HHS Public Access

Author manuscript

Cell Signal. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Cell Signal. 2015 October ; 27(10): 2131–2136. doi:10.1016/j.cellsig.2015.06.003.

Epigenetic signaling in schizophrenia

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Abstract

Histone modifications and DNA methylation represent central dynamic and reversible processes that regulate gene expression and contribute to cellular phenotypes. These epigenetic marks have been shown to play fundamental roles in a diverse set of signaling and behavioral outcomes. Psychiatric disorders such as schizophrenia and depression are complex and heterogeneous diseases with multiple and independent factors that may contribute to their pathophysiology, making challenging to find a link between specific elements and the underlying mechanisms responsible for the disorder and its treatment. Growing evidences suggest that epigenetic modifications in certain brain regions and neural circuits represent a key mechanism through which environmental factors interact with individual's genetic constitution to affect risk of psychiatric conditions throughout life. This review focuses on recent advances that directly implicate epigenetic modifications in schizophrenia and antipsychotic drug action.

Keywords

Schizophrenia; epigenetics; antipsychotics; histone deacetylases (HDACs); histones

1. Introduction

Schizophrenia is a chronic, debilitating mental disorder that affects about 1% of the world's population [1–5]. It is estimated to be the seventh most costly medical illness to society in

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Conflicts of interest statement

None

terms of cost of care and loss of productivity, with rates of prevalence that are similar throughout diverse cultures and geographic areas. Diagnostic features of schizophrenia include hallucinations and delusions. In addition to these psychotic or “positive” symptoms, various deficits or negative symptoms occur, including inability to pay attention, the loss of sense of pleasure, and social withdrawal. Cognitive deficits, such as abnormalities in memory, perception, motor functioning, and language processing, are also essential features in schizophrenia that substantially account for limitations in functional outcomes associated with this disease such as work, independent living and social relationships [6–9].

The available symptomatic treatment is only partially successful, and therefore the development of rational therapeutics, based on an understanding of the etiology and pathogenesis of schizophrenia, is imperative [10–14]. Advances in the understanding of schizophrenia have been limited by a number of factors, including the heterogeneity in its phenotype, and the lack of clear pathological lesions like those that have provided reference points in the study of neurological diseases such as Alzheimer’s and Parkinson’s. Both typical, such as chlorpromazine and haloperidol, and atypical, such as clozapine and olanzapine, were serendipitously discovered as secondary effects of drugs tested for different therapeutic targets. For instance, the first antipsychotic drug chlorpromazine was discovered in 1952 as an antihistaminic which appeared to actually decrease psychosis [15]. Haloperidol was designed as a pain reliever [16], and clozapine was described in 1958 as “tricyclic antidepressant but with *neuroleptic* properties” [17,18]. Following these early discoveries, both the mechanisms of actions of antipsychotic drugs and the molecular basis of schizophrenia have been the focus of much attention in basic and translational neuroscience research. As yet, the pharmacological profiles of all the antipsychotic medications currently prescribed have in common a high affinity for monoaminergic neurotransmitter receptors, including dopamine D_2, dopamine D_1, serotonin 5-HT_{2A}, serotonin 5-HT_{2C}, serotonin 5-HT_{1A}, adrenergic $\alpha_{1A/1B}$, adrenergic $\alpha_{2A/2B/2C}$, and muscarinic $M_{1/2/3/4/5}$ [19]. Furthermore, whereas in some patients with schizophrenia both typical and atypical antipsychotic drugs produce either complete or partial remission of “positive” psychotic symptoms, these medications currently available are ineffective against cognitive deficits, and consequently treated patients have either small improvements or even deterioration in several cognitive domains [20–24]. During recent years, as it has become clearer that epigenetic molecular mechanisms, specifically DNA methylation and chromatin modification, generate and maintain behavioral changes in animal models, functional and translational approaches are more needed to characterize the basic signaling and neuronal circuit processes whereby drugs that directly or indirectly affect nucleosome structure and function, and its implications in CNS function [25–32]. Here we review recent observations that implicate epigenetic signaling mechanisms as a novel target to treat schizophrenia and other psychiatric disorders.

