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Transcriptional co-repressors and memory storage

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Abstract

Epigenetic modifications are a central mechanism for regulating chromatin structure and gene expression in the brain. A wide array of histone- and DNA-modifying enzymes have been identified as critical regulators of neuronal function, memory formation, and as causative agents in neurodevelopmental and neuropsychiatric disorders. Chromatin modifying enzymes are frequently incorporated into large multi-protein co-activator and co-repressor complexes, where the activity of multiple enzymes is both spatially and temporally coordinated. In this review, we discuss negative regulation of gene expression by corepressor complexes, and the role of co-repressors and their binding partners in neuronal function, memory, and disease.

Keywords

Epigenetics; Memory; Co-repressor; NCOR; SIN3A; Chromatin remodeling

Epigenetic modifications comprise a stable code that can exert a strong influence on the expression of the genome by regulating the biochemical and structural properties of chromatin. Epigenetic modifications are most often studied in the context of DNA methylation and post-translational modification of histones, but can include nucleosome remodeling and incorporation of histone variants (Kouzarides, 2007; Maze et al., 2013). Post-translational modification of histone N-terminal tails is a complex and tightly regulated process that has been linked to regulation of key aspects of gene expression including timing and levels of transcriptional activation, mRNA splicing, and poly-A site selection (Kouzarides, 2007; Maze et al., 2013; Sims et al., 2007; Zhou et al., 2012). Disruption of epigenetic regulation has been implicated in multiple neurodevelopmental, neuropsychiatric and neurodegenerative disorders (Abel and Zukin, 2008; Fischer et al., 2010; Peixoto and Abel, 2013). Much of the research in epigenetic regulation of cognition has focused on the regulation of co-activator complexes and histone acetyltransferase (HAT) enzymes involved in increasing acetylation of histone lysine residues, a mark often associated with increased chromatin accessibility and active gene expression (Abel and Zukin, 2008; Borrelli et al., 2008; Fischer et al., 2007; Peixoto and Abel, 2013). Fewer studies address positive and negative regulation of gene expression by lysine methylation of histones; a modification that

functions as a binding surface for protein interactions (Bannister and Kouzarides, 2011). Overall, little is known about how changes in histone acetylation and methylation mediate negative regulation of gene expression and silencing by co-repressor complexes.

Co-repressors assemble multi-protein complexes containing structural, chromatin-binding, and DNA- and histone-modifying enzymes that suppress transcription. Catalytic components are assembled around structural proteins, and bound to DNA or histones by chromatin-binding proteins (Fig 1A). Gene silencing is associated with the removal of activating epigenetic marks, such as acetylation or H3K4 methylation of histones; or through addition of repressive epigenetic marks including DNA methylation and histone methylation at H3K9, H3K27, and H3K36 (Bannister and Kouzarides, 2011). Co-repressor complexes frequently contain multiple catalytic components involved in both addition and removal of epigenetic modifications, suggesting that gene silencing may involve combinatorial or serial effects on modifications across multiple residues and substrates (Fig. 1B)(Bannister and Kouzarides, 2011; Kouzarides, 2007; Maze et al., 2013). Studies of histone modifications indicate that the presence of certain marks can regulate the modification of other residues, even across histones (Kouzarides, 2007). Thus, the diversity of catalytic activities within individual co-repressor complexes is likely a critical aspect of their function.

