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The role of MeCP2 in CNS development and function

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Abstract

Rett syndrome is a neurodevelopmental disorder that is a direct consequence of functional mutations in the methyl-CpG-binding protein-2 (MeCP2) gene, which has focused attention on epigenetic mechanisms in neurons. MeCP2 is widely believed to be a transcriptional repressor although it may have additional functions in the CNS. Genetic mouse models that compromise MeCP2 function demonstrate that homeostatic regulation of MeCP2 is necessary for normal CNS functioning. Recent work has also demonstrated that MeCP2 plays an important role in mediating synaptic transmission in the CNS in particular, spontaneous neurotransmission and short-term synaptic plasticity. This review will discuss the role of MeCP2 in CNS development and function, as well as a potential important role for MeCP2 and epigenetic processes involved in mediating transcriptional repression in Rett syndrome.

Keywords

Rett syndrome; Synaptic transmission; Development; Animal models

Introduction — epigenetics and MeCP2

Epigenetics is the study of stable and enduring changes in gene expression that result from mechanisms that do not involve alterations in the actual DNA sequence. Epigenetic mechanisms, such as DNA methylation and histone tail modifications (e.g., acetylation at lysine residues, methylation at lysine or arginine residues, and phosphorylation at serine or threonine residues), can either activate or repress gene transcription. These epigenetic changes are carried out by specific proteins and interpreted by additional proteins to ultimately affect the expression of individual genes. One example of such proteins, and the main focus of this review, is the methyl-CpG-binding protein 2 (MeCP2).

MeCP2 was first identified as a transcriptional repressor that inhibits gene expression through the interpretation of two epigenetic markers, DNA methylation and histone acetylation. The protein encoded by the MeCP2 gene was found to contain a methyl-CpG-binding domain (MBD), which binds to symmetrically methylated cytosines, and a transcriptional repression domain (TRD), which interacts with corepressor proteins, including specific histone deacetylases (HDACs) and mSin3a (Nan et al., 1998). The discovery of this cooperative action among MeCP2, HDACs and DNA methylation suggested a mechanistic link between chromatin modifications and DNA methylation resulting in less active gene transcription. While research demonstrating the transcriptional repression activity of MeCP2 is well established, additional functions of MeCP2 have recently been suggested. New evidence has proposed that MeCP2 may also bind to active

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genes (Yasui et al., 2007; Chahrour et al., 2008; Skene et al., 2010), and MeCP2 has also been shown to interact with RNA to influence alternative splicing (Young et al., 2005).

Mutations in the MeCP2 gene have been shown to cause the neurodevelopmental disorder Rett syndrome (RTT), symptoms of which are primarily neurological (Amir et al., 1999). Much research has focused on how mutations in a ubiquitously expressed transcriptional repressor can result in specific neuronal deficits. This review describes MeCP2's role in the etiology of RTT and how the use of RTT mouse models has been useful for determining the functions of MeCP2 during CNS development. Discussion of putative MeCP2 target genes highlights the importance of proper regulation of gene expression in the control of neuronal maturation, dendritic morphology, and synaptic transmission. Overall, current research suggests that homeostatic regulation of MeCP2 is critical in the maintenance of CNS function in that, mutations in MeCP2, and their downstream consequences on gene expression, result in abnormal behavioral and neurophysiological phenotypes.

Mutations in MeCP2 cause Rett syndrome

Rett syndrome (RTT) is a debilitating neurodevelopmental disorder occurring predominantly in females and characterized by normal development up to the first year and a half of age, at which point apraxia, loss of purposeful hand movements, slowed brain and head growth, gait abnormalities, compulsive hand movements (e.g., hand wringing/washing), and mental retardation typically begin to develop. RTT patients may also display seizures, breathing irregularities, scoliosis, and an abnormal cardiac cycle that can result in sudden death (Zoghbi and Francke, 2001). Approximately 1 in 10,000 females are clinically diagnosed with RTT (Hagberg et al., 1983). While the disorder was originally described in 1966 (Rett, 1966), there was a major medical breakthrough in 1999 when mutations in the gene MeCP2 were discovered to be the primary cause (Amir et al., 1999). This discovery helped to explain the female prevalence of RTT, as MeCP2 is located on the X chromosome (Quaderi et al., 1994), and females that are heterozygous for the mutated MeCP2 allele are able to survive with this debilitating disorder due to X chromosome inactivation (Amir et al., 2000). Males that are hemizygous for MeCP2 mutations have a drastically shortened lifespan of approximately 2 years and typically develop congenital encephalopathy (Ravn et al., 2003; Villard et al., 2000).

