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Epigenetic Mechanisms in Schizophrenia

Kimberly R. Shorter[1] and **Brooke H. Miller**[1,2,3]

[1]Department of Psychiatry, University of Florida College of Medicine, Gainesville, FL 32610

[2]Departments of Psychiatry and Medicine and McKnight Brain Institute, University of Florida College of Medicine, Gainesville, FL 32610

Abstract

Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, have been implicated in a number of complex diseases. Schizophrenia and other major psychiatric and neurodevelopmental disorders are associated with abnormalities in multiple epigenetic mechanisms, resulting in altered gene expression during development and adulthood. Polymorphisms and copy number variants in schizophrenia risk genes contribute to the high heritability of the disease, but environmental factors that lead to epigenetic modifications may either reduce or exacerbate the expression of molecular and behavioral phenotypes associated with schizophrenia and related disorders. In the present paper, we will review the current understanding of molecular dysregulation in schizophrenia, including disruption of the dopamine, NMDA, and GABA signaling pathways, and discuss the role of epigenetic factors underlying disease pathology.

Keywords

Schizophrenia; epigenetics; neurodevelopment; DNA methylation; histones; microRNA

1. Introduction

In recent years, many diseases, particularly neuropsychiatric disorders, have been found to be the result of complex interactions between genetic susceptibility and environmental insults (Gavin and Akbarian, 2012; Robertson, 2005; Robertson and Wolffe, 2000; Schanen, 2006; Tsankova et al., 2007). Schizophrenia is a complex and disabling disorder defined by psychotic, affective, and cognitive symptoms. Positive symptoms include hallucinations, psychosis, and mania, while negative symptoms include anhedonia and social withdrawal. Although cognitive functioning is generally intact, working memory may be severely impaired. The onset of the disease typically occurs during late adolescence or early adulthood, a critical period in neurodevelopment that is characterized by activity-dependent synaptic pruning and final maturation of the prefrontal cortex (PFC), the region of the brain

[3]Corresponding author: brookemiller@ufl.edu; phone: 352-294-4934.

that regulates higher cognitive functions such as working memory and emotional control. The positive symptoms in schizophrenia are primarily associated with upregulation of dopamine (DA) signaling throughout the brain, while the negative and cognitive symptoms are caused both by abnormal dopamine signaling and a complicated interaction between GABAergic signaling and hypoactive NMDA function in the PFC and hippocampus. At a neuromorphological level, brains from schizophrenic patients exhibit a reduction in the number and complexity of neuronal connections in the cortex, suggesting aberrant synaptic pruning during the late stages of neurodevelopment. Reduced dendritic complexity in the PFC correlates with the cognitive deficits common to schizophrenia.

Despite the global impairment and severity of the disease, there are few effective therapies available, many of which have severe side effects. Antipsychotic drugs primarily target dopamine receptor signaling at the dopamine D2 receptor. In animal models, antipsychotics that target D2 receptors induce dopamine neuron inactivation or block depolarization; treatment with amphetamine increases hyperactivity and other psychosis-relevant behaviors, and that treatment with the antipsychotic clozapine reverses these effects (Herrera et al., 2013; Valenti et al., 2011). Recently it has been suggested that hyperactivity of the DA signaling system may be related to reduced inhibitory neuron function in the hippocampus and ventral tegmentum, as selective reduction of parvalbumin interneurons in the hippocampus results in an increase in downstream dopamine neuron activity (Boley et al., 2014; Gilani et al., 2014).

The importance of dopamine signaling in schizophrenia is based on 3 lines of evidence: first, the most effective drugs for schizophrenia are the D2R-targeting antipsychotics, with up to 90% D2 receptor occupancy; second, most patients with schizophrenia are highly sensitive to dopamine agonists, showing an immediate re-emergence of psychosis and other positive symptoms; and third, functional imaging studies have provided overwhelming evidence for dopamine hyperactivity in the brain, even in asymptomatic or drug naive patients (Salavati et al., 2014; Seeman, 2010). Functional imaging has overwhelmingly shown an upregulation of presynaptic striatal dopamine activity, variations in dopaminergic signaling correlate with executive functioning in the prefrontal cortex, and manipulation of dopamine signaling results in network disruption in numerous brain regions including the prefrontal cortex, hippocampus, striatum, basal ganglia, and putamen (Cole et al., 2013; Tan et al., 2007).

