Exploring the MeCP2-LEDGF Interaction: Implications for Transcriptional Regulation and Rett Syndrome Pathogenesis

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Methyl-CpG-binding protein 2 (MeCP2) is a ubiquitously expressed nuclear protein that is involved in transcriptional regulation and chromatin remodeling. Depending on its interaction partners, MeCP2 can act as transcriptional activator or repressor. The two isoforms, MeCP2 E1 and MeCP2 E2, share the same functional domains, but differ in function. Loss-of-function mutations in the MeCP2 gene are the main cause of Rett syndrome (RTT). RTT patients who carry a MeCP2 mutation have increased susceptibility for LINE-1 retrotransposition since MeCP2 is an epigenetic regulator of LINE-1 genes. Previous studies identified a direct interaction between MeCP2 and Lens Epithelium-derived Growth Factor (LEDGF), another important regulator of transcription that exists in 2 isoforms, LEDGF/p75 and LEDGF/p52. In this study we determined the molecular and functional interaction between MeCP2 and LEDGF. We characterized the interaction domains of both MeCP2 and LEDGF including the possible differences between their respective isoforms using co-immunoprecipitation. Our data indicates that MeCP2 has a higher affinity for the LEDGF/p52 isoform. Purified proteins were used to further confirm the interaction in AlphaScreen experiments. We found that the ID-TRD domain of MeCP2 and the PWWP-CR1 region of LEDGF are crucial for the direct binding of the proteins. Additionally, we show that the interaction between MeCP2 and LEDGF is partially DNA-dependent. Using the LINE-1 retrotransposition assay as an indirect functional assay to investigate the effect of the MeCP2/LEDGF interaction, we show that LEDGF increases LINE-1 retrotransposition. Unraveling the molecular interaction and functional effect of the MeCP2/LEDGF interaction will increase our understanding of the underlying pathogenic mechanisms in RTT and may provide a novel target for therapeutic strategies.