There is an array of RTT-causing MeCP2 mutations, from missense, nonsense, insertions, deletions, and splice site variations, which are dispersed throughout the gene. Most of these mutations occur de novo and are predicted to result in a loss of function of the MeCP2 protein (Matijevic et al., 2009). However, attempts to uncover any genotype to phenotype correlations have been more difficult to discern. It was later discovered that certain RTT patients also carry duplications of the entire MeCP2 locus, suggesting that high levels of MeCP2 expression can also result in similar phenotypes (Archer et al., 2006; Van Esch et al., 2005). Furthermore, mutations in MeCP2 not only result in classic forms of RTT, but also cause a range of related neuropsychiatric disorders. For example, patients diagnosed with Angelman syndrome (Watson et al., 2001), non-syndromic mental retardation (Miltenberger-Miltenyi and Laccone, 2003), Prader–Willi syndrome (Samaco et al., 2004), and some forms of autism (Shibayama et al., 2004) have mutations in the MeCP2 gene that significantly reduce MeCP2 protein expression levels. These data indicate that the effects of MeCP2 mutations are not necessarily consistent and that understanding the developmental trajectory of MeCP2 expression, and the coupling of developmental stage-specific expression with neuronal function, may provide important insight into the etiology of RTT and other MeCP2-associated disorders.

Animal models of Rett syndrome

Utilizing rodent models of RTT has substantially enhanced the general understanding of how MeCP2 mutations can lead to the observed phenotypes. Attempts were first made to generate constitutive MeCP2 KO mice in order to study possible behavioral effects due to the loss of MeCP2 (Tate et al., 1996; Guy et al., 2001; Chen et al., 2001). Mice with a constitutive deletion of MeCP2 displayed severe neurological symptoms, including uncoordinated gait, hindlimb clasping and irregular breathing, following a 3 to 8-week period of normal development (Guy et al., 2001). Reduced brain size and smaller, more densely packed neurons were also seen in the hippocampus, cortex, and cerebellum (Chen et al., 2001). A conditional KO approach was then used to specifically delete MeCP2 expression in the brain during embryonic development. Using the Nestin-Cre transgene, conditional MeCP2 KO mice showed phenotypes similar to those observed in MeCP2-null mice suggesting that the defect was due to neuronal dysfunction. Both MeCP2 constitutive null and Nestin-Cre driven conditional MeCP2 KO mice began to die off between 6 and 12 weeks of age, making behavioral studies on these mice difficult (Chen et al., 2001; Guy et al., 2001).

The delay in phenotypic effects due to the loss of MeCP2 during development suggested that MeCP2 function may be more critical in mature neurons. To test this theory, postmitotic deletion of MeCP2 in broad forebrain regions using calcium-calmodulin-dependent protein kinase II mice produced phenotypes comparable to MeCP2 null mice but with a later onset (Chen et al., 2001). Behavioral characterization of these conditional MeCP2 knockouts revealed phenotypes that are strikingly similar to RTT patients, with significant defects in motor learning, as well as increases in anxiety-like behavior, impairments in social interaction and altered learning and memory-related behaviors (Gemelli et al., 2006). Shahbazian et al. also impaired MeCP2 function by introducing a truncating disease-causing mutation into the murine MeCP2 gene effectively deleting only the C-terminus end of MeCP2's coding sequence. These mice also displayed impairments in motor learning, anxiety-related behaviors, seizures, and deficits in social interaction (Shahbazian et al., 2002a).

Transgenic mouse models with overexpression of MeCP2 recapitulate many of the same behavioral phenotypes seen in RTT patients and MeCP2 KO mice. Mouse lines that overexpress MeCP2 have been created either by using a large insert genomic clone from a P1-derived artificial chromosome containing the MeCP2 locus (Collins et al., 2004) or by targeting MeCP2 DNA into the Tau locus allowing for postmitotic neuron-specific overexpression (Luikenhuis et al., 2004). Mice with elevated levels of MeCP2 develop seizures and become hypoactive (Collins et al., 2004). Mice that overexpress MeCP2 specifically in postmitotic neurons also display significant impairments in motor learning, as well as tremors and gait ataxia (Luikenhuis et al., 2004).

