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Invited review

Decoding transcriptional repressor complexes in the adult central nervous system

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ABSTRACT

Cells maintain precise gene expression by balancing transcriptional activation and repression. While much work has focused on elucidating transcriptional activation in the central nervous system (CNS), little is known about transcriptional repression. One means to repress gene expression is to initiate binding of transcription factors to DNA, which then recruit co-repressors as well as other accessory proteins, forming a multi-protein repressor complex. These multi-protein repressor complexes include histone modifying enzymes that trigger processes such as histone acetylation, methylation, and ubiquitylation, altering chromatin structures to impact gene expression. Within these complexes transcriptional repressor proteins per se do not exhibit enzymatic reactions to remodel chromatin structure, whereas histone modifying enzymes lack intrinsic DNA binding activity but have an ability to process post-translational modifications on histones. Thus, the mutual association between transcriptional repressors and histone modifying enzymes is essential to sculpt chromatin to favor transcriptional repression and down regulate gene expression. Additionally, co-repressors are integral components in the context of gene repression as they bridge the association of transcriptional repressors and histone modifying enzymes. In this review, we will discuss the roles of some of the major components of these repressor complex in the CNS as well as their cellular functions that may underlie fundamental behavior in animals.

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1. Introduction

Over the past several years studies have started to elucidate the role of transcriptional activators in the central nervous system with many shown to be involved in various aspects of brain function during embryonic and postnatal development, as well as throughout adulthood (Hoch et al., 2009; West and Greenberg, 2011; Wonders and Anderson, 2006). By contrast, the role of transcriptional repressors in the adult nervous system is far less characterized; however, accumulating data indicates they play a critical role in brain function. Mechanisms of transcriptional repression can be divided into three categories; inhibition of the basal transcriptional machinery, ablation of transcriptional activator function, and remodeling of chromatin (Gaston and Jayaraman, 2003). The first category represents the repressors that interfere with the binding of RNA polymerase, TATA box-binding protein, and/or general transcription factors to transcription start sites; thus, preventing transcription initiation. The second mechanism occurs by repressors targeting transcriptional activators and co-activators, resulting in their degradation, nuclear export, or inhibiting their ability to bind DNA. The third mechanism involves recruitment of chromatin remodeling factors, which cause epigenetic alterations on the genome. In addition to the above categories of gene repression, recent studies further establish an emerging role of non-coding RNAs in transcriptional repression by interacting with chromatin modifying factors (Wang et al., 2010).

There has been much interest in investigating the role of individual transcriptional repressors as well as proteins that form part of transcriptional repressor complexes in vivo. In initial studies, constitutive knockout mice were generated to many individual transcriptional repressors as well as proteins that are part of the transcriptional repressor complex, however the loss of these factors often resulted in perinatal, embryonic, or early postnatal lethality precluding in depth characterization of the mice (Perissi et al., 2010). To circumvent this problem, researchers have turned to site-specific recombination technology that allows for targeted gene deletion in a spatially and temporally controlled manner.

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Conditional knockout mice have started to demonstrate distinct roles of individual transcriptional repressors, as well as for proteins that assemble into repressor complexes, in the adult brain. In this review, we will summarize the current understanding of two of the most extensively studied transcriptional repressors in the brain, namely MeCP2 and REST, as well as individual components of repressor complexes in which they associate, and their impact on primarily adult brain function.

2. Transcriptional repressors

2.1. MeCP2

Methyl-CpG-binding protein 2 (MeCP2) is a ubiquitous protein present in both neuronal and non-neuronal tissues and was originally purified from the brain as a heterochromatin protein that binds to DNA containing a single methyl-CpG dinuceotide (Lewis et al., 1992). Subsequently in vitro experiments demonstrated inhibition of transcription from DNA templates in a methylation-dependent manner that occurs through recruitment of a co-repressor complex containing Sin3A, histone deacetylase (HDAC)1, and HDAC2 at the target gene promoter; thus, providing the first indication that MeCP2 links two epigenetic mechanisms involved in transcriptional repression, DNA methylation, and histone deacetylation (Jones et al., 1998; Meehan et al., 1992; Nan et al., 1998). Research into the role of MeCP2 in the brain has been further advanced by the identification of mutations in the *MECP2* gene in >95% of patients with the neurodevelopmental disorder, Rett syndrome (RTT) (Amir et al., 1999). The disease causing mutations within the *MECP2* gene are believed to result in loss of MeCP2 function. Many of the mutations in the *MECP2* gene identified in RTT patients are localized within either the DNA binding or transcriptional repression domains, suggesting that loss of MeCP2 activity could alter chromatin architecture by either interfering with the binding to DNA or to the formation of the co-repressor complex, leading to abnormal brain functions and behavioral phenotypes associated with RTT. However, rather intriguingly there are people with *MECP2* mutations that do not display the characteristic features of RTT, highlighting the importance of clinical diagnosis for this disorder (Suter et al., in press).

Rather unexpectedly, data from array comparative genomic hybridization has shown that increased *MECP2* copy number can lead to *MECP2* duplication syndrome, a neurodevelopmental disorder with some overlapping features of RTT (Van Esch et al., 2005). In order to study the impact of MeCP2 overexpression in the CNS, we recently characterized a mouse line in which MeCP2 overexpression was restricted to neurons and found that these mice recapitulate key behavioral phenotypes of the disorder (Na et al., 2012). We also found that neurons overexpressing MeCP2 have significant reductions in specific aspects of neurotransmission that appear to be due to MeCP2 as a transcriptional repressor. As there have been only a few studies investigating MeCP2 overexpression in animal models (Collins et al., 2004; Na et al., 2012), we will restrict our discussion to MeCP2 loss of function.

To understand the role of MeCP2 loss of function in the brain, several laboratories have generated lines of *Mecp2* mutant mice. Constitutive deletion of the *Mecp2* gene in mice resulted in a variety of aberrant phenotypes reminiscent of RTT patients, including ataxic gait, hindlimb clasping, and irregular breathing; however, the mice also had a shortened lifespan that prevented a more thorough characterization of them as adults (Chen et al., 2001; Guy et al., 2001; Pelka et al., 2006). Conditional *Mecp2* knockout mice, in which the deletion was targeted to specific subsets of neurons, has started to dissect the role of specific neuronal populations in mediating behavioral phenotypes related to RTT, and in some cases has revealed unexpected phenotypes that are presented in atypical RTT patients. For example, our laboratory demonstrated that postnatal deletion of *Mecp2* in broad forebrain regions was sufficient to recapitulate some of the core clinical features of RTT, such as impaired motor coordination, heightened anxiety, and deficits in social interaction (Gemelli et al., 2006). In separate work, mice lacking *Mecp2* specifically in GABAergic neurons displayed several RTT features including impaired motor coordination, altered social behavior, and deficits in hippocampal-dependent learning and memory (Chao et al., 2010). Additionally, these mice developed stereotypies, self-injury, and compulsive behavior, which are more reminiscent of autistic features but overlap with RTT symptoms. The characterization of additional conditional *Mecp2* mouse lines has revealed that some of these lines also recapitulate atypical clinical features, including aggression and obesity, not seen in classical RTT patients (Couvert et al., 2001; Kleefstra et al., 2002). For example, the restricted deletion of *Mecp2* in the hypothalamus resulted in increased aggression, hyperphagia, and obesity and was accompanied by an increased physiological response to stress as shown by elevated corticosterone levels in serum (Fyffe et al., 2008). The reader is referred to a recent review by Li and Pozzo-Miller discussing the characterization and phenotypes of *Mecp2* mutant mice (Li and Pozzo-Miller, 2012).

