The Arabidopsis (ASHH2) CW domain binds monomethylated K4 of the histone H3 tail through conformational selection

Olena Dobrovolska[1], Maxim Brilkov[1], Noelly Madeleine[1,4], Øyvind Ødegård-Fougner[3], Øyvind Strømland[4], Stephen R. Martin[5], Valeria De Marco[6], Evangelos Christodoulou[5], Knut Teigen[4], Jarl Underhaug[2], Nathalie Reuter[2], Reidunn B. Aalen[7], Rein Aasland[7], Øyvind Halskau[1]

[1]*Department of Biological Sciences, University of Bergen, N-5020 Bergen, Norway.*
[2]*Department of Chemistry, University of Bergen, N-5020 Bergen, Norway.*
[3]*Cell Biology and Biophysics Unit, European Molecular Biology Laboratory, 69117 Heidelberg, Germany.*
[4]*Department of Biomedicine, University of Bergen, N-5020, Bergen, Norway.*
[5]*Structural Biology Science Technology Platform, Francis Crick Institute, NW1 1AT London, United Kingdom.*
[6]*King's College London, Strand, London WC2R 2LS, United Kingdom.*
[7]*Department of Biosciences, University of Oslo, N-0316 Oslo, Norway.*
noelly.madeleine@uib.no

Chromatin post-translational modifications (PTM) are thought to be important for epigenetic effects on gene expression. Methylation of histone N-terminal tail lysine residues constitutes one of many such modifications, executed by families of Histone Lysine Methyltransferase (HKMTase). One such protein is ASHH2 from the flowering plant Arabidopsis thaliana, equipped with the interaction domain CW and a HKMTase domain, SET. The CW domain of ASHH2 is a selective binder of monomethylation at Lysine 4 on the N-terminal tail of histone H3 (H3K4me1) and likely helps the enzyme dock correctly onto chromatin sites [1]. The study of CW and related interaction domains have so far been emphasizing lock-key models, possibly missing important aspects of histone-tail CW interactions. We here present an analysis of the ASHH2 CW:H3K4me1 complex using high-resolution NMR spectroscopy and molecular dynamics. ASHH2 CW emerges as a flexible domain that undergoes stabilization and compaction upon ligand binding. β-augmentation and a rearrangement of coils coincides with changes in the flexibility of the complex, in particular its coils but also in the β1 and β2 strands and the C-terminal part of the ligand. Overall, the binding process is consistent with conformational selection. We propose that this binding mode presents an advantage when searching out the correct PTM state among the highly modified and flexible histone tails, and also that the binding shifts the catalytic SET domain towards the nucleosome.

References

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