Diverse Epigenetic Roles of Protein Methyltransferases via Nonhistone Methylation

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Epigenetic regulations are involved in establishing cell-lineage diversity and the errors in these processes have been linked to many diseases including developmental abnormalities, neurological disorders and cancer. Among the key biochemical modifications in epigenetics is protein methylation, a process orchestrated by over 60 human protein methyltransferases (PMTs) with *S*-adenosyl-*L*-methionine (SAM) as a cofactor. Defining the targets of the PMTs is pivotal toward elucidating their roles in normal physiology and disease states. To address this situation, the Luo laboratory recently developed BPPM (Bioorthogonal Profiling of Protein Methylation) technology for profiling the histone and nonhistone targets of multiple PMTs inside living cells. Here, human SAM synthetase was engineered to process metabolite mimics (terminal-alkyne-containing methionine analogs), thus allowing *in situ* production of the corresponding SAM analogues. We have successfully implemented the BPPM approach to > 20 human PMTs and showed that each of the PMTs can readily methylate 200 ~ 2000 nonhistone targets, whose functions can associate with most essential biological pathways such as DNA replication, RNA processing, other posttranslational modulars and metabolic enzymes. Here we particularly followed up the functional roles of RBM15 methylation by PRMT1. The single methylation event of RBM15 is sufficient to recruit E3 ligase (CNOT4) and program RBM15 to degradation. We further showed that acute megakaryoblastic leukemia (AMKL, M7) depends on the high level of PRMT1 to down-regulate RBM15 and thus RBM15-involved splicing. PRMT1-RBM15 pathway in AMKL leads to multiple alternative splicing isoforms such as RUNX1, c-Mpl and GATA1, which suppress differentiation and promote differentiation. Our results imply that targeting PRMT1/RBM15 pathway might have therapeutic potential in AMKL.