J Clin Epigenet 2017, 3:4
DOI: 10.21767/2472-1158-C1-003

Methyl-CpG binding proteins: Guardians of the epigenome

M Cristina Cardoso
Technische Universität Darmstadt, Germany

All members of the Methyl-CpG-binding domain (MBD) protein family, except for MBD3, have been described to bind with high affinity to single methyl-CpG di-nucleotides, thereby silencing gene expression and dampening transcriptional noise of highly methylated, repetitive elements. In contrast, Ten-Eleven-Translocation (TET) proteins were shown to catalyze the conversion of 5 mC to 5 hmC, 5 fC and 5 caC in an iterative, Fe(II)-and oxoglutarate-dependent oxidation reaction, which is followed by the erasure of the repressing epigenetic mark. In this context, we aimed to elucidate the interplay of the MBD protein family and the recently described TET-mediated, active demethylation process. To this end, we quantified and compared global levels of 5 mC and its derivatives, transcriptional level, genomic stability and chromatin structure in human and murine cells as physiological consequences of 5 mC elimination. Moreover, we extended these analyses to the loss of function of the X-linked MECP2 gene, which causes Rett syndrome, a debilitating neurological disorder. We show that Mecp2 and Mbd2 protect 5 mC from Tet1-mediated oxidation in a concentration dependent manner *in vivo* and *in vitro*. The protection mechanism is not based on competition for 5 mC per se but rather on sequence unspecific coverage of DNA and correlates with the respective MBD protein dwell time on DNA. As a biological consequence, we measured increased 5 hmC level in neurons of a mouse model for Rett syndrome with concomitant reactivation of epigenetically silenced peri-centric DNA repeats.