Early studies of co-repressor function in yeast and cell culture models found that co-repressors regulate critical cellular functions from cell growth to differentiation, signal transduction and apoptosis, but the functions of many co-repressors in the brain are very poorly understood (Kato et al., 2011; McDonel et al., 2009). Very few biochemical studies of co-repressor complexes have been conducted in neuronal cells. Much of our knowledge regarding the functional properties of co-repressors in mammalian systems has come from the fields of cancer research and developmental biology, where alterations in the function or localization of co-repressors were linked to aberrant regulation of growth, cell morphology, and tissue organization (Kumar et al., 2005; Lai and Wade, 2011; McDonel et al., 2009). In the adult brain, which is primarily populated with post-mitotic, terminally differentiated cells, we are only beginning to appreciate the important roles co-repressors play in signal transduction, plasticity, and cellular memory. It has been well established that epigenetic mechanisms are engaged by and critically important for mnemonic and cognitive functions in the brain. In the context of these uniquely neuronal processes, it is not reasonable to assume that the function and composition of corepressors in the brain are equivalent to those of non-neuronal tissues. Additionally, the expression of neuron-specific components of co-repressor complexes strongly hints at the existence of specialized functions for these complexes in the brain (Palm et al., 1998; Potts et al., 2011; Vogel-Ciernia et al., 2013). Multiple corepressors have been linked to dynamic changes in gene expression and neuronal activity-dependent regulation, but the specific roles co-repressors play in the brain are only starting to be uncovered (Chen et al., 2003; Ebert et al., 2013; Youn and Liu, 2000). Further studies of co-repressors and their function in neuronal tissue are needed to ascertain whether unique functions for these complexes exist within the nervous system, especially with regard to dynamic mechanisms of transcriptional repression/de-repression following neuronal activity.

The roles of co-repressor complexes in neural function and cognition are only starting to be uncovered. Many core and accessory components of co-repressor complexes have been linked to neurodevelopment and neurological disorders, but there is an overall lack of functional studies directly addressing the role of co-repressors in cognitive processes. Future studies of the composition and function of co-repressors in the brain are likely to provide powerful insights into gene regulation and how its disruption can lead to neurological and cognitive disorders. In this review, we will discuss four co-repressor complexes implicated in memory and cognition [nuclear receptor co-repressor (NCOR), nucleosome remodeling and deacetylase (NuRD) complex, switch-insensitive 3a (SIN3A), and RE1-element silencing transcription factor corepressor (CoREST)] focusing on their composition, and on their roles in activity-dependent transcriptional regulation, neuronal function, and cognition.

1. Co-repressors and their function in the brain

1.1. NCOR

The nuclear receptor co-repressor NCOR is a well-studied regulator of gene expression that plays critical roles both in neural development and in cognitive processes in the adult brain. NCOR assembles a multi-protein co-repressor complex that interacts with nuclear receptor transcription factors and represses expression of their target genes (Fig. 1B). NCOR and its sister repressor, silencing mediator of retinoic acid and thyroid hormone receptors (SMRT/NCOR2), were discovered as reversible repressors that interact with the ligand-binding domain of T3 thyroid hormone receptors and are released by T3 (Fig. 3A). These corepressors have been shown to bind to a wide range of nuclear receptors (NR) including the retinoid receptors and NR4A family of orphan nuclear receptors, and the methyl CpG binding protein MeCP2 (Codina et al., 2004; Ebert et al., 2013; Hörlein et al., 1995; Kato et al., 2011). NCOR forms a complex that binds HDAC3, the SIN3A co-repressor (discussed below), and the H3K9/H3K36 demethylase JMJD2A (Ishizuka and Lazar, 2005; Nagy et al., 1997; Zhang et al., 2005).

Repression by NCOR is necessary for both neural development and memory storage in the adult brain. Regulation of neuronal genes through the retinoid receptors (RAR/RXR) by NCOR is a critical component of neuronal function from the earliest stages of development (Gilbert and Lasley, 2013). In the mature brain, disruption of NCOR-regulated TR- and NR4A-dependent gene expression has been linked to cognitive dysfunction and memory impairment in human disorders and rodent models (Bono et al., 2004; Gilbert and Lasley, 2013; Hawk et al., 2012; Hawk and Abel, 2011; Xing et al., 2006). A recent study identified an NCOR-binding domain on MeCP2 that is affected by multiple mutations linked to Rett syndrome, a neurodevelopmental disorder characterized by severe motor and cognitive disability (Lyst et al., 2013). Elimination of a critical phosphorylation site within the NCOR-binding domain of MECP2 recapitulates motor and lethality endophenotypes associated with loss of MECP2 function, but the impact of this mutation in cognitive functioning is not known (Ebert et al., 2013; Lyst et al., 2013). Mutation analysis of NCOR identifies HDAC3 as a critical component of the NCOR complex in the brain (McQuown et al., 2011). Mice carrying a point mutation in the HDAC3-interaction domain of NCOR show enhanced hippocampus-dependent object location memory, indicating that histone deacetylation by

