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Post-Translational Modifications of Nucleosomal Histones in Oligodendrocyte Lineage Cells in Development and Disease

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Abstract

The role of epigenetics in modulating gene expression in the development of organs and tissues and in disease states is becoming increasingly evident. Epigenetics refers to the several mechanisms modulating inheritable changes in gene expression that are independent of modifications of the primary DNA sequence and include post-translational modifications of nucleosomal histones, changes in DNA methylation, and the role of microRNA. This review focuses on the epigenetic regulation of gene expression in oligodendroglial lineage cells. The biological effects that post-translational modifications of critical residues in the N-terminal tails of nucleosomal histones have on oligodendroglial cells are reviewed, and the implications for disease and repair are critically discussed.

Keywords

Chromatin; Development; Epigenetics; Brain; Myelin; Differentiation; Glia

Introduction

Epigenetic regulation of gene expression has been recently shown to play a critical role in the development of organs and tissues, including the brain. It refers to the inheritable pattern of gene expression that is transmitted to daughter cells and that is independent of changes or mutations in the DNA sequence (Gottschling 2006; Bird 2007). Several factors are known to contribute to epigenetic regulation of gene expression during neural development, including microRNA (Cheng et al. 2005; Cao et al. 2006; Mehler and Mattick 2006, 2007), DNA methylation (Feng et al. 2007), ATP-remodeling complexes, changes in histone variants and post-translational modifications of nucleosomal histones (Fukuda and Taga 2005; Feng et al. 2007). This review will focus on the role of post-translational modifications of nucleosomal histones (Fig. 1).

Nucleosomes are the basic unit of chromatin. They are formed by 150 bp of DNA wrapped around octamers of nuclear proteins called histones. At least four major nucleosomal histones have been identified: H2A, H2B, H3, and H4. Additional histone proteins (i.e., H1) are distributed in the intervening regions called linker regions.

Structural studies of nucleosomal histones have revealed that they are arranged as globular core with the N-terminal tails projecting outward (Dutnall and Ramakrishnan 1997). Because of these structural features, it becomes evident that the amino acids on the tails of these histones are the most easily accessible targets to enzymatic activities downstream of multiple signaling pathways.

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Extracellular signals can communicate with the machinery responsible for the epigenetic regulation of gene expression by inducing phosphorylation on specific serine residues, transferring or removing acetyl or methyl groups on lysine residues, and methylating or deiminating arginine residues (Magnaghi-Jaulin et al. 1999; Thomson et al. 1999; Spencer and Davie 2000).

Post-Translational Modifications of Lysine Residues on Histone Tails: Acetylation and Methylation

Acetylation is the transfer of acetyl groups to the epsilon position of lysine residues in the tail of nucleosomal histones. It is important to distinguish this modification from N-alpha acetylation of eukaryotic structural proteins that occurs on alanine, serine, and methionine residues, and that is catalyzed by N-acetyl transferases. Histone acetylation is catalyzed by a family of enzymes called histone acetyltransferases (HAT), and it is functionally correlated with transcriptionally competent chromatin. The removal of acetyl groups is catalyzed by a family of enzymes called histone deacetylases (HDAC or HD) and is functionally correlated with transcriptionally inactive chromatin (Vidali et al. 1988; Wolffe 1996; Grunstein 1997; Kuo and Allis 1998; Struhl 1998; Spencer and Davie 1999; Tyler and Kadonaga 1999; Cheung et al. 2000; Turner 2000; de Ruijter et al. 2003). Hence, the ratio of HDAC to HAT activity determines the level of histone acetylation.