2. Schizophrenia: Genes and Environment

Schizophrenia has traditionally been viewed as a genetic disorder with heritable rates estimated at 73–90%. This hypothesis was strengthened by genome-wide search studies in the mid-2000s that showed schizophrenia-associated genetic alterations including large recurrent microdeletions [33], copy number variations [34], and rare chromosomal

microdeletions and duplications [35] especially in neurodevelopmental pathways [36]. Results of these studies also suggest that the risk of schizophrenia is associated with polygenic pathways involving thousands of common alleles each of which with a very small effect [37]. More recent large genome-wide association study (GWAS) arrays have narrowed down the list of genetic loci associated with schizophrenia. Notably, several of these genes include dopamine D_2 (*DRD2*) and serotonin 5-HT_{2A} (*Htr2a*) receptors, as well as genes involved in glutamatergic neurotransmission [38], voltage-gated ion channel, and the signaling complex formed by activity-regulated cytoskeleton-associated scaffold protein (ARC) at the postsynaptic density [39]. These findings might allow the classification of subjects with schizophrenia on the basis the pathways involved in their etiology.

Nevertheless, although as discussed above, alterations in the genetic code are assumed to play a fundamental role in schizophrenia-risk, these are not the only factors responsible for the disease. As an example, monozygotic twins, who share almost 100% of their genetic material, have a 50% concordance rate for schizophrenia relative to the 15% concordance for dizygotic twins [40–42]. Such results further support a significant contribution of genetic factors to this complex disease. At the same time, however, they also attribute an important role of environmental factors in the development of schizophrenia-related neuropsychological deficits. Epidemiological studies have indicated that maternal exposure during pregnancy to infectious agents, including virus (influenza [43–45] and rubella [46]), bacteria (bronchopneumonia) [47], and protozoa (*Toxoplasma gondii*) [48] significantly increase the risk of schizophrenia in the adult offspring. As an example, the Spanish influenza pandemic of 1918–1919, whose coding sequence has recently been used to characterize the extraordinary virulence of the reconstructed 1918 influenza pandemic virus [49], was contracted by more than 500 million individuals worldwide. In 1919, Karl Menninger published a classic article describing for the first time an association of influenza and psychoses in patients [44]. These findings have been validated in numerous population groups, and more recent nested case-control studies showed that the risk of schizophrenia is increased 7-fold for maternal influenza infection during the first trimester of pregnancy [43].

Additionally, maternal adverse life events that occurred during pregnancy, such as war [50,51], famine [52], and death or illness in a first-degree relative [53], have been associated with an elevated risk of schizophrenia in the adult offspring. Based on these epidemiological studies, numerous research groups have developed rodent models of influenza viral infection [54–60] and maternal variable and severe variable and unpredictable stress [61–64] that induce schizophrenia-related biochemical and behavioral changes in the newborns. Remarkably, these animal models of prenatal insults during pregnancy support a uniform conclusion that changes in the adult offspring are related to alterations in the maternal immune system, with immune components particularly influential such as TNF-α, IL-1β, IL-6 and IL-8 [65–70]. Interesting is also the finding that the incidence of schizophrenia is strongly increased in people born and raised in cities as compared to rural areas [71]. Additional basic experimental and clinical studies are needed to interrogate the molecular mechanisms whereby genes and environment interact to influence schizophrenia risk.

3. Basic concepts in epigenetics

The first sequencing and analysis of the human genome in 2001 is considered as a fundamental landmark in biological research [72,73]. However, all the diploid somatic cells in eukaryotic multicellular organisms share a virtually identical genome, whereas their function is completely unique within individual cell populations. The mechanism that allows a particular cell type to acquire its function is related to what parts of the whole genome are exposed to the transcriptional machinery and hence define cell type specific identity. The term epigenetics (the prefix *epi-* derived from Greek for “over” or “above”) was coined by Conrad Waddington in the 1940s and referred to the processes by which a particular genome is able to construct and maintain a proteome whose overall biological properties form the underlying basis of life [74]. Over the past decade, the term epigenetics has been adopted to define mechanisms that control chromatin remodeling and the accessibility of genes to transcriptional machinery. The total length of DNA in a single somatic cells exists in the nucleus in complex with histone proteins that have been described as a highly compressed structure referred to as chromatin.