the NCOR complex is a key negative regulator of hippocampal gene expression during memory consolidation (Fig. 2) (McQuown et al., 2011).

In addition to HDAC3, NCOR recruits epigenetic regulators SIN3A and JMJD2A, but the roles of these regulators in the NCOR complex are not well understood. SIN3A and JMJD2A both bind to the N-terminal RD1 repression domain of NCOR and exhibit repressor activity in reporter assays, but it is not clear whether these interactions are co-occurring or mutually exclusive (Nagy et al., 1997; Zhang et al., 2005). JMJD2A appears to play a complex role in transcriptional regulation as a remover of both repressive H3K9me and permissive H3K36me modifications via its dual Jumonji demethylase domains. The SIN3A co-repressor has also been linked to both activating and repressive functions through its many catalytic binding partners (discussed below) (Silverstein and Ekwall, 2005). Without knowing which enzymatic components of the SIN3A-HDAC complex are present in association with NCOR, it is difficult to guess what impact the complex may have on the regulation of NCOR target genes. Future studies of NCOR and SIN3A co-repressors will provide important insights into mechanisms of gene repression in the brain, and the roles it plays in both development and cognition.

1.2. NuRD

In addition to histone modifications, nucleosome repositioning is linked to gene regulation through regulation of chromatin structure and DNA accessibility. Recent studies of chromatin remodeling complexes have uncovered a complex ATP- dependent mechanism by which these complexes uncouple the DNA from the histone surface to allow for looping of DNA and mono-directional sliding of the nucleosome along the DNA (Allen et al., 2013; Tang et al., 2010). One nucleosome repositioning complex involved chromatin compaction is the NuRD complex. A multi-functional complex containing both chromatin remodeling and histone modifying activities, the NuRD complex has been linked to rapid heterochromatin formation by nucleosome compaction via the MI-2/CHD3/4 ATPase/helicase, and histone deacetylation by HDAC1/HDAC2 (Fig. 1B) (Allen et al., 2013). The catalytic activity of the NuRD complex is directed to chromatin by H3K9me-binding plant homology domain s (PHD) on MI-2, the transcription factor binding metastasis-associated gene family (MTA1-3), and by methyl CpG binding domain proteins MBD2 and MBD3, which bind methylated and hydroxyl-methylated DNA respectively (Allen et al., 2013; Yildirim et al., 2011). Depletion of MI-2 increases chromatin accessibility and induces DNA demethylation, demonstrating a role for the NuRD complex as a critical component of heterochromatin maintenance (Gao et al., 2009).

The role of the NuRD complex in the brain is not well studied, but it has recently been indirectly linked to regulation of neuronal gene expression and cognitive function. A novel CHD ATPase/helicase family member CDH5 is highly enriched in the brain, where it forms a NuRD-like complex that includes HDAC1/HDAC2 and MBD3 and regulates the expression of neuronal genes in cultured neurons (Potts et al., 2011). Mutations in members of the MBD gene family (including MBD2 and MBD3) have been identified in individuals with autism spectrum disorder (ASD), suggesting that NuRD complex association with methylated DNA is important for neural development (Cukier et al., 2012, 2010;

Murgatroyd and Spengler, 2012). Genetic deletion studies of MBD family members in mice have identified autism-related behavioral phenotypes in mice lacking MBD1, but MBD2 and MBD3 KO mice have not been behaviorally characterized (Allan et al., 2008; Allen et al., 2013; Hendrich et al., 2001). Although the role NuRD-mediated chromatin compaction in memory formation is unclear, chromatin opening by the nucleosome repositioning Brg1-associated factor (BAF) complex (mammalian SWI/SNF) is critically important for memory formation. Loss of neuron-specific BAF complex subunit BAF53b impairs synaptic plasticity and long-term memory consolidation in the hippocampus (Vogel-Ciernia et al., 2013). Further studies of the NuRD complex in neuronal function and in behaving animals are needed to gain a more thorough understanding of its role in neural development and cognition.