Histone methylation is a process of adding one, two, or three methyl groups to certain amino acids on histone tails (Ashraf and Ip 1998; Bird and Wolffe 1999; Spencer and Davie 1999; Rice and Allis 2001; Zhang and Reinberg 2001; Bannister et al. 2002; Berger 2002; Goll and Bestor 2002; Kouzarides 2002; Lachner and Jenuwein 2002; Richards 2002). Depending on the specific lysine, methylation may result in gene activation, such as methylation on lysine 4 residue on histone H3 (Me-H3K4) or in repression, such as methylation on lysine 9 or 27 (Fig. 2). It was originally thought that histone methylation was a permanent modification. This theory prevailed until the recent discovery of lysine-specific demethylase 1, which specifically removes mono- and di- but not trimethyl groups from lysine residues, and Jumonji domain-containing, which can demethylate all three status of methylated lysine residue (Kubicek and Jenuwein 2004; Bannister and Kouzarides 2005; Wysocka et al. 2005; Takeuchi et al. 2006; Anand and Marmorstein 2007; Klose and Zhang 2007; Stavropoulos and Hoelz 2007; Wilson 2007). Therefore, similar to histone acetylation, histone methylation is also a regulated dynamic process.

Post-Translational Modifications of Arginine Residues: Methylation and Citrullination

Methylation of arginine residues in histone tails by protein arginine methyltransferases (PRMT) also plays a critical role in dynamic gene regulation (Davie and Dent 2002; Bedford and Richard 2005; Boisvert et al. 2005; Denman 2005; Pahlich et al. 2006; Thompson and Fast 2006; Wysocka et al. 2006). In mammals, PRMT1- and coactivator-associated arginine methyltransferase 1 catalyze the asymmetric methylation of arginine 3 on histone H4 (H4R3) and of arginine 17 on histone H3 (H3R17), respectively, and result in gene activation (Chen et al. 1999; Strahl et al. 2001; Wang et al. 2001a; Bauer et al. 2002). In contrast, the enzyme PRMT5 catalyzes the symmetric methylation of arginine 8 histone H3 (H3R8) and arginine 3 histone H4 (H4R3) (Pal et al. 2004), and this is associated with gene repression (Wysocka et al. 2006). Arginine methylation is also reversible and can be removed by specific deiminases, such as human peptidylarginine deiminase 4 (PAD4), which convert arginine into citrulline (Wang et al. 2004).

Modulation of Oligodendrocyte Lineage-Specific Pathways by HDAC

Model 1 Differentiation Consequent to Derepression of Differentiation Genes

Several studies have contributed to the concept of differentiation consequent to derepression of genes characteristic of the differentiated state. This model implies that neural stem cells or multipotential precursors, which have the potential to differentiate into neurons, astrocytes, and oligodendrocytes, are maintained in an undifferentiated state because of epigenetic silencing of specific lineage markers.

In embryonic neural precursor cells, for instance, the expression of the lineage specific gene glial fibrillary acidic protein (GFAP) is maintained silenced by DNA methylation of CpG islands in the promoter region (Feng et al. 2005). This render inaccessible the binding sites for the transcription factor known as signal transducers and activator of transcription (STAT), which is critical for astroglienesis (Bonni et al. 1997). As development proceeds, the progressive demethylation of the GFAP promoter correlates with the progressive increase of transcript levels (Teter et al. 1994; Takizawa et al. 2001). Besides DNA methylation, the amount of GFAP expression during differentiation is also regulated by histone acetylation and methylation because of the recruitment of a multi-protein complex containing STAT, SMAD, and the HAT p300 (Nakashima et al. 1999; Asklund et al. 2004; Song and Ghosh 2004).

Similarly, in the neuronal lineage, the expression of neural genes is maintained repressed by the activity of multiprotein complexes containing corepressors, HDAC, and the specific transcription factor known as repressor element-silencing transcription (REST) that is responsible for recognizing specific *cis*-element on the promoters (Huang et al. 1999; Roopra et al. 2000; Ballas et al. 2001). REST is a powerful repressor. The N terminus of the molecule has the ability to recruit HDAC1/2 complexes and Sin3A, whereas its C terminus has the ability to form complexes with HDAC1/2 and with Co-REST (Andres et al. 1999; Huang et al. 1999; Naruse et al. 1999; Roopra et al. 2000). Accordingly, neuronal differentiation of embryonic or adult neural progenitors is initiated by the removal component of these large repressive complexes. Consistent with this model, treatment of multipotential neural progenitors with pharmacological inhibitors of HDAC results in the upregulation of neurogenic marker genes, such as NeuroD, and increased neurogenesis (Hao et al. 2004; Hsieh et al. 2004).