The primary structural unit of chromatin is the nucleosome, which comprises a standard length of DNA (147 base pairs) wrapped around a histone octamer make up of four pairs of basic histone proteins (H2A, H2B, H3 and H4). The structure and organization of chromatin depends on covalent modifications known as epigenetic factors that include DNA methylation and histone modifications that occur principally on their N-tails. In vertebrates, methylation of CpG dinucleotides within proximal gene promoters is frequently linked to transcriptional repression (Fig. 1) [75]. Some of the histone modifications are commonly associated with transcriptional activation, such as acetylation, whereas other types, such as methylation, correlate with gene activation and repression depending upon the specific position of the histone tail residue (Fig. 2) (this topic has recently been reviewed elsewhere [25–32]). Here we will review and discuss recent findings related to the role of epigenetic mechanisms in schizophrenia and its treatment.

4. Epigenetic targets in schizophrenia

4.1. DNA methylation

Multiple lines of evidence implicate disturbances in cortical pyramidal neurons [76,77] and cortical parvalbumin (PV)-positive GABAergic interneurons [78,79] as potentially involved in core psychotic and cognitive symptoms in schizophrenia patients. Previous reports have shown down-regulation of expression of the 67 kDa isoform of glutamic acid decarboxylase (GAD67) in postmortem frontal cortex of schizophrenic subjects [80]. Using a reproducible approach to selectively collect DNA from neurons expressing *GAD1*, the gene encoding *GAD67*, it has been demonstrated that the methylation frequency at CpG dinucleotides located at the proximal *GAD1* promoter shows a significant deficit in repressive DNA methylation in schizophrenic subjects [81]. Considering that chronic treatment with clozapine and sulpiride, but not haloperidol, increases cortical and striatal demethylation of the hypermethylated *GAD1* promoter in mice [82], it will be interesting to find out in future studies whether these changes in DNA methylation at *GAD1*-positive nucleosomes of schizophrenic subjects are an epigenetic mark of the disorder or a consequence of

antipsychotic treatment. A similar question arises from the hypermethylation observed at the promoter region of the *Reelin* (*RELN*) gene in postmortem brain samples of schizophrenic subjects. Previous studies had suggested down-regulation of *RELN* expression, gene involved in neuronal migration and differentiation, in postmortem brains of schizophrenic subjects [83]. Although this hypermethylation of the *RELN* promoter suggested in the brain of schizophrenic subjects has not been confirmed subsequent investigations [84], more recent findings demonstrate hypermethylation of the CpG island flanking a CRE and SP1 binding site at the *RELN* promoter [85]. It has also been demonstrated that repeated injection of L-methionine as a mouse schizophrenia model induces hypermethylation of the promoter regions of *GAD1* and *RELN* in mouse frontal cortex [86]. Because this effect was reversed by the structurally unrelated HDAC inhibitors valproate and MS-275, it was suggested that HDAC inhibitors facilitate DNA demethylation [86]. Similarly, chronic antipsychotic treatment dose-dependently demethylate the *RELN* promoter in mouse cortex and striatum [82,87]. These events induced by chronic antipsychotic treatment that epigenetically normalizes the down-regulation of GABAergic genes detected in postmortem brain samples of schizophrenic subjects may be one of the mechanisms underlying their therapeutic effects.

Until recently, the dopamine hypothesis of schizophrenia has been mostly based on the binding target of antipsychotic drugs such as chlorpromazine and haloperidol. This hypothesis has been recently strengthened with convincing genome-wide search studies in schizophrenic subjects and controls (see above). Thus, as discussed above, it has been shown that associations at the *DRD2* gene may lead to pathophysiological alterations in schizophrenia patients [38]. Studies in peripheral blood lymphocytes from schizophrenic and control pairs, however, found absence of alterations in DNA methylation at the CpG island located within the 5′-regulatory region of the *DRD2* gene [88]. This does not support site-specific cytosine methylation of *DRD2* as playing a role in the psychopathology of schizophrenia.

