

Discovery of a Novel Epigenetic Mechanism: MeCP2 Integrates DNA and Histone Methylation Signals

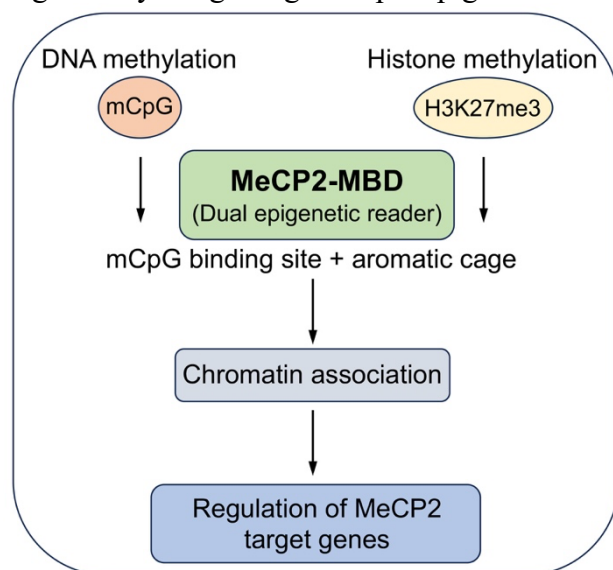
We are pleased to share the publication of a recent research study led by Dr. Babu Sudhamalla and his student Jyotirmayee Padhan, published in the *Journal of Biological Chemistry*, revealing that Methyl-CpG-binding protein 2 (MeCP2), traditionally known as a reader of DNA methylation, can also recognize histone methylation, uncovering a new mechanism for integrating epigenetic signals in chromatin.

Methyl-CpG-binding protein 2 (MeCP2) is a chromatin-associated protein that plays a central role in regulating gene expression by interpreting epigenetic signals in the genome. It is widely known for binding methylated DNA and is critical for neuronal development and gene regulation. Mutations that disrupt MeCP2 function lead to the neurological disorder Rett syndrome, while increased gene dosage results in MeCP2 duplication syndrome. Although MeCP2 has been extensively studied as a reader of DNA methylation, the mechanisms through which it interacts with chromatin and regulates gene expression have remained incompletely understood. In this study, the researchers demonstrate that MeCP2 can directly recognize methylated histone residues in addition to methylated DNA. Structural and biochemical analyses identified a specialized methyllysine recognition pocket within the methyl-CpG binding domain (MBD) of MeCP2. This pocket forms an aromatic cage composed of five conserved aromatic residues (W104, F132, Y141, F142, and F155), a structural motif commonly found in chromatin reader proteins that recognize methylated lysine residues on histone tails.

Mutational and biochemical binding studies further revealed that disruption of these aromatic cage residues significantly reduces the ability of MeCP2 to bind methylated histone peptides. These mutations also affect chromatin association and influence the regulatory activity of MeCP2 on gene expression. Together, these findings demonstrate that MeCP2 functions as a dual epigenetic reader, capable of recognizing both DNA methylation and histone methylation signals. By integrating multiple epigenetic cues, MeCP2 may act as a chromatin “interpreter,”

coordinating layers of epigenetic information to regulate genome activity, particularly in neuronal cells where precise gene regulation is essential.

Overall, this work expands the current understanding of MeCP2 biology by identifying a structural mechanism through which it recognizes histone methylation marks. The discovery that MeCP2 contains an aromatic cage capable of binding methyllysine residues highlights an additional layer of chromatin regulation and provides new insight into how epigenetic signals are integrated at the molecular level.



For more details, refer to the article, Padhan J, and Sudhamalla B. Methyl-CpG-binding protein 2 reads histone methylation *via* an aromatic cage to regulate gene expression and chromatin association. *J. Biol. Chem.*, 2026, 302, 111115. DOI: [10.1016/j.jbc.2025.111115](https://doi.org/10.1016/j.jbc.2025.111115).