While recent work has demonstrated that MeCP2 plays important roles in mediating complex behavior and synaptic function, the molecular mechanisms behind how this seemingly straightforward-acting transcription factor leads to such a wide array of clinical features presented in RTT is still elusive (Chao et al., 2010; Dani et al., 2005; Moretti et al., 2006; Nelson et al., 2006). Given the fact that MeCP2 represses gene transcription in a DNA methylation dependent manner, earlier studies investigated whether the loss of MeCP2 causes genome-wide misregulation of gene expression. Initial attempts to identify MeCP2 target genes from whole-brain gene expression profiling analysis resulted in rather surprisingly, only subtle changes in gene expression and gained little information on the putative genes relevant to RTT (Tudor et al., 2002). Subsequent candidate gene approaches using tissues from specific brain regions have identified promising putative genes regulated by MeCP2, including serum glucocorticoid-inducible kinase, FK506-binding protein 5, corticotropin-releasing hormone, Fxyd1 encoding Na^+/K^+ ATPase, and protocadherin beta 1, in which MeCP2 binds to methylated promoters and down-regulates their expression (Deng et al., 2007; Miyake et al., 2011; Nuber et al., 2005). Additionally, microarray analysis from hypothalamic RNA revealed down-regulation of a majority of genes in *Mecp2* deficient tissue, suggesting that MeCP2 may also function as an activator of gene transcription (Chahrour et al., 2008). Identification of target genes supports the premise that MeCP2 acts at specific gene promoters whose expression changes contribute to overt neurological symptoms seen in RTT patients. Notably, this was contradicted by a recent study demonstrating that MeCP2 binding occurs globally, rather than at specific gene loci, across the genome in the adult brain and that MeCP2 functions to track the density of methylated CpG sites; i.e., MeCP2 binds wherever DNA is methylated (Skene et al., 2010). It is plausible that widespread binding of MeCP2 across the genome could be a critical factor to reduce unnecessary transcriptional noise as well as prevent aberrant transcription from areas such as intergenic regions. Global distribution of MeCP2 in the genome could be a prerequisite condition for activity-dependent neuronal gene transcription. For example, expression of brain-derived-neurotrophic factor (BDNF) is induced upon depolarization of neurons that triggers phosphorylation of MeCP2 at amino acid serine 421 leading to dissociation of MeCP2 from the *Bdnf* gene promoter (Chen et al., 2003; Martinowich et al., 2003). Thus, neuronal activity may alter

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MeCP2 occupancy on the chromatin leading to the induction of gene transcription, leading one to postulate that alterations in activity dependent processes may impact MeCP2 dependent gene transcription and underlie aspects of RTT.

A recent study by Li et al. indicates a more complex role for MeCP2 in maintaining transcriptional programs, particularly in neurons (Li et al., 2013). Using neurons derived from human embryonic stem cells of RTT patients, unbiased gene expression analysis revealed a drastic decrease in total RNA on a per-cell level, as well as reduction of active transcription in mutant *MECP2* neurons. Importantly, this phenomena was coupled to reduced protein translation. This finding suggests that MeCP2 rather facilitates gene transcription, at least in neurons, and supports the previously proposed function of MeCP2 as a transcriptional activator in hypothalamus (Chahrour et al., 2008).

Another important question regarding MeCP2 is whether its loss of function alters epigenetic signatures at target gene promoters or globally in the genome. A study of *Mecp2* mutant mice with a stop codon at amino acid 308, *Mecp2*^{308}, recapitulate many RTT symptoms and demonstrate global hyperacetylation of histones H3 and H4 in the brain (Shahbazian et al., 2002). More recently, Skene et al. confirmed elevated acetylation of histone H3 in neurons but not glia. We also observed increased acetylation of histone H3 following the deletion of *Mecp2* specifically in the basolateral amygdala of mice, as well as heightened anxiety and deficits in fear-associated learning and memory (Adachi et al., 2009). Importantly, we were able to demonstrate that chronic infusion of an HDAC inhibitor into the basolateral amygdala produced behavioral deficits similar to those observed in mice with specific knockdown of *Mecp2* in this brain region. These studies suggest that MeCP2 potentially shapes epigenetic landscapes through the regulation of HDACs, and that dysfunction of MeCP2 disrupts these processes, which may contribute to the pathophysiology of RTT. The rapid advancements in next generation sequencing technologies such as RNA-Seq and ChIP-Seq will be important to construct epigenetic patterns under normal as well as MeCP2-defective conditions to further investigate these possibilities.

2.2. REST

Repressor element-1 silencing transcription factor (REST), also known as neuron-restrictive silencer factor (NRSF), was initially identified as a transcription factor that represses genes containing a repressor element-1/neuron restrictive silencer element (RE1/NRSE) cis-regulatory DNA sequence in their promoters. Earlier investigations revealed predominant expression of REST in non-neuronal tissues and the presence of RE1 in many neuronal genes, such as Nav1.2 sodium channel, SCG10, and synapsin 1, establishing the classical view that REST suppresses neuronal gene in non-neuronal tissues to establish and maintain phenotypic identity of non-neuronal cells (Chong et al., 1995; Schoenherr and Anderson, 1995; Schoenherr et al., 1996). The binding of REST to the RE1 promoter permits the assembly of a corepressor complex containing CoREST, which recruits HDAC1 and HDAC2 (Andres et al., 1999; Ballas et al., 2005). This assembly alters chromatin status by decreasing histone acetylation; thus, favoring a silent transcription state.

In pluripotent stem cells and neural progenitors, REST has been reported to orchestrate a network of genes related to neural development during embryonic and adult neurogenesis (Aoki et al., 2012; Ballas et al., 2005; Covey et al., 2012; Yamada et al., 2010). In undifferentiated neurons, REST expression declines as these cells mature during brain development. Therefore, it was surprising that REST expression is present in the adult brain, including neurons in the hippocampus, pons/medulla, and midbrain (Palm et al., 1998). A couple of recent studies have begun to examine the role of REST in the adult brain. During postnatal development in rodents, one hallmark of synaptogenesis is the developmental switch of NMDA receptor subunit expression from GluN2B to GluN2A, conferring NMDA receptors with different channel properties and kinetics. It was found that at a specific developmental time window, a transient increase in REST expression occurs in the hippocampus leading to increased occupancy of REST at the GluN2B promoter; thus, repressing its gene expression (Rodenas-Ruano et al., 2012). This event correlates with increased epigenetic markers for gene repression at the GluN2B promoter, indicating REST's ability to repress the target gene via epigenetic remodeling.

Another emerging role of REST in the adult brain is its involvement in ischemia-induced cell death in hippocampal neurons. Ischemic strokes induce not only REST expression in the CA1 subregion of hippocampus, but also enrichment of REST at a discrete subset of genes promoters and leads to subsequent transcriptional repression of genes including those encoding ionotropic glutamate receptors (Noh et al., 2012). Following ischemia, it has been shown the REST-CoREST repressor complex, which also contains MeCP2 and Sin3A, assembles at the *Gria2* (AMPA receptor subunit, GluA2) gene promoter. The recruitment of this repressor complex is also accompanied by alterations in epigenetic marks of the GluA2 promoters that represent silencing of gene transcription. It was demonstrated that RNAi-mediated knockdown of *Rest* in the hippocampus normalized GluA2 expression suppressed by the ischemic strokes and prevented neuronal death. Thus, REST has a variety of functions in the CNS ranging from the regulation of postnatal development to ischemia-associated neurodegeneration, via the remodeling of epigenetic signatures.

