How Histone Marks Activate a Key DNA-Methylation Enzyme

New research shows how specific histone marks reshape and activate DNMT3B, revealing a long-sought mechanism that links chromatin signals to gene-silencing pathways.

Our genes are packaged in a complex structure called chromatin, where proteins known as histones help control which genes are active or silent. Another layer of control is DNA methylation—chemical tags added directly to DNA that can turn genes off (**Fig. 1**). For years, scientists have known that histone marks and DNA methylation interact, but the mechanism underlying this crosstalk has remained unclear.

A recent study published in *Science Advances* by Hanna S. Yuan's team (Academia Sinica) uncovers a major piece of this puzzle.[1] The researchers investigated DNMT3B, an enzyme responsible for adding new methylation marks to DNA. DNMT3B is essential during early embryonic development and is also misregulated in several diseases, including cancer.[2,3]

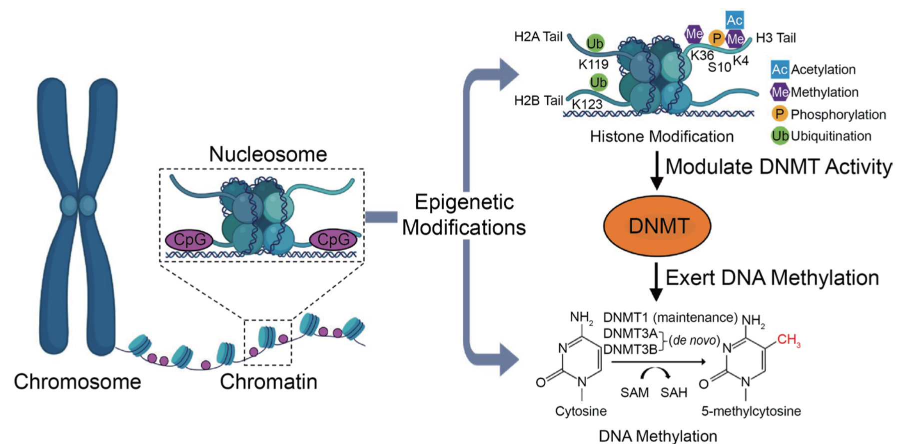

Fig. 1: Schematic representation of the interplay between DNA methylation and histone modifications at nucleosomes. CpG dinucleotides within nucleosomal DNA are methylated at the C5 position of cytosine through transfer of a methyl group from S-adenosylmethionine (SAM), catalyzed by DNA methyltransferases (DNMTs), including DNMT1, DNMT3A, and DNMT3B. Core histones (H2A, H2B, H3, and H4) undergo various post-translational modifications, such as ubiquitination, acetylation, methylation, and phosphorylation. The catalytic activity of DNMT3B is regulated by specific histone marks, notably unmethylated H3K4 and trimethylated H3K36.

Yuan's team discovered that a histone H3 peptide containing unmethylated H3K4 and methylated H3K36 markedly enhances the enzymatic activity and DNA-binding capacity of DNMT3B (**Fig. 2(a)**, see next page). In addition, using the X-ray protein crystallography facilities at beamlines **TLS 15A1** and **TPS 05A**, the team determined the structure of the PWWP domain of human DNMT3B. Their structural analysis showed that differences in the orientations of lysine side chains on the protein surface generate a more positively charged surface potential when the PWWP domain binds the histone H3 tail with a tri-methylated K36 residue (**Figs. 2(b) and 2(c)**), thereby explaining how histone modifications modulate DNMT3B activity by facilitating PWWP-mediated DNA binding.

Using the small-angle X-ray scattering (SAXS) facility at the beamline **TPS 13A**, Yuan's team discovered that DNMT3B does not passively await DNA binding. Instead, it is typically maintained in an inactive conformation, in which the ADD domain interacts with the catalytic domain and occludes the DNA-binding site. Specific histone modifications—particularly the combination of unmethylated H3K4 and methylated H3K36—serve as a molecular key that unlocks and reconfigures DNMT3B. In the presence of these histone signals, DNMT3B undergoes a substantial structural rearrangement: the ADD domain shifts to a position beneath the catalytic domain, while the PWWP domain moves into closer alignment with it, fully activating the enzyme and enabling DNA methylation (**Figs. 2(d) and 2(e)**).

This finding shows that histone modifications do more than recruit enzymes to specific genomic locations—they can directly activate those enzymes. The study also examined a DNMT3B mutation, R545C, found in advanced prostate cancer and showed that this mutant form is more readily activated, potentially leading to abnormal DNA methylation patterns.

