å resolution. J Mol Biol 2002;319:1097–1113. [PubMed: 12079350]

De Sandre-Giovannoli A, Chaouch M, Kozlov S, Vallat JM, Tazir M, Kassouri N, Szepetowski P, Hammadouche T, Vandenberghe A, Stewart CL, Grid D, Lévy N. Homozygous defects in LMNA, encoding lamin A/C nuclear-envelope proteins, cause autosomal recessive axonal neuropathy in human (Charcot–Marie–Tooth disorder type 2) and mouse. Am J Hum Genet 2002;70:726–736. [PubMed: 11799477]

Di Liegro I, Cestelli A. The relative proportion of H1(0) and A24 is reversed in oligodendrocytes during rat brain development. Cell Mol Neurobiol 1990;10:267–274. [PubMed: 2163755]

Dickey JS, Redon CE, Nakamura AJ, Baird BJ, Sedelnikova OA, Bonner WM. H2AX: functional roles and potential applications. Chromosoma. 200910.1007/s00412-009-0234-4

Eden S, Hashimshony T, Keshet I, Thorne AW, Cedar H. DNA methylation models histone acetylation. Nature 1998;394:842–843. [PubMed: 9732866]

Fancy SP, Baranzini SE, Zhao C, Yuk DI, Irvine KA, Kaing S, Sanai N, Franklin RJ, Rowitch DH. Dysregulation of the Wnt pathway inhibits timely myelination and remyelination in the mammalian CNS. Genes Dev 2009;23:1571–1585. [PubMed: 19515974]

Flynn SW, Lang DJ, Mackay AL, Goghari V, Vavasour IM, Whittall KP, Smith GN, Arango V, Mann JJ, Dwork AJ, Falkai P, Honer WG. Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem with analysis of oligodendrocyte proteins. Mol Psychiatry 2003;8:811–820. [PubMed: 12931208]

Grubinska B, Laszkiewicz I, Royland J, Wiggins RC, Konat GW. Differentiation-specific demethylation of myelin associated glycoprotein gene in cultured oligodendrocytes. J Neurosci Res 1994;39:233–242. [PubMed: 7532722]

Haroutunian V, Katsel P, Dracheva S, Stewart DG, Davis KL. Variations in oligodendrocyte-related gene expression across multiple cortical regions: implications for the pathophysiology of schizophrenia. Int J Neuropsychopharmacol 2007;10:565–573. [PubMed: 17291370]

Hashimshony T, Zhang J, Keshet I, Bustin M, Cedar H. The role of DNA methylation in setting up chromatin structure during development. Nat Genet 2003;34:187–192. [PubMed: 12740577]

He Y, Dupree J, Wang J, Sandoval J, Li J, Liu H, Shi Y, Nave KA, Casaccia-Bonnefil P. The transcription factor Yin Yang 1 is essential for oligodendrocyte progenitor differentiation. Neuron 2007a;55:217–230. [PubMed: 17640524]

He Y, Sandoval J, Casaccia-Bonnefil P. Events at the transition between cell cycle exit and oligodendrocyte progenitor differentiation: the role of HDAC and YY1. Neuron Glia Biol 2007b; 3:221–231. [PubMed: 18634613]

Hébert SS, Horré K, Nicolaï L, Papadopoulou AS, Mandemakers W, Silahtaroglu AN, Kauppinen S, Delacourte A, De Strooper B. Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/beta-secretase expression. Proc Natl Acad Sci USA 2008;105:6415–6420. [PubMed: 18434550]

Honer WG, Falkai P, Chen C, Arango V, Mann JJ, Dwork AJ. Synaptic and plasticity-associated proteins in anterior frontal cortex in severe mental illness. Neuroscience 1999;91:1247–1255. [PubMed: 10391432]

Hua S, Kallen CB, Dhar R, Baquero MT, Mason CE, Russell BA, Shah PK, Liu J, Khramtsov A, Tretiakova MS, Krausz TN, Olopade OI, Rimm DL, White KP. Genomic analysis of estrogen cascade reveals histone variant H2A.Z associated with breast cancer progression. Mol Syst Biol 2008;4:188. [PubMed: 18414489]