By analogy with other lineages, it is likely, although not yet proven, that progressive acetylation of nucleosomal histones and relaxed chromatin structure occurs during the differentiation of precursors into myelinating oligodendrocytes. A number of studies have reported the presence of histone deacetylases (i.e., HDAC1 and 2) in the proximal promoter region of myelin genes in oligodendrocyte progenitors (OPC). For example, HDAC1 has been shown to be recruited by transcriptional factors Nkx2.2 (Wei et al. 2005) and also by Hes5 (Wei et al. 2005; Liu et al. 2006) to the promoter of myelin basic protein (MBP). Similarly, HDAC1/2 heterodimers, in association with Sin3B, were detected in complex with Myt-1 on the proximal region of the proteolipid protein (PLP) promoter (Romm et al. 2005). These findings suggested that the expression of myelin genes in progenitor cells was inhibited by HDAC and predicted that pharmacological inhibition of these enzymes should favor myelin gene expression and promote oligodendrocyte differentiation.

In contrast to the prediction, however, the administration of HDAC inhibitors, such as trichostatin A (TSA) or valproic acid, prevented myelin gene expression in vivo (Shen et al. 2005) and in vitro (Marin-Husstege et al. 2002; Liu et al. 2003). These data suggested at least two possible models of myelin gene activation mediated by chromatin compaction. One possibility suggests that the effect of pharmacological inhibitors of HDAC on myelin gene expression is direct. According to this possibility, activation requires the compaction of

silencers caused by the remodeling of the nucleosomal tails in the chromatin regions containing negative regulatory elements. The presence of HDAC inhibitors would prevent the inactivation of these silencers by halting the formation of zones of compaction. The second possibility is that myelin gene expression results from a balance between positive and negative signals of differentiation. In this case, the post-translational modification of nucleosomes would occur in the promoter of inhibitory molecules, and myelin gene expression would result from a balance tilted in favor of the activators. Future studies providing a careful mapping of histone modifications in the regulatory regions of myelin genes will contribute to the elucidation of the model.

Model 2 Differentiation Consequent to HDAC-mediated Repression of Alternative Lineage Choices

The role of epigenetics in modulating the lineage progression of OPC and the fate choice of multipotential neural precursors have received multiple independent validations.

The first report of the negative effect of HDAC inhibitors on oligodendrocyte differentiation was in 2002 (Marin-Husstege et al. 2002). However, it was not determined whether the cells that were unable to differentiate into oligodendrocytes were redirected to other lineages.

Using adult hippocampus neural progenitor cells, Hsieh and Gage suggested that administration of HDAC inhibitors promoted neurogenesis at the expense of other lineages, possibly because of the increased neuronal gene transcripts, such as NeuroD, in response to high levels of histone acetylation (Hsieh et al. 2004). Therefore, it was conceivable that OPC were redirected to other lineages when unable to differentiate into myelin-forming cells. This concept was recently shown in a series of in vitro and in vivo experiments that clearly indicated that the probability of OPC to generate functional neurons or astrocytes (Bleached et al. 2003; Aguirre et al. 2004; Nishiyama 2007) is dependent on HDAC activity (Liu et al. 2007). These conclusions were further validated by transplantation studies of GFP-labeled OPC in recipients that were either untreated or treated with HDACi. Also in this case, HDACi treatment prevented the ability of GFP transplanted cells to generate mature oligodendrocytes, while redirecting their lineage into astrocytes or neurons (Liu et al. 2007).