In addition to HDAC1 and 2, REST has been co-purified with other chromatin modifiers, such as jumonji AT-rich interactive domain 1C protein (JARID1C)/SMCX histone H3K4 demethylase, suggesting a link between REST-mediated gene repression and trimethylation of histone H3 (Tahiliani et al., 2007). Co-occupancy of REST and JARID1C/SMCX histone demethylase within the promoters of several REST target genes further supports this notion. Importantly, knockdown of *Jarid1C*/*Smcx* leads to decreased trimethylation of histone H3 at the REST target gene promoters, accompanied by de-repression of their gene expression. In relation to CNS function of REST-JARID1C/SMCX histone demethylase interaction, mutations in the *JARID1C*/*SMCX* gene have been found in some patients with X-linked mental retardation. These mutations result in reduced activities of histone demethylase, suggesting that impairment in REST-JARID1C/SMCX mediated chromatin modification and gene repression may underlie the pathophysiology of some mental disorders (Iwase et al., 2007).

3. HDACs and other corepressor proteins

Gene transcription can be modulated by post-translational modifications of amino acids in histone tails. Histone acetylation is a key modulator of chromatin structure and gene transcription and is determined by the balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs) activities. The acetylation of histones occurs at lysine residues of histone tails that relaxes chromatin and allows recruitment of transcription factors; thereby, favoring active gene transcription. In contrast, histone deacetylation is the removal of the acetyl group that results in chromatin compaction and favors transcriptional repression. However, the role of HATs and HDACs is complex in that recent genome wide analyses has mapped the presence of both HATs and HDACs at transcriptionally active loci which are bound by RNA polymerase, indicating tight equilibrium of histone acetylation levels in maintaining gene transcription in non-neuronal cells

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(Wang et al., 2009). Consistent with this observation, in rodent hippocampus an HDAC inhibitor preferentially, but not globally, targets its action on the transcriptionally active loci (Lopez-Atalaya et al., 2013). In addition to histone modifications some of the HDACs, in particular those that belong to the Class II HDAC family, have been shown to act on many other non-histone substrates in the nucleus, suggesting they have complex roles in impacting gene transcription that is not yet fully understood. While there is little known about the role of individual HATs in the adult CNS, recent data has started to elucidate the role of individual HDACs in the brain.

3.1. Inhibition of HDACs

Recent studies have suggested that HDACs may play an important role in learning and memory. A role for HDACs in learning and memory was initially based on the finding that increased histone H3 acetylation in the CA1 subregion of the hippocampus occurs during consolidation of memory formation in the fear conditioning paradigm (Levenson et al., 2004). This study also showed that systemic injection of sodium butyrate, a broad histone deacetylase inhibitor, prior to the fear conditioning enhanced long-term memory formation and long-term potentiation (LTP) at Schaffer-collateral synapses in the CA1 region. In subsequent studies, intrahippocampal infusion of additional HDAC inhibitors, such as Trichostatin A, valproic acid, and suberoylanilide hydroxamic acid (SAHA), were shown to enhance learning and memory in a variety of behavioral tests (Bredy and Barad, 2008; Guan et al., 2009; Haettig et al., 2011; Hawk et al., 2011; Vecsey et al., 2007). Furthermore, increased histone acetylation in response to memory formation has been linked to specific gene promoters, including, *Bdnf*, *Creb*, *Zif268*, and *Nr4a* orphan nuclear receptor genes (Guan et al., 2009; Hawk et al., 2012; McNulty et al., 2012; Vecsey et al., 2007). These data suggest that inhibition of HDAC activities facilitates learning and memory via remodeling of chromatin landscapes within a limited number of genes. In the following sections, we will discuss the contribution of individual HDACs in the brain with an emphasis on their role in learning and memory.

3.2. The HDAC gene family

The mammalian genome encodes eleven individual HDAC genes, which are categorized into three subclasses I, II, and IV, based on amino acid identity and subcellular localization (Haberland et al., 2009; Yang and Seto, 2008). The class I HDAC family consists of HDAC1, 2, 3, and 8 and are expressed predominantly in the nuclei of many cell types. The class II HDAC family consists of HDAC4, 5, 6, 7, 9, and 10. The class IV HDAC family currently consists of only HDAC11, and little is known about its function despite its enrichment in a variety of tissues including the brain (Liu et al 2008). Recent work has only begun to delineate the role of individual HDACs in the adult brain, and these studies have largely concentrated on the class I HDACs in the context of learning and memory (for review see, Morris and Monteggia, 2013), which will be briefly discussed below.

3.3. Class I HDACs

The members of the class I HDAC family share high homology in the deacetylase domain; yet, each HDAC member forms a variety of corepressor complexes depending on cellular context. For example, HDAC1 and HDAC2 are often found to interact with one other and associate with Sin3A, CoREST, and the nucleosome remodeling and histone deacetylation (NURD). In contrast, HDAC3 is found in a complex containing nuclear receptor corepressor (NCoR) and silencing mediator of retinoic and thyroid hormone receptor (SMRT). To date, the identity of corepressor complex for HDAC8 is not fully understood.

3.4. HDAC1 and HDAC2

HDAC1 and HDAC2 have a high degree of sequence homology (86% identity) and differ only within short stretches of their N- and C-termini, suggesting functional redundancy. However, constitutive deletion of either *Hdac1* or *Hdac2* in mice resulted in lethality. Constitutive *Hdac1* knockout mice displayed severe proliferation defects and general growth retardation, leading to embryonic death (Lagger et al., 2002; Montgomery et al., 2007). Null *Hdac2* mice were unable to survive beyond 24 h after birth due to severe cardiac malformations (Montgomery et al., 2007; Trivedi et al., 2007). These observations indicate that HDAC1 and HDAC2 possess distinct roles and do not necessarily share full functional redundancy during development despite their high amino acid sequence identity.

To delineate the cellular functions of HDAC1 and HDAC2 in the CNS, we investigated their impact on synaptic transmission using primary hippocampal cultures and found distinct contributions to excitatory neurotransmission that were dependent on the developmental stage of the neurons (Akhtar et al., 2009). In immature hippocampal neurons, loss of both *Hdac1* and *Hdac2* together, but not individually, resulted in an increase in spontaneous excitatory neurotransmission that was accompanied by increased synapse numbers indicating facilitated maturation of excitatory synapses. In contrast, *Hdac2* deletion in mature hippocampal neurons, but not *Hdac1*, results in a decrease in basal excitatory neurotransmission without alterations in synapse numbers or cell viability. These in vitro data indicate a developmental switch in the functions of HDAC1 and HDAC2 in that HDAC1 and HDAC2 in immature neurons are negative drivers for the maturation of excitatory synaptic networks, whereas HDAC2, but not HDAC1, in mature neurons is necessary to maintain basal neurotransmission.