Iwamoto K, Bundo M, Yamada K, Takao H, Iwayama-Shigeno Y, Yoshikawa T, Kato T. DNA methylation status of SOX10 correlates with its downregulation and oligodendrocyte dysfunction in schizophrenia. J Neurosci 2005;25:5376–5381. [PubMed: 15930386]

Izzo A, Kamieniarz K, Schneider R. The histone H1 family: specific members, specific functions? Biol Chem 2008;389:333–343. [PubMed: 18208346]

Kamakaka RT, Biggins S. Histone variants: deviants? Genes Dev 2005;19:295–310. [PubMed: 15687254]

Kim DH, Saetrom P, Snøve O Jr, Rossi JJ. MicroRNA-directed transcriptional gene silencing in mammalian cells. Proc Natl Acad Sci USA 2008;105:16230–16235. [PubMed: 18852463]

Kim VN, Han J, Siomi MC. Biogenesis of small RNAs in animals. Nat Rev Mol Cell Biol 2009;10:126–139. [PubMed: 19165215]

Kokandakar HR, Tembhare PR, Mamoon A, Mulay VM, Bhople KS. Acute basophilic leukaemia: a case report. Indian J Pathol Microbiol 2007;50:443–446. [PubMed: 17883105]

Kondo T, Raff M. Basic helix-loop-helix proteins and the timing of oligodendrocyte differentiation. Development 2000a;127:2989–2998. [PubMed: 10862737]

Kondo T, Raff M. The Id4 HLH protein and the timing of oligodendrocyte differentiation. EMBO J 2000b;19:1998–2007. [PubMed: 10790366]

Kornberg RD, Thomas JO. Chromatin structure; oligomers of the histones. Science 1974;184:865–868. [PubMed: 4825888]

Kozik MB. The electron-microscopic picture of postnatal development of oligodendroglia. Folia Histochem Cytochem (Krakow) 1976;14:99–106. [PubMed: 1270029]

Lau P, Verrier JD, Nielsen JA, Johnson KR, Notterpek L, Hudson LD. Identification of dynamically regulated microRNA and mRNA networks in developing oligodendrocytes. J Neurosci 2008;28:11720–11730. [PubMed: 18987208]

Li B, Carey M, Workman JL. The role of chromatin during transcription. Cell 2007;128:707–719. [PubMed: 17320508]

Li H, He Y, Richardson WD, Casaccia P. Two-tier transcriptional control of oligodendrocyte differentiation. Curr Opin Neurobiol. in press. 10.1016/j.conb.2009.08.004

Lin ST, Fu YH. miR-23 regulation of lamin B1 is crucial for oligodendrocyte development and myelination. Dis Model Mech 2009;2:178–188. [PubMed: 19259393]

Liu A, Li J, Marin-Husstege M, Kageyama R, Fan Y, Gelinas C, Casaccia-Bonnefil P. A molecular insight of Hes5-dependent inhibition of myelin gene expression: old partners and new players. EMBO J 2006;25:4833–4842. [PubMed: 17006542]

Liu A, Han YR, Li J, Sun D, Ouyang M, Plummer MR, Casaccia-Bonnefil P. The glial or neuronal fate choice of oligodendrocyte progenitors is modulated by their ability to acquire an epigenetic memory. J Neurosci 2007a;27:7339–7343. [PubMed: 17611286]

Liu Y, Tseng M, Perdreau SA, Rossi F, Antonescu C, Besmer P, Fletcher JA, Duensing S, Duensing A. Histone H2AX is a mediator of gastrointestinal stromal tumor cell apoptosis following treatment with imatinib mesylate. Cancer Res 2007b;67:2685–2692. [PubMed: 17363589]

Liu H, Hu Q, D'ercole AJ, Ye P. Histone deacetylase 11 regulates oligodendrocyte-specific gene expression and cell development in OL-1 oligodendroglia cells. Glia 2009;57:1–12. [PubMed: 18627006]

Lovis P, Roggli E, Laybutt DR, Gattesco S, Yang JY, Widmann C, Abderrahmani A, Regazzi R. Alterations in microRNA expression contribute to fatty acid-induced pancreatic beta-cell dysfunction. Diabetes 2008;57:2728–2736. [PubMed: 18633110]

