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Biochemical and dynamic basis for combinatorial recognition of H3R2K9me2 by dual domains of UHRF1

Suman Abhishek, M. Angel Nivya, Naveen Kumar Nakarakanti, Waghela Deeksha, Sanjeev Khosla, Eerappa Rajakumara



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UHRF1 is a multi-domain protein comprising of a tandem tudor (UHRF1 TTD), a PHD finger, and a SET and RING-associated domain. It is required for the maintenance of CG methylation, heterochromatin formation and DNA repair. Isothermal titration calorimetry binding studies of unmodified and methylated lysine histone peptides establish that the UHRF1 TTD binds dimethylated Lys9 on histone H3 (H3K9me<sub>2</sub>). Further, MD simulation and binding studies reveal that TTD-PHD of UHRF1 (UHRF1 TTD-PHD) preferentially recognizes dimethyl-lysine status. Importantly, we show that Asp145 in the binding pocket determines the preferential recognition of the dimethyl-ammonium group of H3K9me<sub>2</sub>. Interestingly, PHD finger of the UHRF1 TTD-PHD has a negligible contribution to the binding affinity for recognition of K9me<sub>2</sub> by the UHRF1 TTD. Surprisingly, Lys4 methylation on H3 peptide has an insignificant effect on combinatorial recognition of R2 and K9me<sub>2</sub> on H3 by the UHRF1 TTD-PHD. We propose that subtle variations of key residues at the binding pocket determine status specific recognition of histone methyl-lysines by the reader domains.

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