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# Genome-wide CpG and non-CpG methylation regulation by CGGBP1

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## Abstract

DNA cytosine methylation occurs in all three sequence contexts: CpG and CHG (symmetrically on the two strands) and CHH (asymmetrically on one strand). While mechanisms of CpG methylation regulation are well studied; the non-CpG methylation is beginning to be understood. Cytosine methylation patterns genome-wide are required for gene expression regulation, allele-specific functions of genomic loci, genomic integrity and silencing of repetitive elements. Studying proteins that exhibit cytosine methylation methylation-sensitive DNA-binding can unveil novel cytosine methylation regulatory mechanisms and their consequences. One such recently reported cytosine methylation regulator protein is human CGGBP1 that has CpG and non-CpG cytosines both in its binding sites. CGGBP1 depletion affects CpG methylation at repetitive elements. Normal human foreskin fibroblasts 1064Sk cells were stably transduced with lentivirally expressed CGGBP1 shmiR and control shmiR. Genomic DNA was isolated followed by bisulfite treatment and subjected to deep sequencing (Illumina). Cytosine methylation state in presence and absence of CGGBP1 was ascertained by Bismark. Through genome-wide bisulfite sequencing, we describe the effects of CGGBP1 loss-of-function on CpG, CHG and CHH methylation at a base level resolution. We observed a dynamic bimodal balancing of methylation upon CGGBP1 depletion; as it causes both gain and loss of methylation, with spatial overlap at annotated functional regions and not identifiable with any sequence motifs. However, we observed a clear association of methylation changes with GC skew genome-wide. CGGBP1 depletion causes clustered methylation changes in cis, upstream of GC skew promoters complemented by clustered occurrences of methylation changes in proximity of transcription start sites of known cytosine methylation regulatory genes, altered expression of which can regulate cytosine methylation in trans. CGGBP1 maintains a balance between pro- and anti-cytosine methylation mechanisms independent of the nucleotide sequences, but acts at the higher level of DNA structure, nucleotide composition bias and secondary structure formation ability of the strands. Our findings collectively convey that CGGBP1 is a regulator of cytosine methylation in all sequence contexts, including CHG and CHH, genome-wide through a combination of cis and trans-acting mechanisms.

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