As discussed earlier, while pharmacological approaches in vivo suggested that HDACs were negative regulators of long term memory formation, these studies do not provide a clear view as to whether individual HDACs contribute different or redundant roles in hippocampal-dependent learning and memory. In a recent work, Guan et al. demonstrated that mice overexpressing a 2–3 fold increase in HDAC2 displayed impaired memory formation in the fear conditioning paradigm and the Morris water maze, while conversely conditional *Hdac2* knockout mice had facilitated memory formation in these behavioral tests. The conditional *Hdac2* mice were also shown to have increased dendritic spine density and enhanced LTP, suggesting possible correlates to the behavioral enhancement of learning and memory. In contrast, overexpression of HDAC1 did not alter learning and memory or the cellular correlates, suggesting a specificity of HDAC2 to the learning and memory phenotypes. We recently generated conditional *Hdac2*, as well as *Hdac1*, single gene knockout mice lacking the respective gene in broad forebrain regions during postnatal development. We tested these mice in an array of behavioral tests to assess whether all types of learning and memory were enhanced in the *Hdac2* knockout mice or whether there was specificity to the behavioral effect, as well as further characterizing the conditional *Hdac1* knockout mice. We found that conditional *Hdac2* knockout mice, but not conditional *Hdac1*, had enhancements in fear associated learning and memory, as well as in extinction learning and conditioned taste aversion learning (Morris et al., 2013). However, the conditional *Hdac2* knockout mice had normal episodic memory in spatial and novel object recognition tasks, suggesting that inhibition of HDAC2 is sufficient to facilitate performances in specific forms of learning and

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memory. While these data demonstrate that HDAC2 is involved in hippocampal dependent learning and memory, the mechanisms underlying this cognitive enhancement are unknown. The earlier observation that elevated histone H3 acetylation occurred transiently during consolidation of memory implicates a relaxed chromatin structure and subsequent activation of genes (Levenson et al., 2004). It is reasonable to speculate that HDAC2 inhibition, may alter chromatin structure in a similar manner and activate gene expression. Supporting this notion, hyper-acetylation of histones at the *Egr1* and *Creb* promoter regions were documented concomitant with increased protein expression of the respective genes in the hippocampus of *Hdac2* knockout mice (Guan et al., 2009). Intriguingly, a recent study demonstrated elevated levels of HDAC2 expression in the CA1 subregion of hippocampus in a mouse model of neurodegeneration, which coincided with increased occupancy of HDAC2 and decreased histone acetylation at promoters of synaptic plasticity related genes, as well as decreases in their mRNA expression (Graff et al., 2012). Importantly, a manipulation to reduce elevated HDAC2 levels normalized the molecular alterations observed in the mouse model of neurodegeneration and alleviated memory deficits. Thus, selective inhibition of HDAC2 may hold promise as a therapeutic target to counteract cognitive impairments presented in neurodegenerative disorders.

3.5. HDAC3

The HDAC3 gene is also a member of the class I family although its role in the brain has only recently started to be examined. HDAC3 has been shown to form repressor complexes with two closely related corepressors, nuclear receptor corepressor (NCoR) and the silencing mediator of retinoic acid and thyroid hormone receptors (SMRT) (Yang and Seto, 2008). This contrasts to HDAC1 and HDAC2, which are generally found in Sin3A, CoREST, NuRD-mediated complexes. Thus, it is plausible that differential corepressor association drives specificity of individual HDACs in the class I family. In recent studies, McQuown et al. reported that mice with localized deletion of *Hdac3* in the CA1 subregion of the hippocampus displayed enhanced long-term memory in spatial object recognition paradigm, indicating HDAC3 as well may also act as a negative regulator of learning and memory (McQuown et al., 2011). In addition, the localized deletion of *Hdac3* resulted in increased acetylation of histone H4 at the lysine 8 residue as well as increased expression of the *Nr4a2* gene in the hippocampus. The authors went on to show that intrahippocampal delivery of siRNA targeting the *Nr4a2* gene in mice lacking *Hdac3* in the CA1 subregion attenuated the long-term memory enhancement. These data suggest that HDAC3 may regulate long-term memory formation by altering chromatin environments and fine-tuning expression of *Nr4a2* gene.

In addition to the role of HDAC3 in hippocampal learning and memory, HDAC3 has been implicated as a negative regulator for the formation of cocaine associated memory formation (Rogge et al., 2013). Regional deletion of *Hdac3* in the nucleus accumbens facilitated acquisition of cocaine-induced conditioned place preference, and increased *Nr4a2* gene expression, which likely resulted from a decrease in *Nr4a2* gene promoter occupancy by HDAC3 as well as an increase in histone H4 lysine 8 acetylation. Taken together, these recent reports suggest that HDAC3 is involved in hippocampal long-term as well as psychomotor stimulants induced memory formation by altering chromatin status at the specific gene promoter, *Nr4a2*.

3.6. HDAC8

HDAC8 is also a member of the class I HDAC family, however the components of the repressor complex containing HDAC8 are not as well delineated and little is known about the role of this HDAC in CNS function. HDAC8 is widely expressed in the brain, and differs in sequence identity much more than the rest of members in the class I family, suggesting it may have a distinct role in the brain compared to HDAC1, 2 and 3. Future work is necessary to elucidate the role of this HDAC in the CNS.

3.7. Class II HDAC

A few studies have started to examine the role of class II HDACs in the CNS; thus, we will briefly summarize their functions in this review. Recently generated conditional knockout mice with a brain-specific deletion of *Hdac4*, which shares strong amino acid sequence identity with *Hdac5*, were characterized and found to have impairments in hippocampal-dependent memory formation as well as deficits in LTP without impacting basal synaptic transmission (Kim et al., 2012). In the same study, constitutive *Hdac5* knockouts were shown to have normal locomotor activity, motor coordination, anxiety, and learning and memory as well as intact basal synaptic transmission, suggesting distinct roles for these HDACs in learning and memory. In separate work, HDAC5 has been linked to the action of the psychomotor stimulant, cocaine. Chronic cocaine has been shown to induce phosphorylation of HDAC5 and trigger its nuclear export (Renthal et al., 2007). Transient overexpression of HDAC5 in the nucleus accumbens attenuates the locomotor response to chronic cocaine treatments, whereas loss of HDAC5 results in hypersensitivity to chronic cocaine. Collectively, this data suggests that HDAC5 does not play a significant role in learning and memory as well as several other behavioral measures under normal conditions but may be an important factor in certain disease states such as addiction.

3.8. Corepressors

Five corepressor proteins, Sin3a/3b, NCoR, SMRT, CoREST, and NURD have been reported to interact with the class I HDAC family, with their biochemical associations well characterized (Perissi et al., 2010; Yang and Seto, 2008). These corepressors do not possess DNA binding or chromatin remodeling activities, rather they serve as scaffolding proteins to help stabilize assembly of each repressor complex. Constitutive deletion of Sin3a/3b, NCoR, or SMRT in mice results in embryonic lethality and defective cardiovascular and erythrocyte development during embryogenesis, indicating the distinct and necessary roles of these nuclear scaffolding proteins during development (Dannenberg et al., 2005; David et al., 2008; Jepsen et al., 2008, 2000). More recently, NCoR and SMRT were reported to participate in cell fate determination of neural stem cells (Hermanson et al., 2002). In the current issue, Schoch and Able discuss the roles of these corepressors in the adult brain and whether chromatin-based alterations are underlying mechanisms for adult brain function in the context of activity-dependent transcription and cognition.

4. Conclusions

Accumulating evidence has uncovered essential roles for transcription repressors and the components of their repressor complexes in many aspects of brain function. Transcriptional repression takes place only when DNA-binding proteins, chromatin-remodeling enzymes, and corepressors are assembled together at target gene promoters. However, when the gene encoding each component in a repressor complex has been individually deleted, the resultant phenotypes were not necessarily similar and in some cases have been quite distinct. One such example involves HDAC2 and MeCP2, which are the components of a Sin3a-containing

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repressor complex. Mice lacking *Hdac2* in the broad-forebrain display enhanced performance in many forms of learning and memory without affecting other behavioral phenotypes, whereas *Mecp2*-deficient mice in the same brain region manifest a variety of behavioral deficits (Gemelli et al., 2006; Morris et al., 2013). In particular, the *Mecp2*-deficient mice performed worse in cue-dependent fear conditioning (amygdala-dependent learning) with a trend in impaired context-dependent fear conditioning (hippocampal-dependent learning). One possible reason for this disparity could be the corepressor-dependent action of each factor. Each behavioral phenotype might be attributed to a particular set of changes in gene expression defined by a distinct corepressor. HDAC2 is found not only with Sin3a, but also in NURD and CoREST-mediated repressor complexes (Fig. 1) (Ballas et al., 2001; Tong et al., 1998; You et al., 2001; Zhang et al., 1998). Similarly, some studies report the presence of MeCP2 with CoREST in addition to Sin3A (Ballas et al., 2005; Lunyak et al., 2002). Moreover, recent studies demonstrated association of MeCP2 with NCoR and SMRT complexes (Ebert et al., 2013; Lyst et al., 2013). This latter association is functionally significant as mice expressing a mutant MeCP2 that either lacks the ability to bind NCoR or results in constitutive binding of NCoR, reproduced some RTT-like phenotypes. Therefore, careful consideration of transcriptional repressors and their associated chromatin modifiers as unique corepressor units may unveil clearer roles of these complexes in the adult CNS.