Marin-Husstege M, Muggironi M, Liu A, Casaccia-Bonnefil P. Histone deacetylase activity is necessary for oligodendrocyte lineage progression. J Neurosci 2002;22:10333–10345. [PubMed: 12451133]

Marin-Husstege M, He Y, Li J, Kondo T, Sablitzky F, Casaccia-Bonnefil P. Multiple roles of Id4 in developmental myelination: predicted outcomes and unexpected findings. Glia 2006;54:285–296. [PubMed: 16862533]

Mastronardi FG, Wood DD, Mei J, Raijmakers R, Tseveleki V, Dosch HM, Probert L, Casaccia-Bonnefil P, Moscarello MA. Increased citrullination of histone H3 in multiple sclerosis brain and animal models of demyelination: a role for tumor necrosis factor-induced peptidylarginine deiminase 4 translocation. J Neurosci 2006;26:11387–11396. [PubMed: 17079667]

Mastronardi FG, Noor A, Wood DD, Paton T, Moscarello MA. Peptidyl argininedeiminase 2 CpG island in multiple sclerosis white matter is hypomethylated. J Neurosci Res 2007;85:2006–2016. [PubMed: 17469138]

Mehler MF. Epigenetics and the nervous system. Ann Neurol 2008;64:602–617. [PubMed: 19107999]

Miller RH, Mi S. Dissecting demyelination. Nat Neurosci 2007;10:1351–1354. [PubMed: 17965654]

Menn B, Garcia-Verdugo JM, Yaschine C, Gonzalez-Perez O, Rowitch D, Alvarez-Buylla A. Origin of oligodendrocytes in the subventricular zone of the adult brain. J Neurosci 2006;26:7907–7918. [PubMed: 16870736]

Mori S, Leblond CP. Electron microscopic identification of three classes of oligodendrocytes and a preliminary study of their proliferative activity in the corpus callosum of young rats. J Comp Neurol 1970;139:1–28. [PubMed: 4191626]

Moscarello MA, Wood DD, Ackerley C, Boulias C. Myelin in multiple sclerosis is developmentally immature. J Clin Invest 1994;94:146–154. [PubMed: 7518827]

Nicolay DJ, Doucette JR, Nazarali AJ. Transcriptional control of oligoden-drogenesis. Glia 2007;55:1287–1299. [PubMed: 17647291]

Nielsen JA, Hudson LD, Armstrong RC. Nuclear organization in differentiating oligodendrocytes. J Cell Sci 2002;115:4071–4079. [PubMed: 12356912]

Ooi SK, Qiu C, Bernstein E, Li K, Jia D, Yang Z, Erdjument-Bromage H, Tempst P, Lin SP, Allis CD, Cheng X, Bestor TH. DNMT3L connects unmethylated lysine 4 of histone H3 to de novo methylation of DNA. Nature 2007;448:714–717. [PubMed: 17687327]

Padiath QS, Saigoh K, Schiffmann R, Asahara H, Yamada T, Koeppen A, Hogan K, Ptácek LJ, Fu YH. Lamin B1 duplications cause autosomal dominant leukodystrophy. Nat Genet 2006;38:1114–1123. [PubMed: 16951681]

Pal S, Vishwanath SN, Erdjument-Bromage H, Tempst P, Sif S. Human SWI/SNF-associated PRMT5 methylates histone H3 arginine 8 and negatively regulates expression of ST7 and NM23 tumor suppressor genes. Mol Cell Biol 2004:9630–9645. [PubMed: 15485929]

Papagiannakopoulos T, Shapiro A, Kosik KS. MicroRNA-21 targets a network of key tumor-suppressive pathways in glioblastoma cells. Cancer Res 2008;68:8164–8172. [PubMed: 18829576]

Peters, A.; Palay, SL.; Webster, HDF. The Fine Structure of the Nervous System: Neurons and Their Supporting Cells. Oxford Univ. Press; New York: 2001.