Adverse environmental or physical experiences during early life negatively influence appropriate behavioral responses and cause maladaptive behaviors [89–91]. Interestingly, when comparing maternal care behavior in rat models, it has been reported that offspring of mothers that showed high levels of “pup licking and grooming” and “arched-back nursing” present differences in DNA methylation at the promoter region of the *glucocorticoid receptor* (*GR*) gene [92]. This epigenetic alteration induced by maternal behavior was associated with increased acetylation of histone H3 at lysine 9 (H3K9ac)—marker of transcriptional activation at the *GR* promoter [92]. These findings in rodent models related with the pattern of DNA methylation at the GR gene are further supported by epigenetic differences at the *GR* promoter (*NR3C1*) between postmortem hippocampus obtained from suicide victims with a history of childhood abuse and those from either suicide victims with no childhood abuse or controls. Stress has also been shown to affect the epigenetic status of the *glial cell-derived neurotrophic factor* (*Gdnf*) gene in ventral striatum—adaptation that modulates susceptibility to chronic stress [93]. Thus exposure to a paradigm of chronic ultra-mind stress induces hypermethylation of *Gdnf* promoter in two genetically distinct mouse strains [93]. This fundamental role of postnatal environment in behavioral patterns in

the adulthood is further supported by studies suggesting that mild isolation stress during adolescence affects function of dopaminergic neurons via alterations in DNA methylation of the *tyrosine hydroxylase* gene only when combined with mutant mouse models of genetic risks associated with schizophrenia, such as transgenic mice with a putative dominant-negative *DISC1* (*disrupted in schizophrenia 1*) [94]. Adverse life events have also been found to dynamically control DNA methylation in postmitotic neurons to generate a persistent increase in arginine vasopressin (*AVP*) expression [95]. These findings further support the hypothesis that interactions between gene and environment are crucially important in schizophrenia-related phenotypes and in clinical psychiatry [94]. Because methylation of cytosines at CpG sites might play a fundamental role normal and pathophysiological behavior it will be also influential to investigate the potential role of the recently discovered 5-hydroxymethylcytosine (5-hmC) in psychiatric conditions (Fig. 1). Thus, the 5-hmC form has been proposed to be the first step in the mechanism through which DNA methylation is reversed [96].

4.2. Histone modifications

Electroconvulsive therapy involves the induction of a seizure for therapeutic purposes by the administration of a variable frequency electrical stimulus to the brain via electrodes applied to the scalp [97]. Although repeated administration of electroconvulsive seizures is one of the most conventional and effective treatments of psychiatric disorders such as schizophrenia and depression, the molecular mechanisms underlying its clinical effect are incompletely understood. By assaying post-translational modifications of histones at the promoter region of several genes in rat hippocampus, it was demonstrated that electroconvulsive seizures induce histone modifications that correlate with transcriptional activation, such as acetylation of histone H4 and acetylation of histone H3 [98]. Alterations in expression of some of these genes, including *c-fos*, *BDNF* and *CREB* were proposed to play a role in the therapeutic-related effects induced after electroconvulsive seizures [98].

Using a native chromatin immunoprecipitation assay in postmortem human brain samples, Akbarian and his group studied the effect of chronic treatment with dopamine, serotonin and NMDA ligands such as quinpirole, raclopride, haloperidol, risperidone and MK801 on phosphorylation of histone H3 at serine 10 and acetylation of histone H3 at lysine 14 [99]. They found that dopamine D2-like receptor antagonists induced H3 phospho-acetylation, an effect that was reversed by MK801 [99]. Additionally, it was demonstrated that a dual modification of H3pS10-acK14 at genomic sites with active transcription [99], suggesting that histone modifications in striatal neurons are regulated by both dopaminergic and glutamatergic inputs.