These findings could be interpreted in terms of trans-differentiation event or in terms of reversion to a stem-cell-like condition, followed by differentiation along an alternate pathway. It is important to mention that the high probability for OPC to generate functional neurons was only detected in vivo in animals receiving systemic administration of HDAC1 or in vitro when cells pretreated with HDACi were cultured in neurogenic conditions. These results suggested that the differentiation of progenitors into alternative lineages was a two-step event that required, first, the “reversion” to a multipotential stage and then the “differentiation” into another cell type. The ability of OPC to revert to a multipotential stem-cell-like stage had been suggested by Kondo and Raff (2000c), who reported that only extensive culturing methods in fibroblast growth factor-2 (FGF2) would allow this reversion step (Kondo and Raff 2000c). A molecular explanation for the reversion step was provided by the same authors few years later, when Sox2 was proposed as the transcription factor responsible for the maintenance of a multipotential stage (Kondo and Raff 2004). Sox2 is the SRY-related, HMG-box-containing transcription factor that is expressed early in the developing neural tube, is essential for maintaining neural stem cells in undifferentiated state (Graham et al. 2003). It was found to be expressed in neural stem cells but not in lineage-committed progenitors because of epigenetic regulation of its promoter (Graham et al. 2003; Kondo and Raff 2004). It was reported that the reversion of OPC to neural stem cells was associated with the reactivation of the sox2 gene because of activating post-transcriptional modifications of Lys 4 and Lys 9 residues in the tail of histone H3 (Kondo and Raff 2004).

Recent findings from an independent group using a very different approach validated the model of epigenetic modulation of oligodendrocyte differentiation modulated by histone deacetylation (Lyssiotis et al. 2007). Using a line of immortalized OPC-expressing GFP from the Sox2 promoter to screen for compounds that were able to revert progenitors to multipotential neural stem cells, the authors identified several HDAC inhibitors. The compounds were able to reactivate the stem cell marker gene Sox2; however, complete reversion was rendered possible only by culturing the cells in the presence of FGF2 (Lyssiotis et al. 2007). Therefore, reactivation of Sox2 by increased histone acetylation is a prerequisite for fate reversion from a lineage-restricted OPC to a neural stem cell. However, Sox2 by itself is insufficient for the reversion, and it requires additional signals, such as FGF to favor the multipotential state (Lyssiotis et al. 2007). Together, these data suggest a model of OPC plasticity that is mediated by histone modifications and is affected by upstream signaling events.

Model 3 Differentiation Consequent to HDAC-Mediated Repression of Transcriptional Inhibitors of Differentiation

The concept of oligodendrocyte lineage progression as sequential steps of repression of inhibitory events was suggested by the observation that oligodendrogliogenesis, at least in vitro, proceeds by default. Oligodendrocytes differentiate from progenitor cells when mitogens are withdrawn from the culture medium (Noble and Murray 1984; Temple and Raff 1985; Gard and Pfeiffer 1993; Bansal and Pfeiffer 1997). This suggested that the oligodendrocytic differentiation process results from the removal of negative signals provided by mitogens. Because growth factors affect the proliferative state of the cell, it was initially proposed that differentiation could be initiated by cell cycle exit (Casaccia-Bonnefil et al. 1997; Durand et al. 1998). In this respect, multiple studies focused on the identification of the molecular regulators of the cell cycle that are responsible for the regulation of the G1 phase of the cell cycle (Durand et al. 1998; Tikoo et al. 1998; Casaccia-Bonnefil et al. 1999; Ghiani et al. 1999; Durand and Raff 2000; Tokumoto et al. 2002). The importance of cell-cycle inhibitors in oligodendrocyte differentiation was further suggested by reports of alternative biological functions for these molecules. P27Kip, for instance, was identified as part of a transcriptional complex activating the MBP promoter (Miskimins et al. 2002), as well as part of a complex with specific RNA-binding proteins like Qki (Larocque et al. 2005). Despite these exciting findings, overexpression of cell-cycle inhibitors per se was not sufficient to induce differentiation (Tikoo et al. 1998; Tang et al. 1999) and suggested that additional events must be responsible for the differentiation of progenitors into mature oligodendrocytes. Our studies using inhibitors of HDAC activity in cultured cells (Marin-Husstege et al. 2002) and in vivo (Shen et al. 2005) provided some clues regarding the additional events responsible for this transition. We proposed that after cell-cycle withdrawal, progenitors might require HDAC activity to down-regulate inhibitory molecules that halt the differentiation into myelinating oligodendrocytes. This model was in agreement with previous studies on the role of transcriptional inhibitors of oligodendrocyte differentiation (Kondo and Raff 2000b, a; Wang et al., 2001b) and with gene expression profiling studies reporting a progressive decrease of inhibitors concomitant with differentiation (Kuhlbrodt et al. 1998; Sohn et al. 2006; Dugas et al. 2007). The concept of derepression of inhibitors as potential explanation for default oligodendroglial differentiation was further supported by the evidence that inhibitors of the Id and Hes family can inhibit differentiation of oligodendroglial progenitors in multiple ways, including recruitment of HDAC (Liu et al. 2006), sequestration of activators (Samanta and Kessler 2004; Liu et al. 2006), and transcriptional inhibition of critical regulators (Guillemot 1995; Sakamoto et al. 2003; Kageyama et al. 2005; Liu et al. 2006).