Robinsin PJ, Rhodes D. Structure of the 30 nm chromatin fiber: a key role for the linker histone. Curr Opin Struct Biol 2006;16:336–343. [PubMed: 16714106]

Samanta J, Kessler JA. Interactions between ID, OLIG proteins mediate the inhibitory effects of BMP4 on oligodendroglial differentiation. Development 2004;131:4131–4142. [PubMed: 15280210]

Sarma K, Reinberg D. Histone variants meet their match. Nat Rev Mol Cell Biol 2005;6:139–149. [PubMed: 15688000]

Sayed D, Hong C, Chen IY, Lypowy J, Abdellatif M. MicroRNAs play an essential role in the development of cardiac hypertrophy. Circ Res 2007;100:416–424. [PubMed: 17234972]

Scaffidi P, Misteli T. Lamin A-dependent nuclear defects in human aging. Science 2006;312:1059–1063. [PubMed: 16645051]

Schneider R, Grosschedl R. Dynamics and interplay of nuclear architecture, genome organization, and gene expression. Genes Dev 2007;21:3027–3043. [PubMed: 18056419]

Sekeri-Pataryas KE, Sourlingas TG. The differentiation-associated linker histone, H1.0, during the in vitro aging and senescence of human diploid fibroblasts. Ann N Y Acad Sci 2007;1100:361–367. [PubMed: 17460199]

Sempere LF, Freemantle S, Pitha-Rowe I, Moss E, Dmitrovsky E, Ambros V. Expression profiling of mammalian microRNAs uncovers a subset of brain-expressed microRNAs with possible roles in murine and human neuronal differentiation. Genome Biol 2004;5:R13. [PubMed: 15003116]

Shen S, Casaccia-Bonnefil P. Post-translational modifications of nucleosomal histones in oligodendrocyte lineage cells in development and disease. J Mol Neurosci 2008;35:13–22. [PubMed: 17999198]

Shen S, Li J, Casaccia-Bonnefil P. Histone modifications affect timing of oligodendrocyte progenitor differentiation in the developing rat brain. J Cell Biol 2005;169:577–589. [PubMed: 15897262]

Shen S, Liu A, Li J, Wolubah C, Casaccia-Bonnefil P. Epigenetic memory loss in aging oligodendrocytes in the corpus callosum. Neurobiol Aging 2008a;29:452–463. [PubMed: 17182153]

Shen S, Sandoval J, Swiss VA, Li J, Dupree J, Franklin RJ, Casaccia-Bonnefil P. Age-dependent epigenetic control of differentiation inhibitors is critical for remyelination efficiency. Nat Neurosci 2008b;11:1024–1034. [PubMed: 19160500]

Sher F, Rossler R, Brouwer N, Balasubramaniyan V, Boddeke E, Copray S. Differentiation of neural stem cells into oligodendrocytes: involvement of the polycomb group protein Ezh2. Stem Cells 2008;26:2875–2883. [PubMed: 18687996]

Shi L, Cheng Z, Zhang J, Li R, Zhao P, Fu Z, You Y. hsa-mir-181a and hsa-mir-181b function as tumor suppressors in human glioma cells. Brain Res 2008;1236:185–193. [PubMed: 18710654]

Shields SA, Gilson JM, Blakemore WF, Franklin RJ. Remyelination occurs as extensively but more slowly in old rats compared to young rats following gliotoxin-induced CNS demyelination. Glia 1999;28:77–83. [PubMed: 10498825]

Shukla A, Chaurasia P, Bhaumik SR. Histone methylation and ubiquitination with their cross-talk and roles in gene expression and stability. Cell Mol Life Sci 2009;66:1419–1433. [PubMed: 19370393]

Sim FJ, Zhao C, Penderis J, Franklin RJ. The age-related decrease in CNS remyelination efficiency is attributable to an impairment of both oligodendrocyte progenitor recruitment and differentiation. J Neurosci 2002;22:2451–2459. [PubMed: 11923409]

Sims RJ III, Reinberg D. Is there a code embedded in proteins that is based on post-translational modifications? Nat Rev Mol Cell Biol 2008;9:815–820. [PubMed: 18784729]

Srivastava N, Gochhait S, Gupta P, Bamezai RN. Copy number alterations of the H2AFX gene in sporadic breast cancer patients. Cancer Genet Cytogenet 2008;180:121–128. [PubMed: 18206537]

