The intervening domain from MeCP2 enhances the DNA affinity of the methyl binding domain and provides an independent DNA interaction site.

SY07-02

R. Clavería-Gimeno[I,II,III], P. Lanuza[I,III,IV], I. Morales-Chueca[I,II], O.D.L.C. Jorge[V], S. Vega[I], O. Abian[I,II,III,IV,VI], M. Esteller[V,VII,VIII], A. Velazquez-Campoy[I,III,IV,IX]

[I]Institute of Biocomputation and Physics of Complex Systems (BIFI), Zaragoza, Spain, [II]Instituto Aragonés de Ciencias de la Salud (IACS), Zaragoza, Spain, [III]Aragon Institute for Health Research (IIS Aragon), Zaragoza, Spain, [IV]Department of Biochemistry and Molecular and Cell Biology, Universidad de Zaragoza, Zaragoza, Spain, [V]Cancer Epigenetics and Biology Program (PEBC), Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain, [VI]Centro de Investigación Biomédica en Red en el Área Temática de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain, [VII]Department of Physiological Sciences II, School of Medicine, University of Barcelona, Barcelona, Spain, [VIII]Institucio Catalana de Recerca i Estudis Avançats, Barcelona, Spain, [IX]Fundacion ARAID, Government of Aragon,, Zaragoza, Spain

Methyl-CpG binding protein 2 (MeCP2) preferentially interacts with methylated DNA and it is involved in epigenetic regulation and chromatin remodelling. Mutations in MeCP2 are linked to Rett Syndrome, the leading cause of intellectual retardation in girls and causing mental, motor and growth impairment. Unstructured regions in MeCP2 provide the plasticity for establishing interactions with multiple binding partners. We present a biophysical characterization of the methyl binding domain (MBD) from MeCP2 reporting the contribution of flanking domains to its structural stability and dsDNA interaction. The flanking disordered intervening domain (ID) increased the structural stability of MBD, modified its dsDNA binding profile from an entropically-driven moderate-affinity binding to an overwhelmingly enthalpically-driven high-affinity binding. Additionally, ID provided an additional site for simultaneously and autonomously binding an independent dsDNA molecule, which is a key feature linked to the chromatin remodelling and looping activity of MeCP2, as well as its ability to interact with nucleosomes replacing histone H1. The dsDNA interaction is characterized by an unusually large heat capacity linked to a cluster of water molecules trapped within the binding interface. The dynamics of disordered regions together with extrinsic factors are key determinants of MeCP2 global structural properties and functional capabilities.