Group II metabotropic glutamate receptors (mGlu2 and mGlu3) have been involved in the pathophysiology and psychiatric disorders such as schizophrenia and depression [100–103]. It is of particular interest that both mGlu2/3 receptor agonists and antagonists induce antidepressant-like effects in rodents. For example, a single treatment with the mGlu2/3 antagonist LY341495 produces a rapid and long-lasting reversal of depressive-like behavior caused by chronic and unpredictable stress in rats [104]. Moreover, the mGlu2/3 agonists such as LY349268 and LY354740 exhibit antidepressant-like activity in rodent models such

as forced-swim test and tail suspension [105]. Although previous findings in postmortem human brain studies suggest that density of mGlu2/3 receptors is unaffected in frontal cortex of subjects with major depression [106], these results in rodent models suggest that mGlu2/3 receptor ligands may provide new therapeutic opportunities for mood disorders. Clearly, however, further investigation is needed to decipher the precise signaling mechanisms and neuronal circuits responsible for the antidepressant-like effects of both mGlu2/3 receptor agonists and antagonists. In addition, it has been demonstrated that L-acetylcarnitine, a well-tolerated drug, induces rapid antidepressant effects via the epigenetic regulation of expression of the mGlu2 gene (*Grm2*) in prefrontal cortex and hippocampus of spontaneously depressed Flinders Sensitive Line (FSL) rats [107]. Similar antidepressant-like effects of L-acetylcarnitine have been reported using depression-like behavior caused by unpredictable chronic stress in male rats [108]. Although these interesting preclinical findings suggest that L-acetylcarnitine may serve as a novel approach to treat depressive disorders, whether this drug elicits antidepressant effects in humans remains to be investigated.

The importance of epigenetic differences induced by environmental factors during the lifetime has been recently confirmed with studies that examined global and locus-specific DNA methylation and histone acetylation in a cohort of monozygotic twins [109]. These findings suggest that both external and/or internal factors can have an impact in the phenotype by altering the pattern of epigenetic modifications [109]. Future studies should address specific mechanisms of gene-environment behavioral adaptations.

4.3. HDAC inhibitors

The histones are covalently modified at the N-terminal tail by acetylation, methylation, phosphorylation, ubiquitination and sumoylation, each of which encodes profound influences on chromatin structure that are either permissive or repressive for gene transcription. In histone acetylation, the inclusion of a negatively charged acetyl group by histone acetyl transferases (HATs) diminishes the electrostatic attractive force between histone proteins and DNA, which leads to chromatin expansion and facilitation of gene transcription. Histone deacetylases (HDACs) remove acetyl groups from lysine/arginine residues in the N-terminal tails, thus reversing the effects of HATs [110–113]. This event shifts the balance toward a compact chromatin that silences gene expression (Fig. 2). The HDACs are phylogenetically divided into four main classes, including the zinc-dependent class I, II and IV HDACs, and the NAD-dependent class III HDACs, with class I and class II as those receiving the most attention in recent years. Class I HDACs (HDACs 1, 2, 3, and 8) are mostly localized within the nucleus, whereas class II HDACs (HDACs 4, 5, 6, 7, 9, and 10) are regulated by shuttling between nucleus and cytoplasm. Unlike HATs, HDACs have a great structural diversity, which makes them attractive targets for drug discovery and therapeutic intervention. This is further supported by the development of HDAC inhibitors that are clinically effective in several cancers [114]. Although it remains to be demonstrated in the clinic, agents that target HDACs have shown potential in rodent models of CNS disorders.

As reviewed above, prenatal insults such as maternal viral infection and maternal severe stress have long-term consequences on behavior of the adult. Based on the comparison of the effect of maternal care on hippocampal transcriptome in adult mice, it was identified that early-life events induce changes in gene expression and anxiety-like behaviors that are reversible by the class I and II HDAC inhibitor TSA [115]. In this context, studies based on findings obtained in mice with either over-expression or deletion (knockout) of HDAC2 suggest that HDAC2 is a particularly attractive target for the treatment of cognitive deficits in patients with psychiatric disorders, including schizophrenia [116]. Thus, chromatin immunoprecipitation assays in mouse hippocampus demonstrates that HDAC2, and not the closely related HDAC1, binds to the promoter region of genes involved synaptic remodeling and memory formation [116]. Transgenic mice that over-express HDAC2, but not HDAC1, in neurons present decreased dendritic spine density and memory formation [116]. Conversely, HDAC2 knockout mice showed increased synapse number and memory function [116]. This phenotype observed in HDAC2 knockout mice paralleled the effects induced by chronic treatment with the class I and II inhibitor SAHA [116]. Intriguingly, although these findings strongly suggest that inhibition of HDAC2 may represent a new therapeutic target to improve cognition in schizophrenia patients, it has recently been shown that chronic treatment with atypical antipsychotic drugs induces a selective up-regulation of HDAC2 expression in mouse and human frontal cortex [117,118]. Because virally mediated over-expression of HDAC2, and not HDAC1 or HDAC4, in mouse frontal cortex increased the predisposition to psychosis-like effects of psychedelic drugs such as LSD and MK801, this study proposed that up-regulation of *HDAC2* promoter activity after chronic atypical antipsychotic exposure represents a compensatory mechanism that restricts their therapeutic effects [117]. Although the signaling mechanism responsible for this effect on HDAC2 expression remains unknown, these findings may have implications for the molecular basis of the limited response to treatment with atypical antipsychotics. Because the administration of a non-specific HDAC inhibitor valproate [119] in conjunction with antipsychotic medication has been shown to accelerate the onset of the antipsychotic effects in patients with schizophrenia [120–123], together, these results emphasize the potential significance of HDAC2 as a new target to improve schizophrenia treatment.