By revealing how histone marks trigger DNMT3B activation, this research deepens our understanding of epigenetic communication within the cell. It also suggests new therapeutic possibilities: drugs that stabilize DNMT3B's inactive state could help prevent harmful DNA hypermethylation in disease, while molecules that mimic

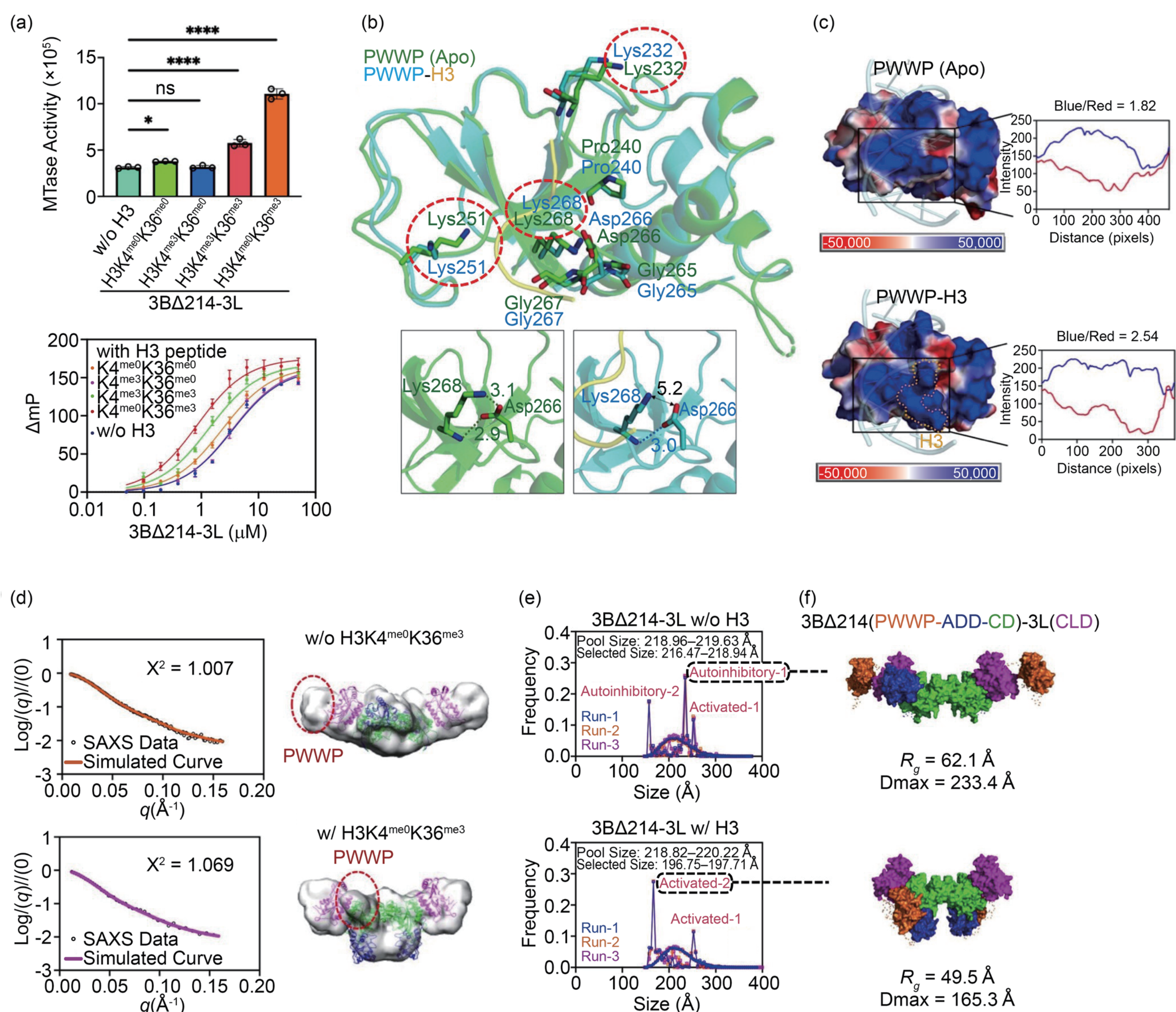

Fig. 2: Histone-driven structural remodeling activates DNMT3B. (a) Biochemical analyses demonstrate how histone H3 tail peptides with different methylation states at K4 and K36 affect the enzymatic and DNA-binding activities of DNMT3B. (b) Crystal structures of apo and H3-bound DNMT3B PWWP domains reveal differences in lysine side chain orientations (red dashed circles) and (c) corresponding surface potentials. (d) SAXS analyses of DNMT3B with and without the H3 peptide, with envelopes generated by GASBOR, indicate that DNMT3B undergoes conformational changes upon H3 binding. (e) Ensemble Optimization Method (EOM) analysis of SAXS data shows that DNMT3B adopts three predominant conformations in the absence of the H3 peptide and two predominant conformations in its presence. [Reproduced from Ref. 1]

activating histone signals might restore methylation where it is deficient. In summary, the study demonstrates that histone modifications not only guide DNMT3B to its DNA targets but also activate its enzymatic function. (Reported by Chao-Cheng Cho, Academia Sinica)

This report features the work of Hanna S. Yuan's team published in Sci. Adv. ***11****, eadu8116 (2025).*

TPS 05A Protein Microcrystallography
TPS 13A BioSAXS
TLS 15A1 Protein Crystallography

- X-ray Crystallography, SAXS
- Structural Biology, Protein Science

References

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3. C. C. Cho, C. J. Lin, H. H. Huang, W. Z. Yang, H. Y. Lin, M. S. Lee, H. S. Yuan, ACS Chem. Biol. **18**, 1335 (2023).