1.3. SIN3A

The Switch-insensitive 3a (SIN3A) co-repressor complex is a massive 1.5–2 MD transcriptional regulatory complex that interacts with a wide array of epigenetic regulatory proteins with critical roles in brain development and cognition. Originally discovered as a suppressor of mating-type switching in yeast, SIN3A is a scaffold protein with multiple protein interaction domains through which it binds a core group of structural proteins along with HDAC1 and HDAC2, and a wide array of additional catalytically active DNA- and protein-modifying enzymes (Fig. 1B) (Nasmyth et al., 1987; Silverstein and Ekwall, 2005; Williams et al., 2011). SIN3A is critically important for embryonic development, and constitutive loss of *Sin3a* leads to peri-implantation lethality (Dannenberg et al., 2005). There is a dearth of studies of SIN3A in the brain; however, recent studies in our lab suggest that mutating SIN3A in the rodent forebrain enhances memory and synaptic plasticity (Schoch et al., 2012), unpublished results).

SIN3A recruits a wide array of epigenetic modifiers that have been linked to memory and cognition both in human genetic disorders and rodent models. The classical role for the Sin3a complex is transcriptional silencing through the deacetylation of histones mediated by HDAC1/2. Blockade of HDAC activity and loss of HDAC2 (but not HDAC1) both increase synaptic connectivity and enhance long-term memory in rodents (Guan et al., 2009). In addition to transient repression by deacetylase activity, Sin3a co-repressor complexes have also been linked to long-term silencing and heterochromatin formation through Sin3a-HDAC structural protein SDS3, and the H3K9 methyltransferase SETDB1 (David et al., 2003; Yang et al., 2003). SETDB1 activity has been implicated in the neuropathology of rodent models of Huntington's disease and Rett syndrome, and mutations in SETDB1 have been linked to ASD (Akbarian and Huang, 2009; Cukier et al., 2012; Jiang et al., 2011; Ryu et al., 2006). Mice conditionally over-expressing SETDB1 in the forebrain have altered emotional responses, but perform normally in cognitive tasks (Jiang et al., 2010). A unique addition to the Sin3a corepressor complex, OGT, catalyzes serine and threonine N-acetyl O-glycosylation, a reversible monosaccharide post-translational modification that is abundant in the brain (Khidekel et al., 2007). O-glycosylation has been linked to structural and functional changes in key transcriptional proteins, including RNA polymerase II and the cyclic AMP response element binding protein CREB (Ranuncolo et al., 2012; Rexach et al., 2012; Wells et al., 2003).

In addition to its roles in gene silencing, Sin3a core complex interacts with factors that have been linked to positive transcriptional regulation during memory formation. The SET1/MLL family of histone methyltransferase stably associate with the Sin3a complex via host cell factor 1(HCF1) and catalyzes H3K4 trimethylation, an activating mark that acts as a binding surface for methyl-lysine binding proteins involved in the assembly of the pre-initiation complex and mRNA splicing machinery at the promoter, and the maintenance of active gene expression (Sims and Reinberg, 2006; Sims et al., 2007; Wysocka et al., 2003; Yokoyama and Wang, 2004). In addition to binding positive transcriptional regulators, methylation at H3K4 also blocks recruitment of the H3K9 me-binding MI-2 subunit of the NuRD chromatin remodeling complex (Allen et al., 2013; Nishioka et al., 2002). Changes in H3K4 histone methylation have also been linked to activity dependent DNA demethylation and release of methyl-CpG binding protein MECP2 from the promoter CpG islands of memory-related genes *Zif268* and *Bdnf* (Gupta et al., 2010). The MLL family of H3K4 methyltransferases has been directly linked to intellectual disability in multiple human genetic disorders (Murgatroyd and Spengler, 2012; Ng et al., 2010). Mice with reduced MLL have less H3K4 methylation in the hippocampus and impaired long-term memory (Gupta et al., 2010). A role for SIN3A in both positive and negative transcriptional regulation is supported by genome-wide expression studies showing that loss of SIN3A is associated with bidirectional changes in expression of its target genes (Cowley et al., 2005; Dannenberg et al., 2005; Van Oevelen et al., 2010).