The recent identification of the transcription factor Ying Yang-1 (YY-1) as a recruiter of HDAC1 on the promoter of transcriptional inhibitors of OPC differentiation and the dramatic

hypomyelinating phenotype in mice with conditional ablation of YY1 in the oligodendroglial lineage provided support to the importance of chromatin modifications for the initiation of oligodendrocyte differentiation in progenitors after they have exited the cell cycle (He et al. 2007). The model of HDAC-dependent repression of differentiation inhibitors was reinforced by the fact that this is a highly conserved event among species. Indeed, it was shown that zebrafish *hdac1* mutants are unable to express oligodendroglial markers, such as plp, sox10, and olig2, while they continue to express sox2 and pax6 (Cunliffe and Casaccia-Bonnefil 2006).

Therefore, together these studies support a model of oligodendrocyte differentiation characterized by the progressive epigenetic repression of inhibitory molecules that is initially dependent on histone deacetylation.

Cytoplasmic HDAC and Non-Histone Substrates: A Role in Morphological Differentiation of Oligodendrocyte Development

The mammalian sirtuin (SIRT) family of proteins, which are related to the silent information regulator 2 (Sir2) of yeast, belong to a special class of HDAC that are regulated by NAD/NADH levels (Tanny et al. 1999; Imai et al. 2000). SIRT have been reported to modulate the morphological changes associated with oligodendrocyte differentiation and myelin assembly. Nuclear SIRT1 is expressed in cultured embryonic neurospheres and in nestin cells at subventricular zone (SVZ) of adult mouse brains. Administration of SIRT1 inhibitors, nicotinamide or sirtinol, potently blocked the differentiation of neurospheres into neurons or oligodendrocytes (Horio et al. 2003).

SIRT2 is cytoplasmically localized, and its expression in the central nervous system (CNS) is oligodendrocyte-specific (Li et al. 2007; Southwood et al. 2007). Indeed, SIRT2 was reported to be a myelin component few years ago, when it was listed as one of the multiple proteins identified in proteomic screens of myelin components (Taylor et al. 2004; Vanrobaeys et al. 2005). In the developing CNS, the appearance and expression pattern of SIRT2 in the cerebrum, cerebellum, and spinal cord have been correlated with that of the myelin protein, CNPase (Li et al. 2007). However, the levels of SIRT2 are not affected by genetic deletion of cnp in mice. At cellular levels, both SIRT2 and CNPase are coexpressed in the processes but not in the cell body of oligodendrocytes, suggesting that SIRT2 may be involved in the morphological changes occurring during oligodendrocyte differentiation and myelin sheath formation (Li et al. 2007). Ultrastructural studies have further supported the localization of SIRT2 to the non-compact outer and terminal loops of myelin sheath (Li et al. 2007; Southwood et al. 2007), suggesting that its function could be important for process outgrowth and membrane expansion of oligodendrocytes.

Recent reports have uncovered an intriguing association between SIRT2 levels and the myelin protein PLP (Werner et al. 2007). It was discovered that the incorporation of SIRT2 into the myelin sheath is myelin protein PLP/DM20-dependent; as in the plp null mice, SIRT2 expression is completely lost (Werner et al. 2007).

