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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