A recently discovered epigenetic modification of DNA involves hydroxylation of 5-methyl-cytosine to 5-hydroxy-methyl-cytosine (hmC), a reaction catalyzed by the TET family of hydroxylases (Zhang et al., 2010). Studies of methyl-binding proteins suggest that hmC may fulfill a role that is analogous but distinct to that of mC, as a substrate for hmC-binding proteins including MBD3 of the NuRD complex (Allen et al., 2013; Yildirim et al., 2011). Over-expression studies of TET1 reduces DNA methylation, but the relationship between hmC and DNA demethylation has not been determined (Zhang et al., 2010). Recent studies identified TET1 as a SIN3A binding partner, suggesting that hydroxyl-methylation may be yet another way that the Sin3a complex is able to influence the association of epigenetic and transcriptional regulators with DNA (Williams et al., 2011). The function of TET1 in DNA demethylation and chromatin remodeling in the brain remains an open question. Future studies of TET1 in behavioral and cognitive functioning are a crucial next step in understanding the role of TET1 and hmC in the brain.

The Sin3a-HDAC co-repressor complex is recruited to chromatin through association with its transcription factor binding partners, many of which have been linked to neurodevelopmental disorders with cognitive symptoms. SIN3A interacts with a variety of transcription factors, including neural-restrictive silencing factor (REST/NRSF), MECP2, and myocyte enhancer factor 2 (MEF2). Constitutive silencing by REST is critical for suppressing expression of neuronal genes in non-neuronal tissues, but the role of SIN3A as a corepressor of REST in the brain is not understood (Ballas et al., 2005). The methyl-CpG binding protein MECP2 is well studied as a repressor of memory-related genes including *Bdnf* and *Zif268* in the brain (Chen et al., 2003; Gupta et al., 2010). Loss of activity-dependent repression by MECP2 in rodent models is also associated with deficits in

memory, motor behavior, and in the structure and function of synapses, but the roles of MECP2 in cognition and transcriptional regulation are complex and not entirely clear (Collins et al., 2004; Li et al., 2011; Moretti et al., 2006; Nelson et al., 2011, 2006; see also Adachi and Monteggia, in this issue). The transcription factor MEF2 interacts with SIN3A in an activity-regulated manner, and bi-directionally regulates the expression of genes involved in memory and synaptic plasticity (Fig. 3B) (Cole et al., 2012; Flavell et al., 2008). Expression of a constitutively-active form of MEF2 that lacks the SIN3A interaction domain impairs memory and dendritic spine growth, supporting a role for SIN3A-MEF2 in memory formation (Cole et al., 2012). Though SIN3A associates with a wide diversity of transcription factors and epigenetic modifiers implicated in neuronal function, the role of SIN3A in the brain is only beginning to be explored.

1.4. CoREST

A relative newcomer to the co-repressor family of transcriptional regulators is CoREST. CoREST (KIAA0071) was discovered by two groups screening for repressors that interact with HDAC2 and REST (Andrés et al., 1999; Humphrey et al., 2001). CoREST is best known as a complex that mediates deacetylation by HDAC1 and HDAC2, but more recently, H3K4 demethylation activity was discovered in the CoREST complex via lysine specific demethylase 1 (LSD1) (Fig. 1B)(Hakimi et al., 2002; Lee et al., 2005). The DNA-binding co-factor BRCA2-associated factor 35 (BRAF35), regulates repression activities of the CoREST complex by directly binding to RE1 elements. (Hakimi et al., 2002). In contrast to the co-repressor complexes with dual regulatory activities discussed previously, CoREST appears to have only silencing activity.

