RESEARCH HIGHLIGHT

DNA methylation: a new twist in the tail

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methylate these target sequences was blocked, strengthening the conclusion that the interaction of H3 tails with the PHD domain of Dnmt3a is required for allosteric activation. From these results, the authors present a novel, two-step model for methylation by Dnmt3a in which the protein is recruited to chromatin via its PWWP domain, or through interactions with Dnmt3L or other chromatin-bound proteins, but is activated only by binding of the PHD domain by unmethylated H3K4.

Does this interesting new twist help us to understand how specific DNA sequences are targeted for methylation? One challenge is how to incorporate these observations into a model that includes Dnmt3a in its association with Dnmt3L. it appears that Dnmt3a depends largely on Dnmt3L, as revealed by genome-wide analysis of CpG island methylation in mouse oocytes [10]. The Dnmt3a:Dnmt3L heterotetramer seems to be a complex bristling with recognition sites receptive to histone tail modifcations, and these might act synergistically (on single or adjacent nucleosomes?) so that at preferred genomic targets all sites are engaged with the complex with ensuing stimulation of Dnmt3a. Is H3 tail binding to the PHD domain of Dnmt3L, which itself lacks catalytic function, communicated within the complex to further enhance the activity of Dnmt3a? Or does the interaction of Dnmt3L with unmodifed H3 tails serve primarily to help specify binding of the complex, as Dnmt3L seems to have a major influence on the subnuclear localiza-