Although there is a strong functional association between DA signaling and schizophrenia, genome-wide association studies (GWAS) have not identified statistically significant loci containing dopamine-related genes. Quantitative trait locus and candidate gene mapping have been somewhat more successful, and several particularly strong candidates have been found, including *DISC1*, *NRG1*, and a cluster of GABA-A receptor subunits on chromosome 5 (Gogos and Gerber, 2006). However, many of these studies have failed to replicate, possibly due to population variability, very small effect sizes of risk genes, epistasis, and environmental factors. Because multiple large genome-wide studies have identified a strong overlap between schizophrenia and other major psychiatric disorders, there is now an effort to define studies based on endophenotypes, rather than diagnosis (Consortium, 2013; Craddock and Sklar, 2013). One DA-related representative of the endophenotypic approach is catechol-O-methyltransferase (COMT), which assists in clearing DA from synapses. The

COMT Val158Met polymorphism has been well-studied in humans: in control subjects and unaffected siblings of schizophrenic patients, the Val allele is associated with reduced prefrontal DA levels and impaired working memory, particularly during more difficult tasks, but function can be rescued with amphetamine treatment (Tan et al., 2007). In both control and schizophrenic patients, the Val allele negatively impacts both working memory and negative symptoms (Ceaser et al., 2013). Interestingly, a number of studies have shown that COMT interacts with polymorphisms in other schizophrenia risk genes, including AKT, MTHFR, DRD2, DTNBP1 (Tan et al., 2012).

While DA antagonists are largely effective at reducing or eliminating psychotic and hallucinatory symptoms in schizophrenic patients, antipsychotics have little effect on the affective and cognitive symptoms in schizophrenia. Recent research suggests that the interaction of NMDA and GABA signaling in the PFC may also be important to the pathogenesis of the disease. NMDA signaling is required for proper synapse formation and maintenance, particularly during adolescence, but is reduced in schizophrenia, a phenotype known as hypofrontality (Bhatt et al., 2009). In animal models, genetic or pharmacological induction of NMDA hypofunction is known to recapitulate both positive and negative behavioral endophenotypes similar to those observed in schizophrenia. NMDA antagonists can produce a wide array of relevant positive, negative, and cognitive behaviors such as hyperactivity, anhedonia, and social withdrawal in both acute and chronic paradigms, along with including dysregulation in dopamine signaling, interruption of normal inhibitory-excitatory circuitry in the prefrontal cortex, and cognitive defects induced by aberrant prefrontal cortex-hippocampus connectivity (Blot et al., 2013; Neill et al., 2014; Svensson, 2000). Mice engineered to express just 5% of the obligatory NMDAR subunit NR1 display schizophrenia-like behavior, including increased locomotion and stereotypies (Mohn et al., 1999).

NMDA function is significantly impaired in patients with schizophrenia. NMDA, D-cycloserine, and other endogenous NMDAR agonists are reduced in post-mortem prefrontal and striatal tissue from schizophrenia patients, as are the NMDAR subunit NR2 and the downstream NMDA signaling components NRG1 and ERBB4 (Benneyworth et al., 2011; Geddes et al., 2011). NMDA antagonists induce psychosis and cognitive impairment in normal subjects, and exacerbate symptoms in psychiatric patients (Enomoto et al., 2007; Malhotra et al., 1997). Most recently, copy number variant analysis and exome sequencing of patients with schizophrenia show a significant over-representation of mutations in brain development-related genes, particularly genes associated with the NMDA signaling pathway (Gilman et al., 2012; Hall et al., 2014).

The activity of prefrontal glutamatergic neurons is tightly regulated by GABAergic interneurons, and, like NMDA signaling, GABAergic signaling is dysregulated in schizophrenia. Levels of GAD1, the enzyme responsible for synthesizing GABA, are reduced in post-mortem schizophrenic brains, as are a number of genes associated with GABA synthesis and signaling (Hashimoto et al., 2008). Polymorphisms in two GABA-expressed genes downstream from NMDA, NRG1 and ERBB4 are associated with aberrant GABAergic interneuron development and migration, and elimination of the NR1 subunit of the NMDA receptor in a subset of cortical GABAergic interneurons during postnatal

development in mice results in a number of behavioral and molecular phenotypes associated with schizophrenia (Belforte et al., 2010; Flames et al., 2004). The most-replicated change is the decrease in the number of parvalbumin (PVALB)-positive interneurons and reduced expression of *PVALB* mRNA (Lewis et al., 2012; Uchida et al., 2014). Parvalbumin neurons are considered crucial to the pathogenesis of schizophrenia, as they are strongly associated with the regulation of NMDA signaling.