CoREST is a versatile repressor linked to both chronic and transient repression of neuronal genes. In non-neuronal cells with high REST expression, CoREST and the SIN3A-HDAC complex bind to paired repressor domains on REST and stably silence the expression of neuronal genes (Lakowski et al., 2006). Gene knockdown studies of CoREST in the developing mouse brain highlight a critical role for this co-repressor complex in the development of cortical pyramidal neurons, and in the maintenance of cortical neuronal precursors (Fuentes et al., 2012). Depletion of CoREST or SIN3A in non-neuronal cells increases expression of neuron-specific genes (Dannenberg et al., 2005; Lee et al., 2005; Van Oevelen et al., 2010). Interestingly, activity-dependent expression of REST isoforms was found in post-mitotic neurons in the adult brain, but the function of REST/CoREST in the mature brain is not known (Palm et al., 1998). In the absence of REST, CoREST is still able to bind RE-1 elements through the HMG DNA binding domain of BRAF35, but SIN3A recruitment is lost (Hakimi et al., 2002; Lakowski et al., 2006). In addition to REST, CoREST interacts with the methyl CpG binding protein MECP2, where it has been linked to activity-dependent regulation of gene expression during memory consolidation (Fig.3C, discussed below) (Chen et al., 2003; Guy et al., 2011; Kavalali et al., 2011). Additional studies of CoREST and its associated factors are needed to understand the role of this corepressor in the brain.

2. Complexity and synergism within co-repressor complexes

Co-repressor complexes recruit a wide variety of epigenetic modifiers, and the impact of this diversity on the function of the complexes is frequently not clear. Much of the literature on corepressors focuses on identifying catalytic and transcription factor binding partners (Allen et al., 2013; Silverstein and Ekwall, 2005). Simply identifying proteins that can interact with a co-repressor provides limited information about the function of the complex. Very little work has been done to determine whether a co-factor is constitutively present or conditionally recruited to a complex. Knowledge of the composition of a complex is critical to the understanding of its function because transient accessory components can impart significant variation in the function of the complex. For example, the presence of both activating and repressive epigenetic modulators NCOR and SIN3A calls into question the 'repressor' status of these complexes, and hints at the existence of multiple subtypes of these complexes with different regulatory outcomes. Detailed structural and functional studies of co-repressor complexes and their interacting proteins are sorely needed to gain an accurate understanding of how these complexes can influence the expression of their target genes.

Studies of histone modification patterns suggest that certain marks are highly dependent on the presence or absence of other modifications, but the role of co-repressors in synergistic coordination of histone modifying enzymes has not yet been explored (Bannister and Kouzarides, 2011). The modification of lysine 9 of H3 is one example of how coordination of multiple epigenetic regulatory enzymes within a single complex could have important implications for the regulatory outcome. Coupling HDAC1/2 with the histone methyltransferase SETDB1 in the Sin3a complex would allow for efficient H3K9 deacetylation to expose the lysine residue for subsequent methylation by SETDB1. On the other hand, methylation of H3K4 by SIN3A-associated SET1 is functionally antagonistic to H3K9 me and blocks recruitment of H3K9me-binding proteins. It is likely that SETDB1 and SET1 are found in distinct subtypes of the Sin3a complex; however, the existence of functional variants of the Sin3a complex has yet to be demonstrated. It is imperative to expand the focus of future studies of epigenetic regulation beyond individual enzymes and single modifications into the larger context of multi-protein complexes regulating chromatin accessibility and protein recruitment.