Alternatively, we cannot exclude the possibility that the ability of HDACs to target non-histone substrates may attribute to phenotypes of *Hdac2* knockout, which are distinct from MeCP2-deficient animals. Acetylation of non-histone proteins, such as transcription factors, NF-kB, GATA, and p53, is a functionally significant post-translation modification that regulates their transcriptional activity. Loss of HDAC1 and HDAC2 have been shown to alter levels of acetylation of the non-histone proteins, leading to abnormal phenotypes in a wide array of tissues, including cardiomyocyte proliferation, epidermal differentiation, and Schwann cell differentiation (Kelly and Cowley, 2013). Thus, examination of non-histone proteins in the context of adult brain lacking HDAC2 and MeCP2 may tease out their specific roles.

Recent mouse studies strongly support HDAC2 playing a predominate role in the regulation of learning and memory among HDACs in the class I family. Despite the fact that HDAC1 and HDAC2 share high sequence identity, it is somewhat surprising that HDAC1 does not possess functional redundancy to HDAC2, at least in the realm of learning and memory. Notably, HDAC1 is expressed in both neurons and glia and HDAC2 predominantly in neurons in the adult rodent brain (MacDonald and Roskams, 2008). In separate studies, western blot analysis revealed similar levels of expression of HDAC1 and HDAC2 in specific brain regions of adult mice (Guan et al., 2009; Morris et al., 2013). Considering the high sequence similarity and the presence of both HDAC1 and HDAC2 in the brain, the preferential role of HDAC2 in the learning and memory may depend on the association of distinct corepressors such as Sin3A, NCoR, CoREST, NURD, with the individual HDACs (Fig. 1). An HDAC2 repressor complex composed of a specific combination of factors may give rise to specific gene regulation essential for enhanced learning and memory. Given that all HDACs are widely expressed at varying levels in the adult brain, it will be important to investigate the role for each individual HDAC in behavioral and cognitive functions.

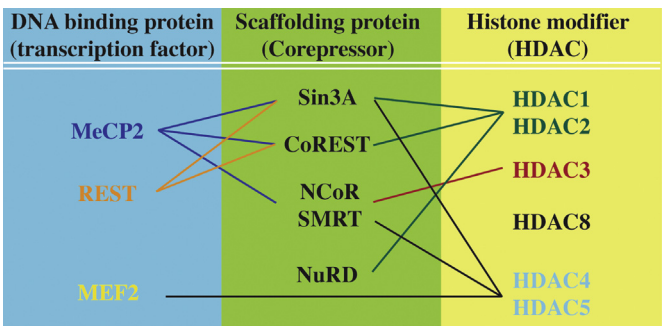

Fig. 1. Composition of repressor complexes in the adult brain.

In light of the therapeutic potential for HDAC inhibitors in enhancing learning and memory, and as putative therapeutic targets for neurodegenerative diseases, it is important to assess if chronic treatment with HDAC inhibitors produces aversive unwanted side effects (Chuang et al., 2009). Many inhibitors target the catalytic domain of HDACs and are likely to block the activity of multiple HDACs, rather than a specific HDAC subtype. In mature hippocampal neurons, chronic inhibition of HDAC activity results in impaired excitatory neurotransmission (Akhtar et al., 2009). In separate work, chronic infusion of SAHA, a class I HDAC inhibitor, to the amygdala led to behavioral abnormalities including deficits in learning and memory as well as heightened anxiety (Adachi et al., 2009). Additionally, specificity of the HDAC inhibitors is a key issue for therapeutic application. While studies from transgenic mice indicate the beneficial role of HDAC2 and more recently HDAC3 in memory formation, *Hdac4* knockout mice revealed surprisingly deficits in learning and memory. Taken together, these data suggest that the therapeutic application of HDAC inhibitors, in particular those requiring chronic treatments, should be carefully examined as they may potentially produce undesirable psychiatric side effects.

As further research elucidates the role of individual components of transcriptional repressor complexes in the CNS, this information will hopefully start to provide information relevant to drug discovery to specific disorders. The identification of these transcriptional processes in the brain as well as in the disease state may provide a more complete approach towards processes that go awry during certain disorders as well as allow one to hone in on individual factors that may prove to be therapeutic targets. The work outlined in this review represents an exciting approach to understanding transcriptional repression in the brain and sets the groundwork for delineating these processes further.

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References

Adachi, M., Autry, A.E., Covington 3rd, H.E., Monteggia, L.M., 2009. MeCP2-mediated transcription repression in the basolateral amygdala may underlie heightened anxiety in a mouse model of Rett syndrome. J. Neurosci. 29, 4218–4227.

Akhtar, M.W., Raingo, J., Nelson, E.D., Montgomery, R.L., Olson, E.N., Kavalali, E.T., Monteggia, L.M., 2009. Histone deacetylases 1 and 2 form a developmental switch that controls excitatory synapse maturation and function. J. Neurosci. 29, 8288–8297.

Amir, R.E., Van den Veyver, I.B., Wan, M., Tran, C.Q., Francke, U., Zoghbi, H.Y., 1999. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat. Genet. 23, 185–188.

Andres, M.E., Burger, C., Peral-Rubio, M.J., Battaglioli, E., Anderson, M.E., Grimes, J., Dallman, J., Ballas, N., Mandel, G., 1999. CoREST: a functional corepressor required for regulation of neural-specific gene expression. Proc. Natl. Acad. Sci. U. S. A. 96, 9873–9878.

Aoki, H., Hara, A., Era, T., Kunisada, T., Yamada, Y., 2012. Genetic ablation of Rest leads to in vitro-specific derepression of neuronal genes during neurogenesis. Development 139, 667–677.

Ballas, N., Battaglioli, E., Atouf, F., Andres, M.E., Chenoweth, J., Anderson, M.E., Burger, C., Moniwa, M., Davie, J.R., Bowers, W.J., Federoff, H.J., Rose, D.W.,