A final important aspect in the pathogenesis of schizophrenia is the neurodevelopmental timecourse. Although some symptoms, such as reduced sociability, may be observed in childhood, the onset of schizophrenia generally does not occur until late adolescence or early adulthood. While neurogenesis and massive dendritic connectivity characterize the early postnatal period, the adolescent period is characterized by NMDA-dependent synaptic pruning and the final maturation of the GABA-glutamate circuitry in the prefrontal cortex (Bale et al., 2010). Schizophrenia is believed to be 70–80% heritable, but the risk for monozygotic twins is only 50%, suggesting that environmental factors may be as important as genetic risk factors (McGuffin and Gottesman, 1999). In the following review, we suggest that the role of environment on the development and course of schizophrenia are mediated by epigenetic factors including DNA promoter methylation/hydroxymethylation, histone expression and post-translational modifications, and the interaction between these factors and other environmentally responsive molecules such as microRNAs (miRNAs) and other non-coding RNAs.

2. DNA Methylation

Alterations in DNA methylation have been detected in many neuropsychiatric disorders, including autism, bipolar disorder, borderline personality disorder, and schizophrenia. DNA methyltransferases (DNMTs) catalyze the transfer of methyl groups to DNA, resulting in 5-methylcytosine (5-mC) modification of CpG islands in or near gene promoter regions. This modification generally represses transcription. In contrast, TET enzymes can catalyze the conversion of 5-mC to 5-hydroxymethylcytosine (5-hmC), resulting in DNA demethylation and subsequent transcriptional de-repression (Figure 1A) (Dong et al., 2012; Grayson and Guidotti, 2013; Guo et al., 2011; Kato and Iwamoto, 2014).

A recent DNA methylome study identified numerous changes in DNA methylation at differentially methylated regions (DMRs) in schizophrenia and bipolar disorder, and a study of monozygotic twins discordant for psychosis found that DMRs involved in known pathways for psychiatric disorders and brain development were over-represented (Dempster et al., 2011; Xiao et al., 2014). Expression of several DNMTs are upregulated in brains from schizophrenia patients, resulting in the hypermethylation and downregulation of schizophrenia-associated genes, including brain-derived neurotrophic factor (*BDNF*), the glucocorticoid receptor (*NR3C1*), *GAD1*, and reelin (*RELN*) (Grayson et al., 2005, Roth, 2009 #604; Wong et al., 2010). Interestingly, *RELN* promoter methylation in temporal-cortical tissue from normal subjects increases 25-fold during adolescence, suggesting that altered epigenetic regulation of RELN may play a role in neurodevelopmental changes associated with schizophrenia (Lintas and Persico, 2010).

COMT promoter methylation is also disrupted in schizophrenia, although the methylation is variable and can be affected by antipsychotic therapy, environmental factors, and genotype, including the COMT Val158Met polymorphism (Lott et al., 2013). In control subjects, those homozygous for the COMT Val allele show *RELN* promoter hypermethylation and decreased RELN expression (Abdolmaleky et al., 2008; Abdolmaleky et al., 2006). Other downstream effects of aberrant *COMT* methylation include up- or down-regulation of dopamine receptor activity, reduced *GAD1* expression, and disrupted prefrontal NMDA signaling (David et al., 2005; Kalkman and Loetscher, 2003).

GADD45, which recruits deaminases and glycosylases to promoter regions, is also a regulatory factor in DNA methylation (Cortellino et al., 2011; Rai et al., 2008). GADD45b binding at the *BNDF* promoter is significantly decreased in major psychosis, and is associated with *BDNF* promoter hypermethylation and reduced expression (Gavin and Akbarian, 2012). This same region is also associated with repressive histone interactions. Another member of the GADD45 family, GADD45a, has been shown to bind acetylated histones, suggesting that this family of proteins may be good targets for therapeutic intervention (Carrier et al., 1999).