3. Not just silencing: co-repressors as dynamic regulators of gene expression

Gene promoters typically contain multiple conserved sequence elements bound by transcriptional regulators to collectively influence expression levels at the locus. Genetic studies of conserved regulatory sequences suggest that multiple transcription factors can mediate highly divergent patterns of expression at a promoter. Especially striking is the recruitment of common repressors to mediate two distinct patterns of silencing at a single gene locus. CoREST/SIN3A regulation has been linked to both constitutive silencing (REST) and activity-regulated repression (MECP2) at the *Bdnf* and *Zif268* loci (Ballas et al., 2005; Chen et al., 2003; Gupta et al., 2010). Both repressor complexes were found at two distinct regulatory sites, a REST-bound repressor element 1 (RE1) site and a MECP2-bound CpG island (Ballas et al., 2005). In non-neuronal cells, repressor complexes were found at

both sites and expression was strongly inhibited (Ballas et al., 2005). In neurons, constitutive silencing by REST was relieved, leaving plastic repression through the activity-regulated MECP2 (Ballas et al., 2005). These studies suggest that repressor complexes may function as adaptable silencing modules that fulfill a wide range of roles depending on the transcription factors with which they associate.

4. Activity-dependent gene regulation by co-repressors

Activity-induced activation of gene expression in neurons is best understood in the context of regulation of HATs and histone acetylation; however, studies of HDAC inhibitor compounds and activity-regulated repressor proteins suggest that relief of repression is a critical component of gene regulation in the brain. The nuclear receptor field has thoroughly demonstrated that corepressor complexes can be responsive to signal transduction pathways. Ligand-mediated release of NCOR co-repressor from nuclear hormone receptors is required to expose the transactivation domain of the receptor to co-activator binding (Fig. 3A). In neurons, signaling is frequently propagated to the nucleus via the effects of calcium influx on calcium-binding proteins and kinase activity. The activity-regulated transcription factor MEF2 regulates in turn the expression of numerous neuronal genes, including *Bdnf*, *Homer1*, *Egr1*, and *Nurr1* (Flavell et al., 2008). MEF2 alternates between recruitment of either the SIN3A-HDAC co-repressor or the co-activator p300 via a calcium dependent switching mechanism (Fig.3B). At rest, MEF2 transactivation is inhibited by the binding of CABIN1, a molecular switch that recruits the SIN3A-HDAC complex (Youn and Liu, 2000). In the presence of calcium, calmodulin binds to CABIN1 and dissociates it from MEF2, alleviating repression by SIN3A, and freeing the MEF2 domain to bind the co-activator/HAT p300 (Youn and Liu, 2000). In addition to calcium-binding proteins, co-repressor activity can also be regulated by phosphorylation, as is the case for MECP2.

MECP2 has long been associated with chronic repression and maintenance of methylated DNA, but recent discoveries strongly suggest that both DNA methylation and MECP2 are dynamically regulated (for review, see Adachi and Monteggia, in this issue). Recent studies suggest that the activity of repressor protein MECP2 is regulated by neuronal activity and calcium signaling (Guy et al., 2011). At promoters with methylated CpG islands, MECP2 has been associated with histone deacetylation and transcriptional silencing, presumably through interactions with repressive SIN3A, NCOR and CoREST complexes (Fig 3C). Phosphorylation of MECP2 is associated with bi-directional changes in affinity of MECP2 for methyl-cytosine, and is reported to occur following neuronal activity (Chen et al., 2003; Ebert et al., 2013; Guy et al., 2011; Li et al., 2011; Tao et al., 2009).

Interestingly, gain- and loss-of-function studies support a role for MECP2 in transcriptional activation at promoters lacking methylated CpG islands as a binding partner for cyclic AMP response element binding protein CREB; however, the function of MeCP2-CREB interactions in gene regulation has not yet been elucidated (Chahrour et al., 2008). One could speculate about a possible role for MECP2 in recruiting an activating SIN3A/HDAC/SET1 complex to locally increase H3K4 methylation, but this hypothesis has yet to be tested (Fig. 3C). Further studies of the dual roles of MEF2, MeCP2, and the Sin3a-HDAC complex

as bidirectional regulators of transcription will yield important new insights into activity-dependent gene regulation, and its dysfunction in neurodevelopmental disorders.