Rosenfeld, M.G., Brehm, P., Mandel, G., 2001. Regulation of neuronal traits by a novel transcriptional complex. Neuron 31, 353–365.
Ballas, N., Grunseich, C., Lu, D.D., Speh, J.C., Mandel, G., 2005. REST and its co-repressors mediate plasticity of neuronal gene chromatin throughout neurogenesis. Cell 121, 645–657.
Bredy, T.W., Barad, M., 2008. The histone deacetylase inhibitor valproic acid enhances acquisition, extinction, and reconsolidation of conditioned fear. Learn. Mem. 15, 39–45.
Chahrour, M., Jung, S.Y., Shaw, C., Zhou, X., Wong, S.T., Qin, J., Zoghbi, H.Y., 2008. MeCP2, a key contributor to neurological disease, activates and represses transcription. Science 320, 1224–1229.
Chao, H.T., Chen, H., Samaco, R.C., Xue, M., Chahrour, M., Yoo, J., Neul, J.L., Gong, S., Lu, H.C., Heintz, N., Ekker, M., Rubenstein, J.L., Noebels, J.L., Rosenmund, C., Zoghbi, H.Y., 2010. Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. Nature 468, 263–269.
Chen, R.Z., Akbarian, S., Tudor, M., Jaenisch, R., 2001. Deficiency of methyl-CpG binding protein-2 in CNS neurons results in a Rett-like phenotype in mice. Nat. Genet. 27, 327–331.
Chen, W.G., Chang, Q., Lin, Y., Meissner, A., West, A.E., Griffith, E.C., Jaenisch, R., Greenberg, M.E., 2003. Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. Science 302, 885–889.
Chong, J.A., Tapia-Ramirez, J., Kim, S., Toledo-Aral, J.J., Zheng, Y., Boutros, M.C., Altshuller, Y.M., Frohman, M.A., Kraner, S.D., Mandel, G., 1995. REST: a mammalian silencer protein that restricts sodium channel gene expression to neurons. Cell 80, 949–957.
Chuang, D.M., Leng, Y., Marinova, Z., Kim, H.J., Chiu, C.T., 2009. Multiple roles of HDAC inhibition in neurodegenerative conditions. Trends Neurosci. 32, 591–601.
Collins, A.L., Levenson, J.M., Vilaythong, A.P., Richman, R., Armstrong, D.L., Noebels, J.L., David Sweatt, J., Zoghbi, H.Y., 2004. Mild overexpression of MeCP2 causes a progressive neurological disorder in mice. Hum. Mol. Genet. 13, 2679–2689.
Couvert, P., Bienvenu, T., Aquaviva, C., Poirier, K., Moraine, C., Gendrot, C., Verloes, A., Andres, C., Le Fevre, A.C., Souville, I., Steffann, J., des Portes, V., Ropers, H.H., Yntema, H.G., Fryns, J.P., Briault, S., Chelly, J., Cherif, B., 2001. MECP2 is highly mutated in X-linked mental retardation. Hum. Mol. Genet. 10, 941–946.
Covey, M.V., Streb, J.W., Spektor, R., Ballas, N., 2012. REST regulates the pool size of the different neural lineages by restricting the generation of neurons and oligodendrocytes from neural stem/progenitor cells. Development 139, 2878–2890.
Dani, V.S., Chang, Q., Maffei, A., Turrigiano, G.G., Jaenisch, R., Nelson, S.B., 2005. Reduced cortical activity due to a shift in the balance between excitation and inhibition in a mouse model of Rett syndrome. Proc. Natl. Acad. Sci. U. S. A. 102, 12560–12565.
Dannenberg, J.H., David, G., Zhong, S., van der Torre, J., Wong, W.H., Depinho, R.A., 2005. mSin3A corepressor regulates diverse transcriptional networks governing normal and neoplastic growth and survival. Genes Dev. 19, 1581–1595.
David, G., Grandinetti, K.B., Finnerty, P.M., Simpson, N., Chu, G.C., Depinho, R.A., 2008. Specific requirement of the chromatin modifier mSin3B in cell cycle exit and cellular differentiation. Proc. Natl. Acad. Sci. U. S. A. 105, 4168–4172.
Deng, V., Matagne, V., Banine, F., Frerking, M., Ohliger, P., Budden, S., Pevsner, J., Dissen, G.A., Sherman, L.S., Ojeda, S.R., 2007. FXYD1 is an MeCP2 target gene overexpressed in the brains of Rett syndrome patients and Mecp2-null mice. Hum. Mol. Genet. 16, 640–650.
Ebert, D.H., Gabel, H.W., Robinson, N.D., Kastan, N.R., Hu, L.S., Cohen, S., Navarro, A.J., Lyst, M.J., Ekiert, R., Bird, A.P., Greenberg, M.E., 2013. Activity-dependent phosphorylation of MeCP2 threonine 308 regulates interaction with NCoR. Nature 499, 341–345.
Fyffe, S.L., Neul, J.L., Samaco, R.C., Chao, H.T., Ben-Shachar, S., Moretti, P., McGill, B.E., Goulding, E.H., Sullivan, E., Tecott, L.H., Zoghbi, H.Y., 2008. Deletion of Mecp2 in Sim1-expressing neurons reveals a critical role for MeCP2 in feeding behavior, aggression, and the response to stress. Neuron 59, 947–958.
Gaston, K., Jayaraman, P.S., 2003. Transcriptional repression in eukaryotes: repressors and repression mechanisms. Cell. Mol. Life Sci. 60, 721–741.
Gemelli, T., Berton, O., Nelson, E.D., Perrotti, L.I., Jaenisch, R., Monteggia, L.M., 2006. Postnatal loss of methyl-CpG binding protein 2 in the forebrain is sufficient to mediate behavioral aspects of Rett syndrome in mice. Biol. Psychiatry 59, 468–476.
Graff, J., Rei, D., Guan, J.S., Wang, W.Y., Seo, J., Hennig, K.M., Nieland, T.J., Fass, D.M., Kao, P.F., Kahn, M., Su, S.C., Samiei, A., Joseph, N., Haggarty, S.J., Delalle, I., Tsai, L.H., 2012. An epigenetic blockade of cognitive functions in the neurodegenerating brain. Nature 483, 222–226.
Guan, J.S., Haggarty, S.J., Giacometti, E., Dannenberg, J.H., Joseph, N., Gao, J., Nieland, T.J., Zhou, Y., Wang, X., Mazitschek, R., Bradner, J.E., DePinho, R.A., Jaenisch, R., Tsai, L.H., 2009. HDAC2 negatively regulates memory formation and synaptic plasticity. Nature 459, 55–60.
Guy, J., Hendrich, B., Holmes, M., Martin, J.E., Bird, A., 2001. A mouse Mecp2-null mutation causes neurological symptoms that mimic Rett syndrome. Nat. Genet. 27, 322–326.
Haberland, M., Montgomery, R.L., Olson, E.N., 2009. The many roles of histone deacetylases in development and physiology: implications for disease and therapy. Nat. Rev. Genet. 10, 32–42.
Haettig, J., Stefanko, D.P., Multani, M.L., Figueroa, D.X., McQuown, S.C., Wood, M.A., 2011. HDAC inhibition modulates hippocampus-dependent long-term memory for object location in a CBP-dependent manner. Learn. Mem. 18, 71–79.
