

ORIGINAL ARTICLE

Unmasking of epigenetically silenced candidate tumor suppressor genes by removal of methyl-CpG-binding domain proteins

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Methyl-cytosine-phosphate-guanine (CpG)-binding domain (MBD) proteins are bound to hypermethylated promoter CpG islands of tumor suppressor genes in human cancer cells, although a direct causal relationship at the genome-wide level between MBD presence and gene silencing remains to be demonstrated. To this end, we have inhibited the expression of MBD proteins in HeLa cells by short hairpin RNAs; and studied the functional consequences of MBD depletion using microarray-based expression analysis in conjunction with extensive bisulfite genomic sequencing and chromatin immunoprecipitation. The removal of MBDs results in a release of gene silencing associated with a loss of MBD occupancy in 5'-CpG islands without any change in the DNA methylation pattern. Our results unveil new targets for epigenetic inactivation mediated by MBDs in transformed cells, such as the cell adhesion protein gamma-parvin and the fibroblast growth factor 19, where we also demonstrate their bona fide tumor suppressor features. Our data support a fundamental role for MBD proteins in the direct maintenance of transcriptional repression of tumor suppressors and identify new candidate genes for epigenetic disruption in cancer cells.