These mouse models clearly indicate that homeostatic regulation of MeCP2 is necessary for normal CNS functioning. Both the loss and overexpression of MeCP2 result in similar neurological deficits as those seen in patients with RTT, revealing a need for precise control over the amount of MeCP2 expression. For example, MeCP2 expression being abruptly restored in the brains of MeCP2 null mice before the onset of symptoms resulted in half of the animals experiencing neurological defects and subsequent death and half avoiding development of any detectable symptoms (Guy et al., 2007). Gradual restoration of MeCP2 levels in MeCP2-deficient mice increased lifespan and reversed deficits in motor coordination and respiratory function in all animals. The study went on to show that restoration of MeCP2 expression levels can reverse neurological defects in both young, asymptomatic and adult, symptomatic mice (Guy et al., 2007). Two other studies

demonstrated that postmitotic neuron-specific MeCP2 restoration rescues the RTT-like phenotypes observed in MeCP2-deficient mice (Giacometti et al., 2007; Luikenhuis et al., 2004). These results raise questions as to how critical MeCP2 is for normal brain development. Is it possible that restoration of MeCP2 at any given time point in development is sufficient to rescue the abnormal phenotypes? These issues have yet to be resolved empirically and, based on the available evidence, it appears that either scenario is equally plausible.

MeCP2's role in CNS development and neuronal maturation

Patients with Rett syndrome display a normal period of development prior to symptom onset and then undergo a period of regression, suggesting that MeCP2 may play a more functional role in early postnatal development rather than during embryonic periods. Additional insight has come from studying the timing of MeCP2 expression in both humans and rodents. In the rodent CNS, MeCP2 expression is first detected in the spinal cord and brainstem around day E12, with mRNA being detected in subcortical regions at the beginning stages of embryonic neurogenesis (Jung et al., 2003; Shahbazian et al., 2002b). The thalamus, caudate putamen, cerebellum, hypothalamus, and hippocampus are immunoreactive for MeCP2 beginning at days E14–16. Expression of MeCP2 in the cerebral cortex also occurs at embryonic day 14, where MeCP2 expression is initially limited to deeper cortical layers before eventually spreading out to more superficial layers by E18. Over the course of cellular differentiation, amounts of MeCP2 protein increase such that, from early postnatal development into adulthood, MeCP2 is highly expressed in neurons throughout the brain (Shahbazian et al., 2002b). In olfactory neurons, MeCP2 expression also appears to increase in correlation with neuronal maturation, during a period between neurogenesis and synaptogenesis (Cohen et al., 2003). In humans, neuronal maturation and synaptogenesis are key developmental processes that occur as early as embryonic weeks 12 and 20, respectively (Marsh et al., 2008). The loss of MeCP2 expression within this time window may be responsible for the observed decrease in neuronal and overall brain size in RTT patients. Disruptions in MeCP2 function might therefore interfere with neuronal maturation and synaptogenesis, culminating in abnormal development of the CNS.

MeCP2 regulates dendritic morphology

The reduction in neuron size seen in MeCP2 null mice and RTT patients is only one of the observed effects resulting from the loss of MeCP2 function during CNS development. Reductions in axonal and dendritic processes, decreased levels of a dendritic cytoskeletal protein known as microtubule associated protein 2 (MAP2), as well as decreased spine density are also characteristic of RTT patients (Armstrong, 2002). In female RTT patients, CA1 pyramidal neurons exhibit decreased dendritic spine density (Chapleau et al., 2010), and substantial decreases in dendritic arborization can be seen in the frontal, limbic, and motor cortices (Armstrong et al., 1998). Pyramidal neurons in the cortex of MeCP2 null mice have smaller somas and reduced dendritic arborization (Kishi and Macklis, 2004). MeCP2-deficient neurons also have fewer dendritic spines and reduced arborization in the hippocampus and exhibit additional impairments in neuronal maturation in both the hippocampus and in the olfactory system (Palmer et al., 2008; Smrt et al., 2007; Zhou et al., 2006). The impacts on dendritic morphology seen with mutations in MeCP2 likely contribute to the cognitive impairments observed in RTT patients. Similar abnormalities have been seen in human subjects with mental retardation (Purpura, 1974; Takashima et al., 1994) and in animal models of Down syndrome (Belichenko et al., 2007; Belichenko et al., 2009; Kurt et al., 2000).