Although many studies have focused on promoter hypermethylation in schizophrenia, recent studies have shown that TET1 and 5-hmC DNA modifications are also elevated in cortical tissue from schizophrenic patients. Expression of both DNMTs and TET enzymes are increased in corticolimbic tissue from post-mortem SCZ brains, and global analysis has shown that methylation is significantly reduced in schizophrenic patients compared to their un-affected twins (Bonsch et al., 2012; Dong et al., 2012; Guidotti et al., 2014). A similar discordant twin analysis found that the most significant difference between affected and unaffected twins was a 25% increase in hypomethylation at the promoter for *ST6GALNAC1*, a gene involved in stress-activated kinase signaling (Dempster et al., 2011).

Finally, there is strong evidence that pre- and postnatal environmental factors can affect promoter methylation of genes associated with schizophrenia and other major psychiatric disorders. Reduced postnatal maternal care can alter genome-wide and specific gene methylation, including at the *GAD1* and glucocorticoid receptor promoters. Many of these early-life DNA modifications are stable and modify adult behaviors and neurobiology, such as regulation of anxiety by GABAergic signaling and propensity of suicidality (Bagot et al., 2012; McGowan et al., 2009; Zhang et al., 2010). DNA methylation may also interact with genomic factors such as parental imprinting, as in hypomethylation of the paternal copy of the schizophrenia risk gene *LRRTM1* (Brucato et al., 2014).

3. Histone Modifications and Chromatin Structure

Chromatin is the DNA-protein complex that regulates the availability of DNA to transcription factors. Chromatin is found in two forms, euchromatin and heterochromatin. Euchromatin is less tightly wound and is associated with active transcription, while heterochromatin is more tightly wound, blocking transcription factor access to gene promoter regions. Histone transition between the euchromatin and heterochromatin state are mediated by post-translational modifications, including acetylation and methylation, of the

four major histone proteins that comprise the nucleosome (Figure 1B). Histone modifications occur at specific amino acids in the protein: acetyl groups are attached by histone acetyltransferases (HATs) and can be removed by histone deacetylases (HDACs), while histone methylation is performed by histone methyltransferases (HMTs).

The use of valproic acid (VPA), an HDAC inhibitor, in the treatment of schizophrenia and bipolar disorder suggests that histone regulation may play an important role in disease pathogenesis. In rats, HDAC inhibitors can reverse the effect of postnatal stress on RELN and glucocorticoid levels by increasing acetylation of at the amino terminal of H3 (Weaver et al., 2006). In patients with schizophrenia, both TET1 and HDAC1 are elevated in postmortem hippocampal and PFC tissue, particularly in tissue from female patients (Benes et al., 2007; Dong et al., 2012). Overexpression of HDAC1 may result in chromatin deactylation, causing transcriptional repression of a number of genes. HDAC inhibitors are therefore considered to be good targets for new therapeutic drugs that are more effective and have fewer off-target effects than VPA.

Histone 3 (H3) seems to be particularly dysregulated in schizophrenia. Specifically, di- and tri-methylation of H3K9 and H3R27, which can regulate GAD1 expression, is elevated in cortical neurons and adjacent non-neuronal cells in post-mortem tissue from schizophrenic patients, reducing expression of genes typically associated with neuronal metabolism (Akbarian, 2010). Lymphocyte studies in schizophrenia patients also indicate in an abnormal increase in heterochromatin, likely due to increased H3K9 methylation and reduced H3K9 acetylation, both modifications associated with an increase in heterochromatin (Chase et al., 2013; Gavin et al., 2009; Kosower et al., 1995). Three HMTs, G9a, GLP, and SETDB1, which are responsible for the majority of H3K9me modifications across the genome, are increased in lymphocytes from SCZ patients; notably, SETDB1 is the only HMT that specifically functions to specifically di- and tri- methylate H3K9 (Wang et al., 2003; Zee et al., 2010). Overall, heterochromatin associated with histone methylation is increased in cortical tissue from schizophrenia patients: levels of methylated H3K4 are reduced at nearly 600 loci, including near multiple NMDAR subunits and genes involved in neurodevelopment (Sharma et al., 2008).