Hawk, J.D., Bookout, A.L., Poplawski, S.G., Bridi, M., Rao, A.J., Sulewski, M.E., Kroener, B.T., Manglesdorf, D.J., Abel, T., 2012. NR4A nuclear receptors support memory enhancement by histone deacetylase inhibitors. J. Clin. Investig. 122, 3593–3602.
Hawk, J.D., Florian, C., Abel, T., 2011. Post-training intrahippocampal inhibition of class I histone deacetylases enhances long-term object-location memory. Learn. Mem. 18, 367–370.
Hermanson, O., Jepsen, K., Rosenfeld, M.G., 2002. N-CoR controls differentiation of neural stem cells into astrocytes. Nature 419, 934–939.
Hoch, R.V., Rubenstein, J.L., Pleasure, S., 2009. Genes and signaling events that establish regional patterning of the mammalian forebrain. Semin. Cell Dev. Biol. 20, 378–386.
Iwase, S., Lan, F., Bayliss, P., de la Torre-Ubieta, L., Huarte, M., Qi, H.H., Whetstine, J.R., Bonni, A., Roberts, T.M., Shi, Y., 2007. The X-linked mental retardation gene SMCX/JARID1C defines a family of histone H3 lysine 4 demethylases. Cell 128, 1077–1088.
Jepsen, K., Gleiberman, A.S., Shi, C., Simon, D.I., Rosenfeld, M.G., 2008. Cooperative regulation in development by SMRT and FOXP1. Genes Dev. 22, 740–745.
Jepsen, K., Hermanson, O., Onami, T.M., Gleiberman, A.S., Lunyak, V., McEvilly, R.J., Kurokawa, R., Kumar, V., Liu, F., Seto, E., Hedrick, S.M., Mandel, G., Glass, C.K., Rose, D.W., Rosenfeld, M.G., 2000. Combinatorial roles of the nuclear receptor corepressor in transcription and development. Cell 102, 753–763.
Jones, P.L., Veenstra, G.J., Wade, P.A., Vermaak, D., Kass, S.U., Landsberger, N., Strouboulis, J., Wolffe, A.P., 1998. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. Nat. Genet. 19, 187–191.
Kelly, R.D., Cowley, S.M., 2013. The physiological roles of histone deacetylase (HDAC) 1 and 2: complex co-stars with multiple leading parts. Biochem. Soc. Trans. 41, 741–749.
Kim, M.S., Akhtar, M.W., Adachi, M., Mahgoub, M., Bassel-Duby, R., Kavalali, E.T., Olson, E.N., Monteggia, L.M., 2012. An essential role for histone deacetylase 4 in synaptic plasticity and memory formation. J. Neurosci. 32, 10879–10886.
Kleefstra, T., Yntema, H.G., Oudakker, A.R., Romein, T., Sistermans, E., Nillessen, W., van Bokhoven, H., de Vries, B.B., Hamel, B.C., 2002. De novo MECP2 frameshift mutation in a boy with moderate mental retardation, obesity and gynaecomastia. Clin. Genet. 61, 359–362.
Lagger, G., O'Carroll, D., Rembold, M., Khier, H., Tischler, J., Weitzer, G., Schuettengruber, B., Hauser, C., Brunmeir, R., Jenuwein, T., Seiser, C., 2002. Essential function of histone deacetylase 1 in proliferation control and CDK inhibitor repression. EMBO J. 21, 2672–2681.
Levenson, J.M., O'Riordan, K.J., Brown, K.D., Trinh, M.A., Molfese, D.L., Sweatt, J.D., 2004. Regulation of histone acetylation during memory formation in the hippocampus. J. Biol. Chem. 279, 40545–40559.
Lewis, J.D., Meehan, R.R., Henzel, W.J., Maurer-Fogy, I., Jeppesen, P., Klein, F., Bird, A., 1992. Purification, sequence, and cellular localization of a novel chromosomal protein that binds to methylated DNA. Cell 69, 905–914.
Li, W., Pozzo-Miller, L., 2012. Beyond widespread deletions to model Rett syndrome: conditional spatio-temporal knockout, single-point mutations and transgenic rescue mice. Autism Open Access 2012, 5.
Li, Y., Wang, H., Muffat, J., Cheng, A.W., Orlando, D.A., Loven, J., Kwok, S.M., Feldman, D.A., Bateup, H.S., Gao, Q., Hockemeyer, D., Mitalipova, M., Lewis, C.A., Vander Heiden, M.G., Sur, M., Young, R.A., Jaenisch, R., 2013. Global transcriptional and translational repression in human-embryonic-stem-cell-derived Rett syndrome neurons. Cell Stem Cell 13, 446–458.
Liu, H., Hu, Q., Kaufman, A., D'Ercole, A.J., Ye, P., 2008. Developmental expression of histone deacetylase 11 in the murine brain. J. Neurosci. Res. 86, 537–543.
Lopez-Atalaya, J.P., Ito, S., Valor, L.M., Benito, E., Barco, A., 2013. Genomic targets, and histone acetylation and gene expression profiling of neural HDAC inhibition. Nucleic Acids Res. 41, 8072–8084.
Lunyak, V.V., Burgess, R., Prefontaine, G.G., Nelson, C., Sze, S.H., Chenoweth, J., Schwartz, P., Pevzner, P.A., Glass, C., Mandel, G., Rosenfeld, M.G., 2002. Corepressor-dependent silencing of chromosomal regions encoding neuronal genes. Science 298, 1747–1752.
Lyst, M.J., Ekiert, R., Ebert, D.H., Merusi, C., Nowak, J., Selfridge, J., Guy, J., Kastan, N.R., Robinson, N.D., de Lima Alves, F., Rappsilber, J., Greenberg, M.E., Bird, A., 2013. Rett syndrome mutations abolish the interaction of MeCP2 with the NCoR/SMRT co-repressor. Nat. Neurosci. 16, 898–902.
MacDonald, J.L., Roskams, A.J., 2008. Histone deacetylases 1 and 2 are expressed at distinct stages of neuro-glial development. Dev. Dyn. 237, 2256–2267.
Martinowich, K., Hattori, D., Wu, H., Fouse, S., He, F., Hu, Y., Fan, G., Sun, Y.E., 2003. DNA methylation-related chromatin remodeling in activity-dependent BDNF gene regulation. Science 302, 890–893.
McNulty, S.E., Barrett, R.M., Vogel-Ciernia, A., Malvaez, M., Hernandez, N., Davatolhagh, M.F., Matheos, D.P., Schiffman, A., Wood, M.A., 2012. Differential roles for Nr4a1 and Nr4a2 in object location vs. object recognition long-term memory. Learn. Mem. 19, 588–592.
McQuown, S.C., Barrett, R.M., Matheos, D.P., Post, R.J., Rogge, G.A., Alenghat, T., Mullican, S.E., Jones, S., Rusche, J.R., Lazar, M.A., Wood, M.A., 2011. HDAC3 is a critical negative regulator of long-term memory formation. J. Neurosci. 31, 764–774.
Meehan, R.R., Lewis, J.D., Bird, A.P., 1992. Characterization of MeCP2, a vertebrate DNA binding protein with affinity for methylated DNA. Nucleic Acids Res. 20, 5085–5092.
Miyake, K., Hirasawa, T., Soutome, M., Itoh, M., Goto, Y., Endoh, K., Takahashi, K., Kudo, S., Nakagawa, T., Yokoi, S., Taira, T., Inazawa, J., Kubota, T., 2011. The protocadherins, PCDHB1 and PCDH7, are regulated by MeCP2 in neuronal cells

