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MeCP2 as an activator of gene expression

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Abstract

Rett Syndrome is a neurodevelopmental disorder that primarily affects females and is caused by mutations in the methyl-CpG-binding-protein 2 (MeCP2) gene. Initially, MeCP2 had been shown to be a repressor of gene transcription. In their 2008 paper, Chahrour and colleagues (DOI: 10.1126/science.1153252) reported that MeCP2 could also function as a transcriptional activator.

Rett syndrome (RTT) is a devastating neurodevelopmental disorder with features of autism that affects approximately 1 in 10,000 live female births. Patients with this syndrome appear to develop normally for the first 6-18 months of life and then enter a period of regression wherein they lose social, motor, and verbal skills and develop seizures, autonomic abnormalities, and microcephaly [1]. Although RTT was first described in 1966 [2] its cause remained unknown for more than 30 years. In 1999, work done in Dr. Huda Zoghbi's laboratory identified mutations in the gene encoding methyl-CpG-binding-protein-2 (*MECP2*) as the cause of RTT in reported patients [3]. Further work has since shown that the majority of RTT cases are caused by mutations in *MECP2* that are expected to result in loss of function of the gene.

MeCP2 is a DNA methyl-binding protein that was first described and characterized in Dr. Adrian Bird's laboratory [4]. MeCP2 was known to selectively bind methyl-CpG residues that can be targets of DNA methylation and thus act as a transcriptional repressor in association with histone deacetylases (HDACs) and Sin3a [5, 6]. Once mutations in *MECP2* were identified as the cause of RTT, many scientists began looking for downstream targets of MeCP2 that could explain the abnormal neuronal phenotypes seen in *Mecp2*-null mice [7]. The assumption was that MeCP2 direct targets would be inappropriately activated in the case of MeCP2 loss-of-function and represent targets for treatment.

Although biochemical evidence suggested MeCP2 primarily functioned as a transcriptional repressor *in vitro* [5, 6], the *in vivo* transcriptional evidence remained unclear. Direct targets of MeCP2 proved difficult to find, and attempts to use microarrays to identify these targets in hippocampus and cortex using *Mecp2*-null mice revealed only subtle changes in gene

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transcription [8]. Work done in Dr. Huda Zoghbi's group by Maria Chahrour and colleagues took a different approach to address these questions [9]. To identify MeCP2 target genes, the authors compared hypothalamic tissue from *Mecp2*-null, WT, and *MECP2* transgenic (Tg) mice that express an extra copy of human *MECP2*. The authors chose the hypothalamus to examine alterations in gene expression because many of the RTT patient phenotypes could be connected to hypothalamic dysfunction. They reasoned that primary targets of MeCP2 would be dysregulated in opposite directions between the loss-of-function model (null) and gain-of-function model (Tg). To their surprise, while they did indeed see opposing regulation of genes, the direction of the effects was the opposite of what was expected: a majority of the genes were *upregulated* in the *MECP2*-Tg tissue, and *downregulated* in the *Mecp2*-null tissue. These findings suggested that MeCP2 *activated* expression of these genes rather than *suppressed* it. Chahrour and colleagues then began the arduous task of validating these results. In a separate cohort of animals, the authors confirmed 66 targets from the initial microarray by qPCR, and then began to investigate the mechanism behind the observed effects.

The notion that MeCP2, a DNA methyl-binding protein, could activate gene expression was perplexing, since more generally, DNA methylation was known to be involved in gene repression. Using bisulfite sequencing, Chahrour *et al.* showed that activated genes had less methylation of upstream CpG islands, while repressed genes had more heavily methylated CpG islands. Despite these methylation patterns, chromatin immunoprecipitation (ChIP) studies demonstrated MeCP2 binds directly upstream of both activated and repressed target genes. A subsequent study reported that MeCP2 binds widely across the genome, coating nearly the entire chromatin, raising the question of functional relevance of upstream MeCP2 binding [10]. Nevertheless, Chahrour *et al.* showed MeCP2 binding was not enhanced upstream of a gene which was not identified as a primary target by their microarray analysis, demonstrating the specificity of their findings and suggesting that enhanced upstream binding of MeCP2 may indeed be functionally relevant. To identify binding partners which could explain MeCP2's role in activation, Chahrour *et al.* immunopurified MeCP2 and performed mass spectrometry analysis on the resultant proteins. The analysis revealed cAMP response element-binding protein 1 (CREB1), a major transcriptional activator, as an interacting protein. This association was confirmed by immunoprecipitation experiments of CREB1 from Neuro2a cells overexpressing MeCP2 and subsequent mass spectrometry analysis identifying MeCP2. These experiments provided a potential mechanistic explanation for how MeCP2 could function as an activator by associating with CREB1 at lightly methylated regions. In their 2008 paper, Chahrour *et al.* demonstrated that MeCP2, which had previously been thought of only as a transcriptional repressor, could function as a transcriptional activator and provided a plausible mechanism for this action.

Subsequent work examining transcriptional profiles of *Mecp2*-mutant neurons in other brain regions and systems has confirmed a pattern consistent with a function for MeCP2 as an activator in the cerebellum, striatum, olfactory sensory neurons, and differentiated human embryonic stem cells [11–14]. Perhaps the greatest legacy of the 2008 paper by Chahrour *et al.* was bringing forward the novel idea that MeCP2 may have transcriptional effects besides repression and that the exact function of MeCP2 may depend on its molecular context. Indeed, in the decade following publication of this paper, scientists have explored and

proposed many roles for MeCP2 including its involvement in transcription, chromatin scaffolding, RNA splicing, and microRNA processing, as well as potential secondary changes in gene expression caused by functional consequences of MeCP2 loss. The broad and subtle impacts of MeCP2 on gene expression shown in the Chahrouh *et al.* paper had important implications in the field by shifting RTT treatment focus from potential interventions directed at individual downstream targets of MeCP2, towards ones directly modulating MeCP2 itself. In fact, a recent article in *Science Translational Medicine* points towards druggable targets that modulate the stability of MeCP2 [15]. The continued work towards elucidating MeCP2 function brings hope that this devastating disorder may someday be curable.

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