4. Association between epigenetic factors and microRNAs

MicroRNAs (miRNAs) assist in the regulation of many mechanisms in the nervous system, including neuronal migration, neuronal differentiation, synaptic plasticity, and adult neurogenesis, by binding to target sites in the 3′ UTR of mRNAs and either preventing translation or targeting the mRNA for degradation (Figure 1C) (Cheng et al., 2009; Kosik, 2006). A number of studies have associated altered miRNA expression or activity with major psychiatric disorders (Miller and Wahlestedt, 2010). DICER1, which plays a major role in miRNA processing, is affected in schizophrenia cases that are associated with copy number variation, as are several miRNAs located nearby, while another enzyme important for miRNA processing, DGCR8, is deleted in DiGeorge Syndrome, a neurodevelopmental disorder that includes schizophrenia-like symptoms. A mouse model of DiGeorge Syndrome exhibits schizophrenia-like behavioral phenotypes, along upregulation of pri-miRNAs and

downregulation of mature miRNAs in the brain. These characteristics are also observed when only *Dcgr8* is deleted (Stark et al., 2008).

Several specific miRNAs, including miR-132, miR-137, and miR-181b, have been implicated in schizophrenia and other psychiatric disorders. MiR-132 is of particular interest, as it is developmentally regulated during adolescence by NMDA signaling, and targets both *MECP2*, a chromatin-modifying protein that causes the neurodevelopmental disorder Rett Syndrome, and *DNMT3A*, an activity-dependent DNA methyltransferase that is elevated in cortical tissue from adult schizophrenic patients (Kundakovic et al., 2009). More than 10% of genes that are over-expressed in PFC tissue from schizophrenic patients are predicted miR-132 targets, consistent with the observed downregulation of miR-132 (Miller et al., 2012).

Polymorphisms near the miR-137 locus have been identified in several large genome-wide association studies, and follow-up work has shown that genes predicted to be miR-137 targets, including *TCF4*, *CACNA1C*, *CSMD1*, and *WBP1L*, are altered in schizophrenia (Consortium, 2013; Consortium, 2011; Hill et al., 2014; Ripke et al., 2011). MiR-137 is expressed in both the developing and adult mouse brain and plays a role in regulating cell proliferation and differentiation. In mice, overexpression of miR-137 in the embryonic brain leads to a reduction in neuronal proliferation and induction of premature differentiation of neural stem cells, but has the opposite effect in adult brains (Hill et al., 2014). In humans, unaffected carriers of the risk allele of the miR-137 risk allele (rs1625579; TT genotype) have working and episodic memory deficits, and schizophrenic patients with the TT genotype exhibit reduced PFC activation during working memory tasks (Cummings et al., 2013; van Erp et al., 2014).

5. Crosstalk between DNA Methylation, Histone Modifications, and miRNAs

Multiple epigenetic factors may act on single genes or gene networks. For example, promoter methylation and SNP polymorphisms in schizophrenia risk genes can interact, as in COMT (Sections 1 and 2), or allele-specific promoter hypomethylation of a single nucleotide polymorphism in the serotonin 2A receptor (HTR2A). HTR2A is a secondary target of a number of antipsychotic medications, and its promoter is hypomethylated in an allele-specific manner in both schizophrenia patients and their unaffected relatives, indicating that this finding is unaffected by antipsychotic treatment (Ghadirivasfi et al., 2011).

We have identified co-regulation of miR-132 and miR-137, both strongly associated with schizophrenia, and BDNF and MECP2, also associated with neurodevelopment and major psychiatric disorders (Figure 2). In this pathway, transcription of miR-132 and *BDNF* is induced by activity-dependent NMDA signaling via the CREB signaling pathway. MiR-132 then targets the 3′ UTR of *MECP2*, which targets both BDNF and miR-137 (Ausio et al., 2014). Finally, miR-132 appears to modulate NMDA receptor signaling in a feedback loop that would regulate its own transcription.