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and brain tissues: implication for pathogenesis of Rett syndrome. BMC Neurosci. 12, 81.
Montgomery, R.L., Davis, C.A., Potthoff, M.J., Haberland, M., Fielitz, J., Qi, X., Hill, J.A., Richardson, J.A., Olson, E.N., 2007. Histone deacetylases 1 and 2 redundantly regulate cardiac morphogenesis, growth, and contractility. Genes Dev. 21, 1790–1802.
Moretti, P., Levenson, J.M., Battaglia, F., Atkinson, R., Teague, R., Antalffy, B., Armstrong, D., Arancio, O., Sweatt, J.D., Zoghbi, H.Y., 2006. Learning and memory and synaptic plasticity are impaired in a mouse model of Rett syndrome. J. Neurosci. 26, 319–327.
Morris, M.J., Mahgoub, M., Na, E.S., Pranav, H., Monteggia, L.M., 2013. Loss of histone deacetylase 2 improves working memory and accelerates extinction learning. J. Neurosci. 33, 6401–6411.
Morris, M.J., Monteggia, L.M., 2013. Unique functional roles for class I and class II histone deacetylases in central nervous system development and function. Int. J. Dev. Neurosci. 31, 370–381.
Na, E.S., Nelson, E.D., Kavalali, E.T., Monteggia, L.M., 2012. The impact of MeCP2 loss- or gain-of-function on synaptic plasticity. Neuropsychopharmacology 38, 212–219.
Nan, X., Ng, H.H., Johnson, C.A., Laherty, C.D., Turner, B.M., Eisenman, R.N., Bird, A., 1998. Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. Nature 393, 386–389.
Nelson, E.D., Kavalali, E.T., Monteggia, L.M., 2006. MeCP2-dependent transcriptional repression regulates excitatory neurotransmission. Curr. Biol. 16, 710–716.
Noh, K.M., Hwang, J.Y., Follenzi, A., Athanasiadou, R., Miyawaki, T., Greally, J.M., Bennett, M.V., Zukin, R.S., 2012. Repressor element-1 silencing transcription factor (REST)-dependent epigenetic remodeling is critical to ischemia-induced neuronal death. Proc. Natl. Acad. Sci. U. S. A. 109, E962–E971.
Nuber, U.A., Kriaucionis, S., Roloff, T.C., Guy, J., Selfridge, J., Steinhoff, C., Schulz, R., Lipkowitz, B., Ropers, H.H., Holmes, M.C., Bird, A., 2005. Up-regulation of glucocorticoid-regulated genes in a mouse model of Rett syndrome. Hum. Mol. Genet. 14, 2247–2256.
Palm, K., Belluardo, N., Metsis, M., Timmusk, T., 1998. Neuronal expression of zinc finger transcription factor REST/NRSF/XBR gene. J. Neurosci. 18, 1280–1296.
Pelka, G.J., Watson, C.M., Radziewic, T., Hayward, M., Lahooti, H., Christodoulou, J., Tam, P.P., 2006. Mecp2 deficiency is associated with learning and cognitive deficits and altered gene activity in the hippocampal region of mice. Brain 129, 887–898.
Perissi, V., Jepsen, K., Glass, C.K., Rosenfeld, M.G., 2010. Deconstructing repression: evolving models of co-repressor action. Nat. Rev. Genet. 11, 109–123.
Renthal, W., Maze, I., Krishnan, V., Covington 3rd, H.E., Xiao, G., Kumar, A., Russo, S.J., Graham, A., Tsankova, N., Kippin, T.E., Kerstetter, K.A., Neve, R.L., Haggarty, S.J., McKinsey, T.A., Bassel-Duby, R., Olson, E.N., Nestler, E.J., 2007. Histone deacetylase 5 epigenetically controls behavioral adaptations to chronic emotional stimuli. Neuron 56, 517–529.
Rodenas-Ruano, A., Chavez, A.E., Cossio, M.J., Castillo, P.E., Zukin, R.S., 2012. REST-dependent epigenetic remodeling promotes the developmental switch in synaptic NMDA receptors. Nat. Neurosci. 15, 1382–1390.
Rogge, G.A., Singh, H., Dang, R., Wood, M.A., 2013. HDAC3 is a negative regulator of cocaine-context-associated memory formation. J. Neurosci. 33, 6623–6632.
Schoenherr, C.J., Anderson, D.J., 1995. The neuron-restrictive silencer factor (NRSF): a coordinate repressor of multiple neuron-specific genes. Science 267, 1360–1363.
Schoenherr, C.J., Paquette, A.J., Anderson, D.J., 1996. Identification of potential target genes for the neuron-restrictive silencer factor. Proc. Natl. Acad. Sci. U. S. A. 93, 9881–9886.
Shahbazian, M., Young, J., Yuva-Paylor, L., Spencer, C., Antalffy, B., Noebels, J., Armstrong, D., Paylor, R., Zoghbi, H., 2002. Mice with truncated MeCP2 recapitulate many Rett syndrome features and display hyperacetylation of histone H3. Neuron 35, 243–254.
Skene, P.J., Illingworth, R.S., Webb, S., Kerr, A.R., James, K.D., Turner, D.J., Andrews, R., Bird, A.P., 2010. Neuronal MeCP2 is expressed at near histone-octamer levels and globally alters the chromatin state. Mol. Cell 37, 457–468.
Suter, B., Treadwell-Deering, D., Zoghbi, H.Y., Glaze, D.G., Neul, J.L., 2013. Brief Report: MECP2 mutations in people without Rett syndrome. J. Autism Dev. Disord. in press.
Tahiliani, M., Mei, P., Fang, R., Leonor, T., Rutenberg, M., Shimizu, F., Li, J., Rao, A., Shi, Y., 2007. The histone H3K4 demethylase SMCX links REST target genes to X-linked mental retardation. Nature 447, 601–605.
Tong, J.K., Hassig, C.A., Schnitzler, G.R., Kingston, R.E., Schreiber, S.L., 1998. Chromatin deacetylation by an ATP-dependent nucleosome remodelling complex. Nature 395, 917–921.
Trivedi, C.M., Luo, Y., Yin, Z., Zhang, M., Zhu, W., Wang, T., Floss, T., Goettlicher, M., Noppinger, P.R., Wurst, W., Ferrari, V.A., Abrams, C.S., Gruber, P.J., Epstein, J.A., 2007. Hdac2 regulates the cardiac hypertrophic response by modulating Gsk3 beta activity. Nat. Med. 13, 324–331.
Tudor, M., Akbarian, S., Chen, R.Z., Jaenisch, R., 2002. Transcriptional profiling of a mouse model for Rett syndrome reveals subtle transcriptional changes in the brain. Proc. Natl. Acad. Sci. U. S. A. 99, 15536–15541.
Van Esch, H., Bauters, M., Ignatius, J., Jansen, M., Raynaud, M., Hollanders, K., Lugtenberg, D., Bienvenu, T., Jensen, L.R., Gecz, J., Moraine, C., Marynen, P., Fryns, J.P., Froyen, G., 2005. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. Am. J. Hum. Genet. 77, 442–453.
Vecsey, C.G., Hawk, J.D., Lattal, K.M., Stein, J.M., Fabian, S.A., Attner, M.A., Cabrera, S.M., McDonough, C.B., Brindle, P.K., Abel, T., Wood, M.A., 2007. Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB: CBP-dependent transcriptional activation. J. Neurosci. 27, 6128–6140.
Wang, X., Song, X., Glass, C.K., Rosenfeld, M.G., 2010. The long arm of long noncoding RNAs: roles as sensors regulating gene transcriptional programs. Cold Spring Harb. Perspect. Biol. 3 a003756.
Wang, Z., Zang, C., Cui, K., Schones, D.E., Barski, A., Peng, W., Zhao, K., 2009. Genome-wide mapping of HATs and HDACs reveals distinct functions in active and inactive genes. Cell 138, 1019–1031.
West, A.E., Greenberg, M.E., 2011. Neuronal activity-regulated gene transcription in synapse development and cognitive function. Cold Spring Harb. Perspect. Biol. 3.
Wonders, C.P., Anderson, S.A., 2006. The origin and specification of cortical interneurons. Nat. Rev. Neurosci. 7, 687–696.
Yamada, Y., Aoki, H., Kunisada, T., Hara, A., 2010. Rest promotes the early differentiation of mouse ESCs but is not required for their maintenance. Cell Stem Cell 6, 10–15.
Yang, X.J., Seto, E., 2008. The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. Nat. Rev. Mol. Cell Biol. 9, 206–218.
You, A., Tong, J.K., Grozinger, C.M., Schreiber, S.L., 2001. CoREST is an integral component of the CoREST- human histone deacetylase complex. Proc. Natl. Acad. Sci. U. S. A. 98, 1454–1458.
Zhang, Y., LeRoy, G., Seelig, H.P., Lane, W.S., Reinberg, D., 1998. The dermatomyositis-specific autoantigen Mi2 is a component of a complex containing histone deacetylase and nucleosome remodeling activities. Cell 95, 279–289.

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