A mechanistic insight into selective de novo DNA methylation regulated by base-specific hydrogen bonding profile

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The mammalian DNA methylation regulates diverse biological processes at the epigenetic level, such as ageing, embryonic development, reprogramming, chromatin modification, and X chromosome inactivation. Abnormalities in the DNA methylation disrupts integral molecular signaling mechanisms, leading to the severe diseases, especially cancer. DNA methylation occurs mainly at CpG islands through the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to the 5' carbon of the target cytosine. De novo methylation is carried out by the enzymes DNMT3A and DNMT3B. In terms of their catalytic domains, DNMT3A/B enzymes share over 80% sequence similarity. However, DNMT3A predominantly methylates CpGpC and CpGpT motifs, while DNMT3B prefers CpGpG and CpGpA. To clarify the mechanistic grounds of this selectivity, we performed extensive molecular dynamics simulations of DNMT3A/B enzymes bound to their cognate and non-cognate CpG motifs. As a result, we found how the DNMT3A/B sequence selectivity is driven by an arginine-lysine substitution and consequent selective hydrogen bond network. DNMT3B-Lys777 forms hydrogen bonds with two flanking guanines on the target strand and works in cooperation with polar Asn779. In DNMT3A, at the corresponding position of DNMT3B-Lys777, DNMT3A-Arg836 recognizes the flanking guanine on the complementary strand thanks to its long and branched side chain. Therefore, reading of guanines located in different chains are sought in both cases. We also observed that the DNMT3A-DNA interaction profile was significantly altered at different CpG motifs, with DNMT3B being less affected by it. We argue that the robust behavior of DNMT3B is associated with its capacity to recognize DNA sequence with two different amino acids acting both as hydrogen donor and acceptor, and non-cooperative operating mechanism sliding on DNA. Taken together, our findings not only provide missing molecular links in the DNMT3A/B action mechanisms, but they also provide additional evidence on how evolution has been gauging enzyme selectivity at the atomistic level.