All members of the miR-132/MECP2/miR-137/BDNF network are subject to epigenetic regulation at multiple levels. MECP2 regulates expression of genes such as *BDNF* through

both protein interactions and histone modification: it inhibits *BDNF* expression by disinhibition of the transcriptional repressor REST, and binds to heterochromatin marked by H3K9me and H3K27me, altering developmental and neurodevelopmental dominant splice variant expression of *BDNF* by controlling transcription factor access to the multiple *BDNF* promoters (Mitchelmore and Gede, 2014). Finally, MECP2 inhibits miR-137 expression through an unknown mechanism (Szulwach et al., 2010); Thambirajah, 2012 #903}.

6. Overlap between Schizophrenia and Other Neurodevelopmental Disorders

The master epigenetic regulator MECP2 can be linked to many other neurodevelopmental disorders. One common neurodevelopmental disorder, Rett Syndrome, is associated with multiple polymorphisms in *MECP2* (Amir et al., 1999). These mutations, which may occur at multiple different nucleotides in the gene, prevent MECP2 from binding to methylated DNA (Goffin et al., 2012). MECP2 is also implicated in both Prader-Willi Syndrome (PWS) and Angelmann Syndrome (AS), two different neurodevelopmental disorders caused by differential parental contributions at a single locus, the Prader-Willi Syndrome/Angelmann Syndrome Imprinting Center (PWS/AS-IC: 15q11.2-q13.1). Abnormal maternal imprinting causes Angelmann Syndrome, which is characterized by severe cognitive and neurological impairments, while lack of a paternal copy of the locus causes Prader-Willi Syndrome, which is associated with obsessive-compulsive behavior and endocrine abnormalities (Johnstone et al., 2006). MECP2 exerts its effects across multiple neurodevelopmental disorders due to its ability to regulate by promoter methylation and histone activity, thereby exerting a transcriptome-wide effect (Monteggia and Kavalali, 2009).

The PWS/AS-IC contains the gene for the E3 ubiquitin ligase *UBE3A*; deletion of this gene causes PWS, while abnormal maternal imprinting prevents MECP2 from binding to the methylated promoter, disrupting *UBE3A* expression and resulting in Angelmann Syndrome (Yasui et al., 2011). Interestingly, another E3 ubiquitin ligase, MIB1, is targeted by the schizophrenia-associated miR-137. A second gene near the PWS/AS Imprinting Center, the GABA-B receptor subunit *GABRB3*, has been shown to be both polymorphic and hypermethylated in some cases of autism (Buxbaum et al., 2002). Finally, having two maternal copies of a fragment of the 15q11.2-q13.1 locus is a risk factor for schizophrenia, psychosis, and autism (Ingason et al., 2011).

7. Conclusion

Schizophrenia and other neuropsychiatric disorders are highly polygenic and heritable, but it has been difficult to identify individual causative genes. Phenotypic expression of the disorders is due to complex interactions between risk alleles and environmental risk factors, including prenatal and postnatal stressors, paternal age, and cannabis use (Abdolmaleky et al., 2004; Lewis and Levitt, 2002; Matrisciano et al., 2013; Rapoport et al., 2012). Epigenetic factors, including DNA methylation, histone post-transcriptional modification and subsequent regulation of chromatin structure, and microRNA regulation of signaling pathways--including those involved in DNA methylation and histone activity--play important roles in neurodevelopment and are all capable of regulating large numbers of

genes at once. Therefore, it is likely that epigenetic mechanisms in schizophrenia and other psychiatric disorders mediate the interaction between genetic risk alleles and environmental factors by dynamic modification of the genome in response to positive or negative environmental stimuli.

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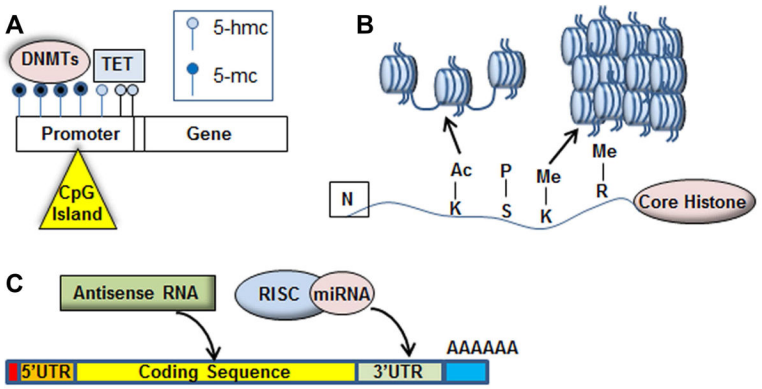