5. Future directions

Epigenetic investigations promise to improve our knowledge of the mechanisms by which environmental factors throughout life are strong determinants of health decades after. Animal models such as maternal infection and maternal stress have shown epigenetic alterations at the promoter regions of genes involved in synaptic plasticity, cognition and memory. However, alterations in chromatin structure are likely to occur in many more regions of the genome, and it is important to carry out genome-wide epigenetic studies to investigate this in animal models. Similarly, ChIP-Seq assays in postmortem human brain samples of schizophrenic subjects and controls will provide a global perspective of epigenetic dysregulation, which is currently largely unknown. This may lead to the development the pharmacological methods and tools for personalized medicine in schizophrenia patients. Such therapeutic approach is currently ongoing in patients with cancer [124], and the recent establishment of global epigenomic maps for histone

modification patterns, DNA accessibility, DNA methylation and RNA expression in primary tissues and cell types of all major lineages in the human cell body will be valuable in the study of neuropsychiatric disorders [125].

Although HDACs are known for modulating chromatin structure in brain regions involved in brain processes that are affected in patients with schizophrenia, the lack of specific inhibitors limits our understanding of the basic mechanisms responsible for these effects. Tools that offer the ability to inhibit specific HDACs or even individual enzymes in strictly defined neuronal populations would not only improve our basic knowledge of behavioral manipulations, but might also provide new therapeutic avenues for disorders such as schizophrenia and depression. Finally, we also need to keep in mind that epigenetic modifications do not occur independently, but rather DNA methylation and histone modifications appear to be linked to each other. Complete understanding of these epigenetic modifications and their crosstalk will lead to the development better therapeutic strategies against psychotic and cognitive impairments in schizophrenia patients.

Acknowledgments

Preparation of this review was supported by grants from the National Institute of Mental Health (R01MH084894). Daisuke Ibi was recipient of postdoctoral fellowships from the Japan Society for the Promotion of Science (Young Scientists JSPS 23-3454) and from the Uehara Memorial Foundation.

Abbreviations

ARC	activity-regulated cytoskeleton-associated scaffold protein
AVP	arginine vasopressin
ChIP	chromatin immunoprecipitation
DISC1	disrupted in schizophrenia 1
FSL	flinders sensitive line rats
GABA	γ-aminobutyric acid
GAD67	67 kDa isoform of glutamic acid decarboxylase
GDNF	glial cell-derived neurotrophic factor
GR	glucocorticoid receptor
GWAS	genome-wide association study
HAT	histone acetyl transferases
HDAC	Histone deacetylases
LY341495	mGlu2/3 receptor antagonist
LY354740	mGlu2/3 receptor agonist
LY379268	mGlu2/3 receptor agonist
MK801 (dizocilpine)	non-competitive NMDA receptor antagonist

NMDA	N-methyl-D-aspartate
PV	parvalbumin
TSA	trichostatin A (HDAC inhibitor)

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Highlights

- Epigenetic marks, such as histone modifications and DNA methylation, play fundamental roles in cellular function.
- Epigenetic modifications are involved in mechanisms by which environmental factors interact with genomic elements to affect behavioral phenotypes.
- Genetic and environmental factors contribute to the risk of schizophrenia.
- This review focuses on recent advances that directly implicate epigenetic modifications in schizophrenia and its treatment.