Stefani G, Slack FJ. Small non-coding RNAs in animal development. Nat Rev Mol Cell Biol 2008;9:219–230. [PubMed: 18270516]

Stolt CC, Rehberg S, Ader M, Lommes P, Riethmacher D, Schachner M, Bartsch U, Wegner M. Terminal differentiation of myelin-forming oligodendrocytes depends on the transcription factor Sox10. Genes Dev 2002;16:165–170. [PubMed: 11799060]

Strahl BD, Briggs SD, Brame CJ, Caldwell JA, Koh SS, Ma H, Cook RG, Shabanowitz J, Hunt DF, Stallcup MR, Allis CD. Methylation of histone H4 at arginine 3 occurs in vivo and is mediated by the nuclear receptor coactivator PRMT1. Curr Biol 2001;11:996–1000. [PubMed: 11448779]

Sturrock RR. Light microscopic identification of immature glial cells in semithin sections of the developing mouse corpus callosum. J Anat 1976;122:521–537. [PubMed: 795801]

Tang X, Tang G, Ozcan S. Role of microRNAs in diabetes. Biochim Biophys Acta 2008;1779:697–701. [PubMed: 18655850]

Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rottbauer W, Frantz S, Castoldi M, Soutschek J, Koteliansky V, Rosenwald A, Basson MA, Licht JD, Pena JT, Rouhanifard SH, Muckenthaler MU, Tuschl T, Martin GR, Bauersachs J, Engelhardt S. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature 2008;456:980–984. [PubMed: 19043405]

Ushijima T. Detection and interpretation of altered methylation patterns in cancer cells. Nat Rev Cancer 2005;5:223–231. [PubMed: 15719030]

Ye F, Chen Y, Hoang T, Montgomery RL, Zhao XH, Bu H, Hu T, Taketo MM, van Es JH, Clevers H, Hsieh J, Bassel-Duby R, Olson EN, Lu QR. HDAC1 and HDAC2 regulate oligodendrocyte differentiation by disrupting the beta-catenin–TCF interaction. Nat Neurosci 2009;12:829–838. [PubMed: 19503085]

Wang H, Huang ZQ, Xia L, Feng Q, Erdjument-Bromage H, Strahl BD, Briggs SD, Allis CD, Wong J, Tempst P, Zhang Y. Methylation of histone H4 arginine 3 facilitating transcriptional activation by nuclear hormone receptor. Science 2001;293:853–857. [PubMed: 11387442]

Wang Y, Wysocka J, Sayegh J, Lee YH, Perlin JR, Leonelli L, Sonbuchner LS, McDonald CH, Cook RG, Dou Y, Roeder RG, Clarke S, Stallcup MR, Allis CD, Coonrod SA. Human PAD4 regulates histone arginine methylation levels via demethylimination. Science 2004;306:279–283. [PubMed: 15345777]

Wegner M. A matter of identity: transcriptional control in oligodendrocytes. J Mol Neurosci 2008;35:3–12. [PubMed: 18401762]

Williams RR, Azuara V, Perry P, Sauer S, Dvorkina M, Jørgensen H, Roix J, McQueen P, Misteli T, Merkenschlager M, Fisher AG. Neural induction promotes large-scale chromatin reorganisation of the Mash1 locus. J Cell Sci 2006;119:132–140. [PubMed: 16371653]

Wood DD, Bilbao JM, O'Connors P, Moscarello MA. Acute multiple sclerosis (Marburg type) is associated with developmentally immature myelin basic protein. Ann Neurol 1996;40:18–24. [PubMed: 8687186]

Wood DD, Ackerley CA, Brand B, Zhang L, Raijmakers R, Mastronardi FG, Moscarello MA. Myelin localization of peptidylarginine deiminases 2 and 4: comparison of PAD2 and PAD4 activities. Lab Invest 2008;88:354–364. [PubMed: 18227806]

Woodcock CL, Skoultchi AI, Fan Y. Role of linker histone in chromatin structure and function: H1 stoichiometry and nucleosome repeat length. Chromosome Res 2006;14:17–25. [PubMed: 16506093]

Wysocka J, Allis CD, Coonrod S. Histone arginine methylation and its dynamic regulation. Front Biosci 2006;11:344–355. [PubMed: 16146736]