Figure 1. Common epigenetic modifications

(A) DNA methyltransferases (DNMTs) modify CpG islands, which are found primarily in the promoter region of genes, with 5-methylcytosine (5-mC). An increase in promoter methylation (dark blue circles) results in reduced gene expression, while TET enzyme modification of 5-mC to 5-hmC results in de-repression of gene expression. (B) The four core histones undergo amino acid-specific acetylation, methylation, and phosphorylation. The post-translational modifications result in either the relaxation of the nucleosome structure (euchromatin), which allows transcription factor access to genes, or causes nucleosomes to tighten into heterochromatin, blocking transcription at specific loci. (C) Post-transcription factors including microRNAs, antisense RNA, and long non-coding RNA act at promoter regions, coding regions, and 3′UTR seed sequences to regulate the expression of target mRNAs.

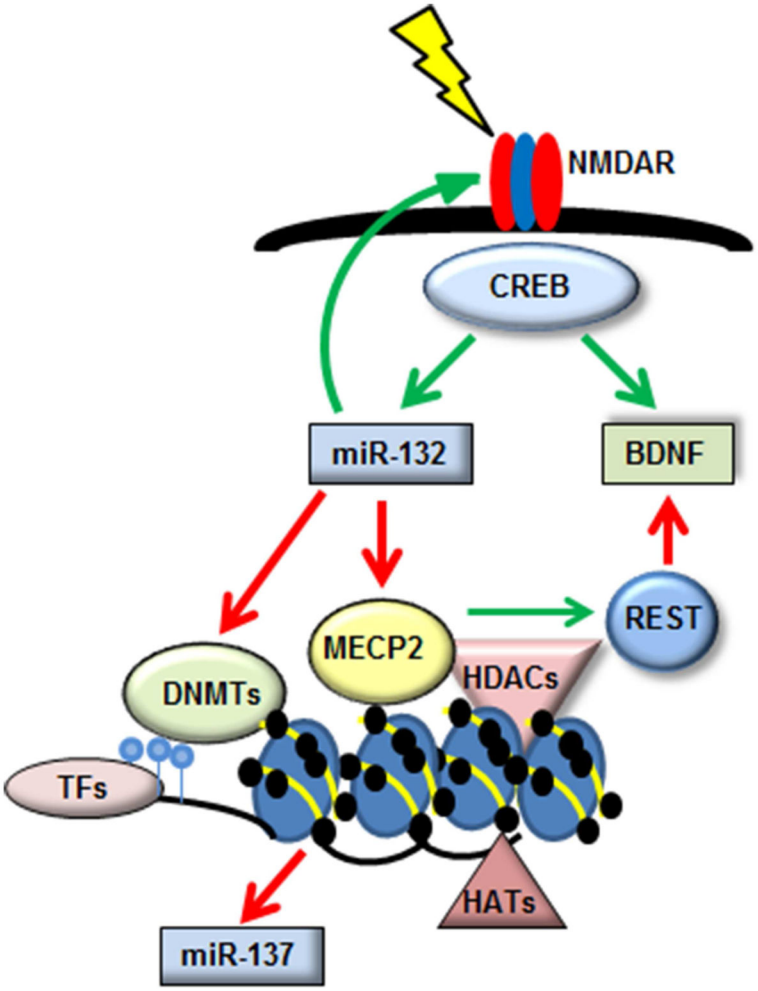

Figure 2. CREB signaling co-regulates epigenetic mechanisms and schizophrenia-associated miRNAs

Activity-dependent NMDA signaling induces the CREB signaling pathway, which upregulates the expression of miR-132 and BDNF. Both NMDA signaling and miR-132 expression are significantly reduced in schizophrenia, and BDNF expression is dysregulated. MiR-132 inhibits multiple genes including DNMT3A, which causes hypermethylation and reduced gene expression of target genes, and MECP2, which regulates both DNA methyltransferase and histone modification activity. MECP2 also inhibits expression of the schizophrenia-associated miRNA miR-137, and inhibits BDNF expression via interaction with the transcriptional repressor REST.