Postnatally, MeCP2 mutant mice display marked differences in dendritic morphology and decreased cortical thickness as early as 2 weeks of age with both somatosensory and motor cortices significantly compromised by decreased levels of MeCP2. Decreases in dendritic spines and diameter are also evident in Mecp2$^{-/y}$ mice at 2 and 6 weeks of age compared to wildtype control littermates (Fukuda et al., 2005). These data correlate with human data indicating that MeCP2 plays a pivotal role in the postnatal brain.

We have previously discussed how overexpression of MeCP2 can lead to comparable behavioral phenotypes as those seen in MeCP2 KO mice and patients with RTT. In a related manner, increased expression of MeCP2 in hippocampal pyramidal neurons results in a significant reduction in the number of spines, like that seen with the loss of MeCP2 (Chapleau et al., 2010). Overexpression of MeCP2 in hippocampal neurons also results in significant decreases in dendritic branching (Zhou et al., 2006). These observations may help explain how duplications of the MeCP2 locus and overexpression of MeCP2 can result in RTT-like behaviors in both human and rodents (Archer et al., 2006).

An obvious consequence of reduced dendritic complexity is an effect on synaptogenesis. The control of MeCP2 expression in hippocampal neurons leads to alterations in dendritic spines, the locations of excitatory synapses along dendrites (Chapleau et al., 2010). An electron microscopic study of cortical neurons from MeCP2 KO mice revealed an increase in premature postsynaptic densities (Fukuda et al., 2005). Postsynaptic density cross-sectional length was also found to be reduced in area CA1 of the hippocampus (Moretti et al., 2006). Excitatory synapse number was found to be decreased in autaptic hippocampal cultures from MeCP2 null mice and conversely increased in MeCP2 overexpressing mice (Chao et al., 2007). These data suggest that functional consequences of the loss of MeCP2 during development include delays in the maturation of neurons and their synaptic connectivity.

MeCP2 and synaptic transmission

The learning deficits and reductions in dendritic arborization observed in mouse models of Rett syndrome suggest that MeCP2 plays a vital role in synapse function. A number of studies have shown that MeCP2 KO hippocampal cultures display significant decreases in spontaneous excitatory synaptic transmission (Asaka et al., 2006; Chao et al., 2007; Nelson et al., 2006). Spontaneous excitatory activity in cortical pyramidal neurons is also decreased, while inhibitory activity is increased in MeCP2-mutant mice (Dani et al., 2005). Alternatively, excitatory synaptic transmission is enhanced in hippocampal neurons overexpressing MeCP2 (Chao et al., 2007). These changes in neurotransmission suggest an overall shift in the ratio of excitation to inhibition. The direct functional consequences of this imbalance have not been identified as of yet. However, it is reasonable to hypothesize that changes in excitatory neurotransmission may reflect changes in action potential firing thresholds, ultimately resulting in significant changes in network activity.

Long-term synaptic plasticity is widely accepted as the cellular basis for learning and memory, which can be observed as long-term potentiation (LTP) or long-term depression (LTD) of synaptic responses. LTP has been shown to be adversely affected by changes in MeCP2 expression. Deletion of MeCP2 produces significant deficits in hippocampal LTP compared to wildtype littermate controls (Asaka et al., 2006; Moretti et al., 2006). While mice that overexpress MeCP2, using an endogenous human promoter in wildtype animals, show enhanced hippocampal LTP (Collins et al., 2004). These results indicate that MeCP2 expression must be tightly regulated to preserve normal synaptic functioning.