An Integrated View of Oligodendrocyte Development

Based on the review of the current literature, we propose a model of OPC differentiation that requires global repressive events that are initiated by histone deacetylation and possibly associated with additional modifications of the chromatin structure. This is in agreement with early ultrastructural studies by electron microscopy on the developing corpus callosum of neonatal rats, reporting the progressive increase of chromatin compaction in the nuclei of OPC during their differentiation into mature oligodendrocytes (Kozik 1976). We propose that a

critical functional role for massive chromatin compaction is the downregulation of molecules that preclude differentiation, including transcriptional inhibitors of myelin genes (Liu et al. 2006; Marin-Husstege et al. 2006), as well as cytoskeletal depolymerizing molecules (Liu et al. 2003; Liu et al. 2005). We further propose that the chromatin compaction initiated by histone deactylation is a critical event to prevent other lineage choice of progenitor cells and possibly prevent precocious myelin gene expression. The analysis of HDAC-mediated histone deacetylation in affecting the timing of oligodendrocyte differentiation and myelination in the developing brain revealed the specific requirement for HDAC activity during a specific temporal window of postnatal development, corresponding to the activation of a transcriptional program of differentiation after progenitors have exited the cell cycle (Marin-Husstege et al. 2002; Shen et al. 2005; He et al. 2007). At later developmental stages, however, histone deacetylation subsides and is replaced by repressive histone methylation and the establishment of a compact chromatin structure, characteristic of the differentiated oligodendrocyte phenotype (Shen et al. 2005). Together these data suggest that HDAC-mediated histone deacetylation is required for the initial stages of OPC differentiation, when the intracellular environment of the cell is “inhibitory.” However, it is dispensable later during the maturation process when the majority of the “obstacles” have been eliminated. For this reason, the role of HDAC is confined to a narrow temporal window, defined by the interface between cell-cycle exit and the beginning of differentiation. This window is characterized by the progressive decline of differentiation inhibitors and is likely to be overcome by signals that tilt the equilibrium in favor of differentiation.

Histone Modifications in the Aging Corpus Callosum and Perspective on the Potential Role of Chromatin Modifications in Neurological Diseases Affecting Myelinating Oligodendrocytes

Since histone deacetylation and methylation are critical epigenetic modulators of gene expression during oligodendrocyte differentiation and myelin formation, they serve the purpose of establishing a “molecular memory,” which is stored in the nuclei of oligodendroglial cells. This memory is responsible for the downregulation and stable repression of inhibitory molecules in differentiated oligodendrocytes (Marin-Husstege et al. 2006). In an attempt to understand the potential mechanisms underlying age-dependent decline of repair function, Shen et al. (2007) reported the progressive loss of this “epigenetic memory” in oligodendrocytes during normal aging. Decreased histone deacetylation and repressive methylation of histone H3 tails were detected in older mice. The direct result of these epigenetic changes was the increased expression of inhibitory molecules, including Hes5, Ids, and Sox2 (Shen et al. 2007). This partially explains why the responsiveness of oligodendrocytes to extracellular factors is decreased with aging and further suggests that chromatin modifications and changes in the “epigenetic memory” of oligodendrocytes may have profound effects on therapeutic outcomes.

Although not formally proven, these findings also suggest that similar epigenetic changes might affect the ability of progenitors in older brains to efficiently repair demyelinating lesions. Previous studies had suggested that remyelination failure was consequent to increased levels of inhibitory extracellular signals (John et al. 2002) or insufficient levels of oligodendrogliogenic signals (Mastronardi et al. 2003). However, it was shown that altering the levels of a single extracellular factor or signaling molecule was not sufficient per se to promote successful remyelination (Fancy et al. 2004; Stidworthy et al. 2004). Taken together, these results support a model of remyelination as a complex interplay between intrinsic changes and extracellular signaling cues.