5. Summary and future directions

Co-repressor complexes regulate chromatin structure and transcriptional regulation with a wide array of epigenetic modifications. In the brain, epigenetic modifications and chromatin dynamics are highly plastic, and are an integral and fundamental component of neuronal responses to developmental and environmental signals. Studies of transcription factors and regulatory factors associated with co-repressor complexes have uncovered evidence of highly dynamic regulation of repression by SIN3A and CoREST complexes in response to calcium influx, a mechanism long associated with positive regulators, but only recently linked to repression. Evidence that individual co-repressors can fulfill a range of roles from activity-regulated repression to long-term stable silencing is opening up exciting new avenues for discovery.

Although co-repressors themselves are relatively poorly studied in the brain, many transcription factors and catalytic enzymes associated with co-repressor complexes have strong connections to neuronal function, and neurodevelopmental and cognitive disorders. A recurring theme in disease models with co-repressor dysfunction is altered recruitment of proteins to chromatin. All of the complexes discussed herein are involved in either regulation of histone or DNA methylation (NCOR, SIN3A, CoREST) or contain components that bind to methylated histones (NuRD) or methylated or hydroxyl-methylated DNA (NuRD, SIN3A, CoREST). Surprisingly, the role of these complexes as regulators of chromatin-binding proteins has not been well studied. Much of what is known about transcriptional regulation by histone- and DNA-binding proteins came from studies of tumor suppressors in cancer research, but many of these same molecules are being identified as causative agents in neurodevelopmental disorders. Increased dialog and collaboration between the fields of neuroscience and cancer biology could be highly beneficial to the study of epigenetic basis of memory and synaptic function.

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Fig. 1.

Structure and composition of co-repressor complexes. A. Co-repressor complexes are composed of structural co-repressor backbones bound to epigenetic modifier effector proteins, and recruited to chromatin by DNA- or histone-binding proteins. B. Factors associated with the NCOR, NuRD, SIN3A, and CoREST co-repressor complexes, including both core components and accessory co-factors.

Fig. 2.

NCOR regulates long-term memory consolidation via HDAC3. A. Wild-type NCOR complex binds HDAC3 and SIN3A co-repressor, and represses transcription of genes regulated by nuclear receptors. B. Mutant NCOR carries a single point mutation in the deacetylase activating domain (DADm) that blocks HDAC3 binding. C. DADm mutant mice exhibit enhanced memory in the hippocampus-dependent object location memory task. DADm mice display robust discrimination under sub-threshold training conditions that do not induce long-term memory in wild-type animals Adapted from McQuown et al. (2011).

Fig. 3.

Predicted roles for co-repressor complexes in dynamic gene regulation. **A.** NCOR recruits HDAC activity both directly and indirectly through association with the SIN3A co-repressor. Unliganded nuclear receptors are transcriptionally silent, and associated with elevated H3K9 methylation and reduced H3K4me and AcH3. Ligand binding induces dissociation of NCOR and recruitment of the histone acetyltransferase p300. **B.** MEF2 alternates between co-repressor recruitment and co-activator recruitment in an activity-dependent manner. The calcium-responsive co-factor CABIN1 binds both MEF2 and SIN3A under basal conditions. Following calcium influx, activated calmodulin (CaM) dissociates CABIN1/SIN3A away from MEF2, allowing p300 binding and activation of MEF2-regulated transcription. **C.** Methyl-DNA bound MECP2 associates with multiple co-repressors, including CoREST and SIN3A. Neuronal activity-dependent phosphorylation of multiple residues on MECP2 alters its affinity for mC. MECP2 can interact with CREB at promoters lacking DNA methylation, but positive transcriptional regulation by MECP2 has not been demonstrated. One potential mechanism of positive regulation could involve SIN3A and the H3K4 methyltransferase SET1.