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Invited review

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 co-repressor complexes, and the role of co-repressors and their binding partners in neuronal function, memory, and disease.

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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

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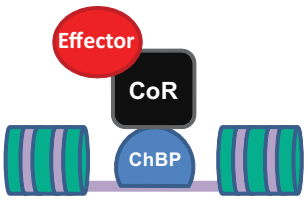
A



B

Co-Repressor Complex	NCOR	NuRD	SIN3A	CoREST
Effector	HDAC3 HDAC1/2 JMJD2A	MI-2 HDAC1/2	HDAC1/2 SETDB1 SET1 OGT	HDAC1/2 LSD1
Structural	NCOR SIN3A	p66 RBBP7/4	SIN3A SDS3 SAP18/30 RBBP7/4	COREST
Chromatin Binding	NR4A TR ER/AR RAR/RXR MECP2	MI-2 MBD2/3 MTA1-3	MECP2 REST MEF2 HCF1 NR/NCOR	REST MECP2 BRAF35

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.

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 co-repressors 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 co-repressors 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 co-repressor (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

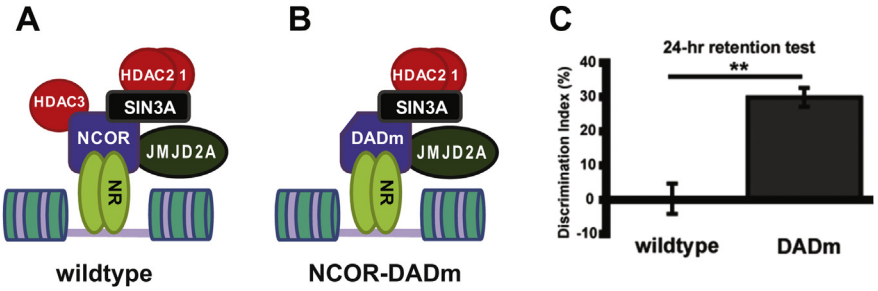


Fig. 2. NCOR regulates long-term memory consolidation via HDAC3. **A**. Wild-type NCOR complex binds HDAC3 and SIN3A co-repressor, and represses transcription of genes regulated by nuclear receptors. **B**. Mutant NCOR carries a single point mutation in the deacetylase activating domain (DADm) that blocks 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).