An additional line of experimental evidence suggested the importance of aberrant modifications of nucleosomal histones in oligodendrocytes as part of the pathogenetic process leading to demyelinating disorders. Increased histone citrullination on arginine residues was reported to be increased in the normal-appearing white matter of MS patients and in animal models of demyelination (Mastronardi et al. 2006). Citrullination of arginine residues on histone tails is catalyzed by peptidylarginine deiminase 4 (PAD4). Under normal conditions, PAD4 is cytosolically localized. However, under pathological conditions, such as in the presence of abnormally increased level of tumor necrosis factor α (TNFα), PAD4 is translocated to the nucleus, and its increased nuclear expression and activity catalyzes the citrullination of nucleosomal histones (Mastronardi et al. 2006). Importantly, these molecular changes occur before the onset of symptoms in animal models of demyelination (Mastronardi et al. 2006), indicating that TNFα-induced PAD4 nuclear localization and subsequent histone citrullination may be part of the etiopathogenesis of the disease.

The potential role of histone modifications in demyelinating disorders has also led to therapeutic attempts with histone-modifying drugs, but the results, at least in the EAE models, have led to controversial results. Administration of the HDAC inhibitor TSA to C57BL/6 mice with active immunization of $MOG_{35–55}$-induced EAE had favorable effects on spinal cord inflammation, demyelination volume, and axonal loss, possibly because of increased expression levels of anti-oxidants (i.e., glutathione peroxidase), glutamate transporters (i.e., excitatory amino acid transporter 2, EAAT2), and neuroprotective factors (i.e., insulin-like growth factor 2; Camelo et al. 2005). However, also the administration of curcumin, a selective HAT (CBP/p300) inhibitor that decreases the total histone acetylation levels, had positive effects on EAE. When curcumin was administered to SJL/J mice with EAE induced by adoptive transfer of MBP-immunized immune cells, it inhibited the induction phase of the disease, possibly, by blocking IL-12 signaling pathway in T lymphocytes (Natarajan and Bright 2002).

Together, these results reveal the need for the development of more specific therapies aimed at targeting epigenetic modulators only in specific cell populations.

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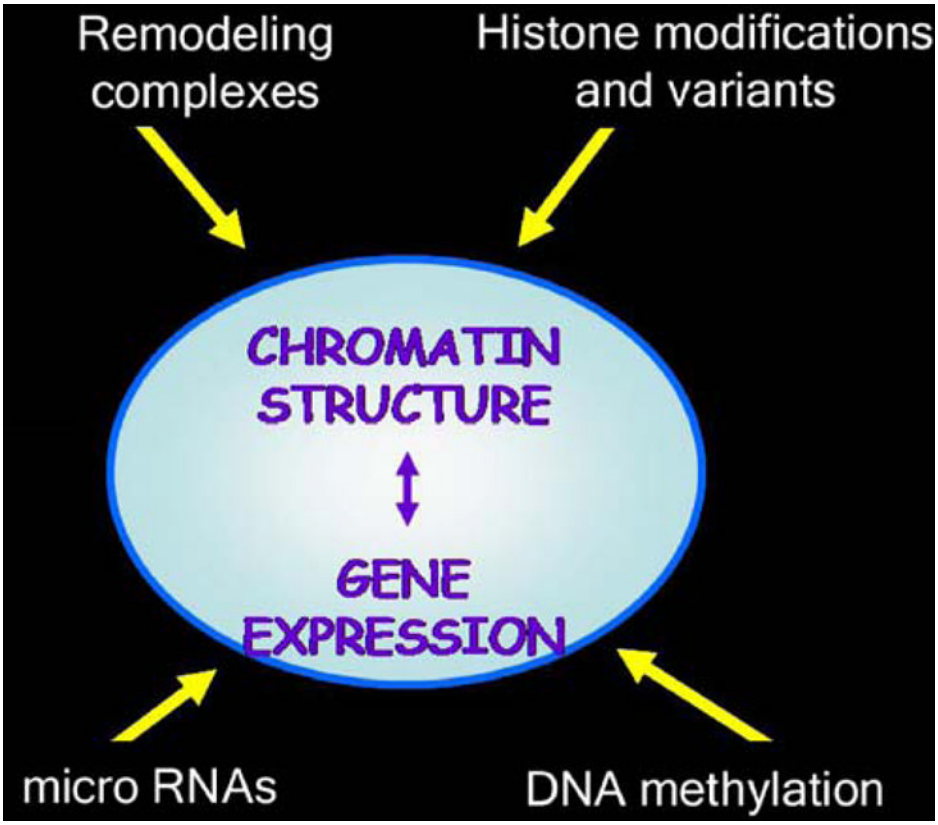