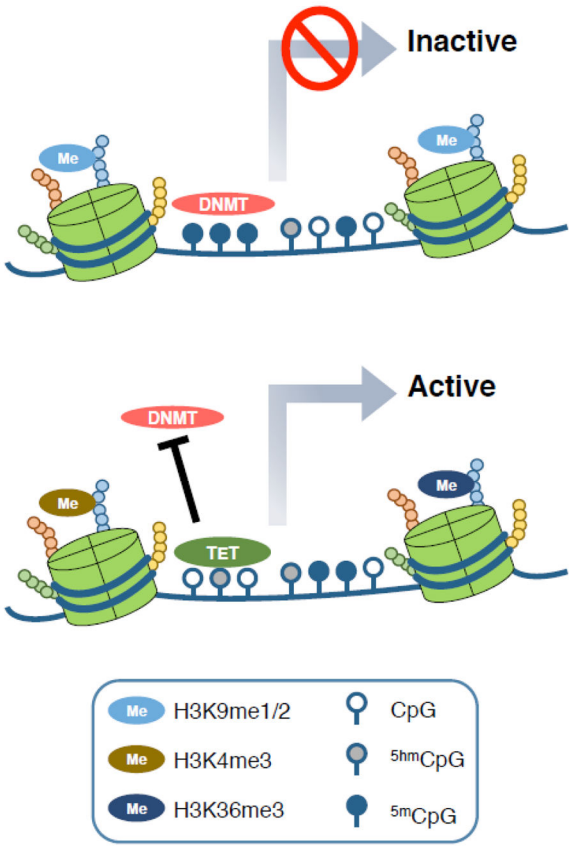

Fig. 1.

This schematic shows the link between DNA methylation and gene expression. The epigenetic mark 5-methylcytosine (5-mC), which is established by DNA methyltransferases (DNMTs), is generally associated with repression of gene transcription and has long been described as a stable and highly heritable mark. Recent findings suggest that oxidation of 5-mC to 5-hydroxymethylcytosine (5-hmC) by ten-eleven translocase (TET) proteins may relieve the repressive effects of 5-mC. Additionally, TET binding may prevent access to DNMTs, further contributing to the maintenance of an unmethylated promoter.

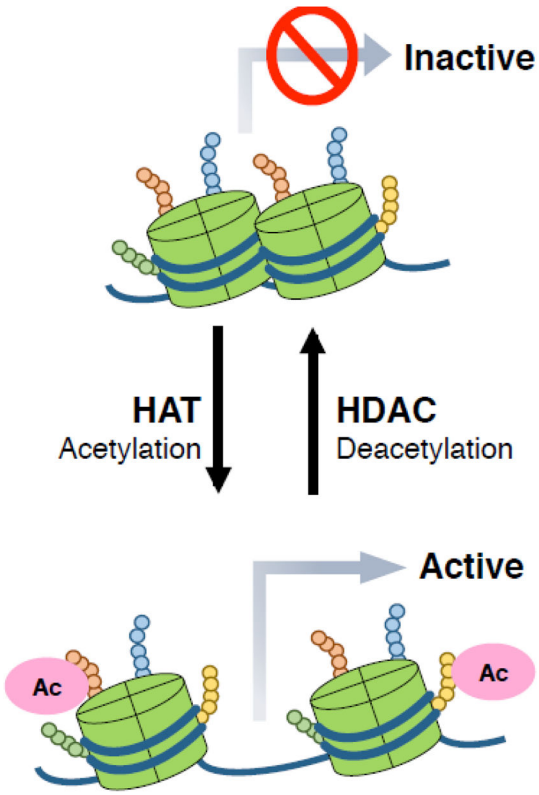

Fig. 2.

This schematic presents a model of histone modifications: acetylation and deacetylation at histone N-terminal tails. Histone acetylation is associated with opening the nucleosome to allow binding of the transcriptional complex. Acetylation is catalyzed by histone acetyltransferase (HATs), and reversed by histone acetylases (HDACs).