A new DNA methylation regulator

CGGBP1 (CGG triplet repeat-binding protein 1) was first identified as a protein that binds unmethylated CGG repeats. It acts as a transcription regulator with target sites at CpG-rich sequences such as CGG repeats and Alu-SINEs (short interspersed elements) and L1-LINEs (long interspersed nuclear element). This protein is involved in several cellular processes like regulating cell proliferation, cell stress response, cytokinesis, telomeric integrity and transcription. However the role of CGGBP1 in the context of regulation of methylation on CpG regions has never been studied. Recently it has been shown that CGGBP1 binds to the transcription-regulatory regions of a subset of Alu-SINEs and L1-LINEs.

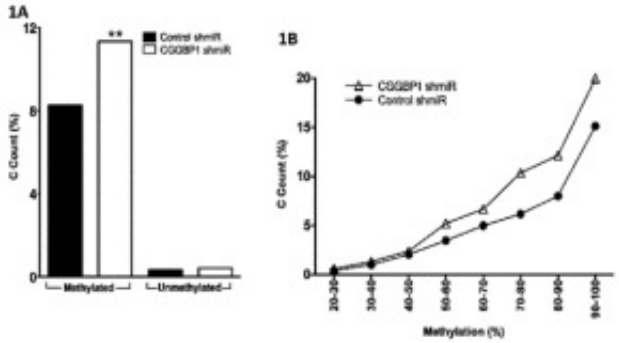

Fig. 1. (A) shows changes in CpG methylation. The increase in methylation is significant between CGGBP1-depleted and Control samples. Y-axis shows C count (%, [calculated as C count x100/total number of nucleotides]).
(B) is the frequency plotting of CpG methylation changes across different ranges of methylation. This plot shows binning of data depicted in 1A. X-axis shows methylation frequency bins and Y-axis shows C count (%).

In eukaryotes methylation occurs on the 5th position of cytosine base in the CG, CHG, and CHH contexts on DNA and it is a pivotal epigenetic mark for development and differentiation. Out of the above three-cytosine methylation, CpG methylation is the most studied. DNA methylation is a complex process and several proteins are involved in its regulation e.g. DNA methyltransferases are involved in its regulation e.g. DNMT3A and DNMT3b (involved in *de novo* methylation), DNMT1 (hemi-methylated sites). Proteins like UV39H, HDACs, HMTs, pRB, p23, DMAP1, PCNA and MBD2 regulate the activities of DNMTs. HDACs and pRB are the positive regulator while others are negative regulators of cytosine methylation. The interplay between the positive and negative regulators of CpG methylation maintain a state of equilibrium between unmethylated and methylated cytosine bases in the genome. However the factors that impede the CpG methylation from plaguing all the cytosine in genome are anonymous. Thus extrication of novel regulators of cytosine methylation becomes important. Cytosine methylation is also required to suppress the transcription of repetitive elements present in the genome.

By taking a whole genome and targeted methylation sequencing (at Alu and LINE-1 repeats) approaches we deciphered the role of CGGBP1 in regulation of CpG methylation. Our results show that upon depletion of CGGBP1 cytosine methylation increases (Fig. 1a). The exciting fact of this finding is that the increase in methylation was on genomic regions that were previously 70% - 90% methylated (Fig. 1b). Thus denoting that CGGBP1 depletion does not lead to anomalous methylation of unmethylated regions rather already methylated regions get slightly but significantly hyper methylated.

In case of Alu's there was a bidirectional change in the methylation where major fraction has increase in methylation while a minor fraction has decrease of methylation while LINE-1 showed a significant increase after CGGBP1 depletion. Overall we have discovered a unique feature of CGGBP1 that is important for regulation of DNA methylation. This has implications on silencing of Alu and LINE-1 repeats, heterochromatin formation on simple and satellite repeats and hence on genome integrity and function.

Prasoon Agarwal
Department of Laboratory Medicine (LABMED),
Division of Clinical Immunology, Karolinska Universitetssjukhuset,
Stockholm, Sweden

Publication

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