Abstract

Rett Syndrome and MECP2 – Status of Knowledge 10 Years after the Gene

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Rett syndrome (RTT) research is challenging and exciting because it combines discoveries in neurobiology and epigenetics; it is a story of continuing surprises. RTT is unique among genetic, chromosomal and other developmental disorders because of usually sporadic occurrence, extreme female gender bias, early normal development and subsequent developmental regression, autonomic dysfunction, stagnation in brain growth and distinctive neuropathology. RTT is caused by loss of function mutations in the *MECP2* gene, located at Xq28, which encodes methyl-CpG binding protein 2. Inactivating *MECP2* mutations that lead to the classical RTT phenotype in heterozygous females - who are cellular mosaics because of X chromosome inactivation - cause profound congenital encephalopathy in hemizygous males. MeCP2 levels in brain need to be tightly controlled since *MECP2* duplication is a frequent cause of mental retardation in males, and mouse models overexpressing the gene are neurologically abnormal.

MECP2 is expressed in many tissues, but expression is highest in the brain and is regulated in a developmental stage and cell-type-specific manner. MECP2 expression is very low or absent in immature neurons and increases during neuronal maturation. It is highest in post-mitotic neurons and remains high throughout life. The identification of *cis*-regulatory elements, such as enhancers and silencers, has defined the 'MECP2 functional expression module' as extending beyond the transcription unit. Interaction between these *cis*-regulatory elements and the promoter have been demonstrated and are likely to be required for the stringent control of MeCP2 protein levels during neuronal maturation and in post-mitotic neurons. Post-translation modification, such as phosphorylation, also plays a role in regulating MeCP2 activity. MeCP2 is expressed in glia cells, but at a much lower level than in neurons. Recently, cell culture experiments revealed a toxic effect of astrocytes lacking MeCP2 on co-cultured wild-type neurons. Such a non-cell autonomous effect would explain the lack of structural mosaicism for the dendritic abnormalities in heterozygous female brains.

MeCP2 is a multifunctional protein that can act as an architectural chromatin-binding protein, a function that is unrelated to its ability to bind methyl-CpG and to attract chromatin modification complexes. Initial expectations that MeCP2 functions as a genome-wide transcriptional repressor were not confirmed by global gene expression studies in various tissues from humans and mouse models with MeCP2 deficiency. Recent evidence points to low-magnitude effects on a small number of target genes and gene networks that are perturbed by MeCP2 deficiency. Reversal of early lethality and of some neurological abnormalities in *Mecp2* Y/- mice by supplying normal MeCP2 postnatally has raised hopes for treatments. Conceptual limitations to therapeutic strategies, and possible avenues for novel therapies based on molecular insights, will be discussed.