Target genes of MeCP2

The function of MeCP2 as a transcriptional repressor suggests that the loss of MeCP2 should result in an increase in the expression of MeCP2 target genes. However, early studies of gene expression in the brains of MeCP2 null mice and RTT patients did not uncover any obvious changes in gene expression (Colantuoni et al., 2001; Tudor et al., 2002). Since these first studies, however, it has become clear that MeCP2 may control the expression of different sets of genes in separate areas of the brain, both negatively and positively, and in an activity-dependent manner (Chen et al., 2003; Cohen et al., 2008). Therefore, research began to focus more on possible candidate gene targets of MeCP2.

Given the observed effects of MeCP2 deletion and overexpression on numerous neurological processes, one of the first genes to be associated with MeCP2 was the brain-derived neurotrophic factor (BDNF). BDNF is a growth factor involved in neurogenesis, neuronal maturation and survival, Ca^{2+} homeostasis, and synaptic plasticity, as well as plays roles in learning and memory and a number of neurological disorders (Binder and Scharfman, 2004). In neuronal cultures, MeCP2 binds to the BDNF promoter III and represses transcription of BDNF (Chen et al., 2003; Martinowich et al., 2003). BDNF protein expression and mRNA is decreased by 70% in Mecp2 mutant brains compared to WT mice (Chang et al., 2006). This reduction in BDNF expression is thought to contribute to the pathogenesis of RTT. Importantly, these findings helped lead to the discovery of the activity-dependent regulation of MeCP2's effects on gene expression. MeCP2 is phosphorylated in response to membrane depolarization, which causes it to be released from the promoters of target genes, allowing for transcriptional activation (Chen et al., 2003). Since neuronal activity is affected in MeCP2 KO mice, direct correlations between the loss of MeCP2 and increases in gene expression become difficult. While MeCP2 has been widely characterized as a transcriptional repressor, recent studies suggest it may bind to active genes and modulate gene expression (Yasui et al., 2007; Chahrour et al., 2008; Skene et al., 2010).

Additional genes whose expression appears to be repressed by MeCP2 have been identified, including Dlx5, Dlx6 (Horike et al., 2005), Fxyd1, Reln, and Gtl2 (Jordan et al., 2007). Transcription of Dlx5 and Dlx6 is significantly enhanced in the frontal cortex region of Mecp2 null mice compared to controls (Horike et al., 2005). FXYD1 is also elevated in the frontal cortex of Mecp2 null mice as well as in RTT patients (Deng et al., 2007). Like BDNF, GABRB3 and UBE3A are significantly reduced in MeCP2 null mice, as well as in the brains of RTT patients (Samaco et al., 2005). These genes are important for normal development of dendritic morphology and the regulation of GABAergic function. For example, FXYD1 appears to mediate dendritic arborization and spine formation, and increases in its expression result in significant reductions in dendritic and spine growth (Deng et al., 2007). Dlx5 and GABRB3 are necessary for GABAergic function, as the former regulates synthesis of GABA and the latter encodes GABA receptor subunits (Hogart et al., 2007; Samaco et al., 2005). These changes in genes associated with GABAergic function in the frontal cortex correlate with dysfunction of GABAergic signaling evident in the frontal cortex of RTT patients (Blue et al., 1999), while changes in the expression of genes involved in dendritic morphology may help explain the observed dendritic alterations in these patients as well as in MeCP2 null mice.

Concluding remarks

MeCP2 is critically important for normal development of the CNS. Mutations in the MeCP2 gene cause a multitude of neurological effects in patients afflicted with RTT. The different phenotypes in MeCP2 mutant mice underscore the global effect of MeCP2 on CNS function.

MeCP2 mutations affect multiple systems, thereby making it particularly difficult to find effective therapeutic drugs. Understanding the basic mechanisms responsible for the etiology of RTT may shed light on how best to treat individual symptoms. Reversal of deficits in mice suggests that gene therapy targeted at restoration of MeCP2 function may be an avenue well worth exploring (Guy et al., 2007). In addition, traditional therapy, including the use of environmental enrichment (Kondo et al., 2008; Lonetti et al.), might also prove to be an effective strategy in mitigating the debilitating effects of RTT. Systemic treatment with growth factors, such as BDNF or IGF, may also be promising for alleviating many of the core symptoms of RTT (Chang et al., 2006; Tropea et al., 2009). Basic research has proved incredibly useful in understanding the etiology of RTT, however, these novel pharmacological therapies have only begun to scratch the surface of potential techniques that can be used in the treatment of RTT symptomatology.

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