Figure 1.
Epigenetic modulation of gene expression. The four main areas of investigation in the field of epigenetics are presented in this diagram

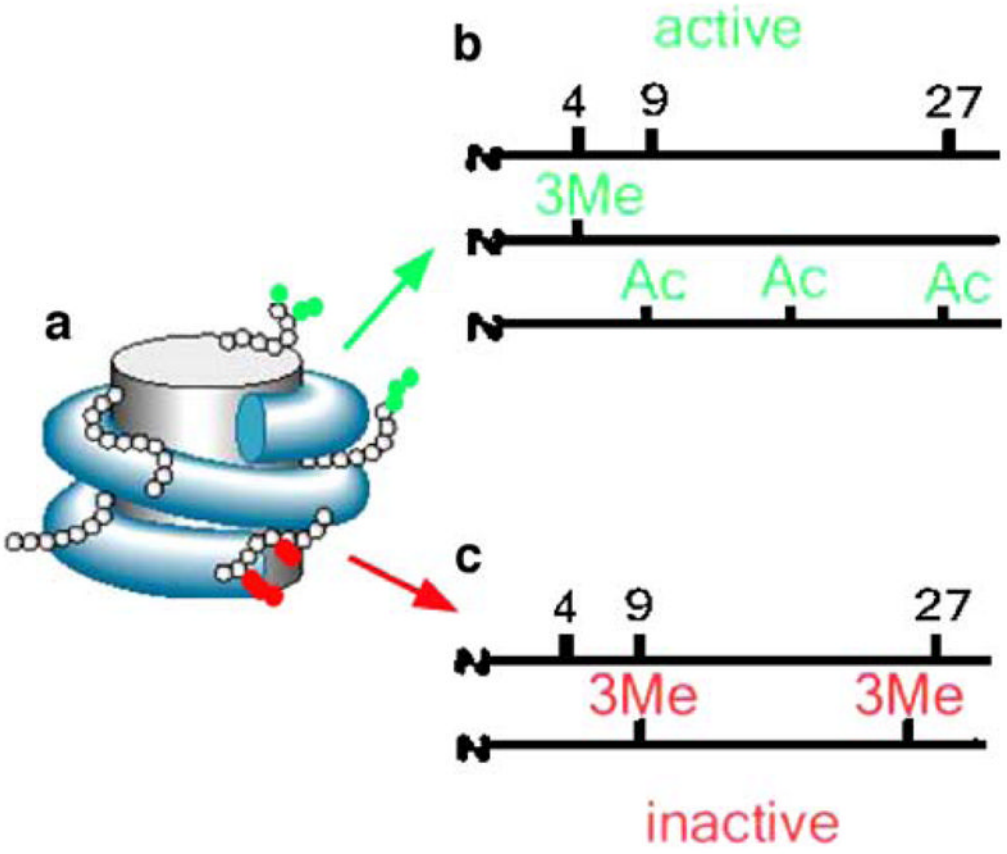

Figure 2.

The histone code. **a** Schematic illustration of the nucleosome. The histones are represented by a gray cylinder and the nucleosomal histone tails are shown as *small beads* irradiating out of the cylinder. The post-translational modifications of the lysine residues in the histone tails are shown by red and green *circles*. **b** Post-translational modifications of lysine residues in the tail of nucleosomal histone H3, associated with active transcription (*green*). Note the inclusion of trimethyl lysine K4 and the acetylation of several residues. **c** Repressive modifications of lysine residues in position 9 and 27