Acetylation-mediated histone tail accessibility governs the read-write mechanism of H3K4

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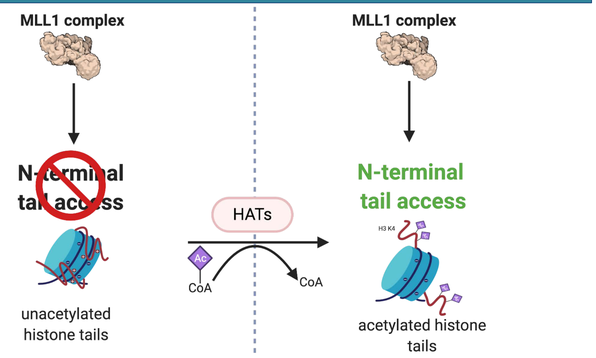
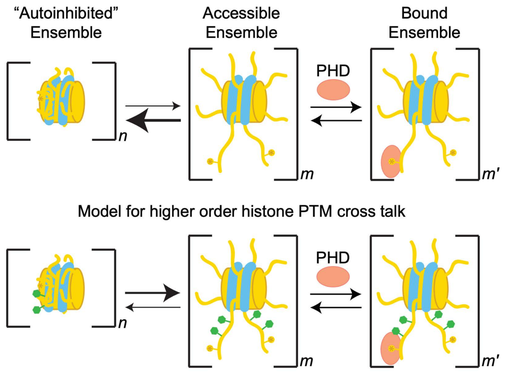
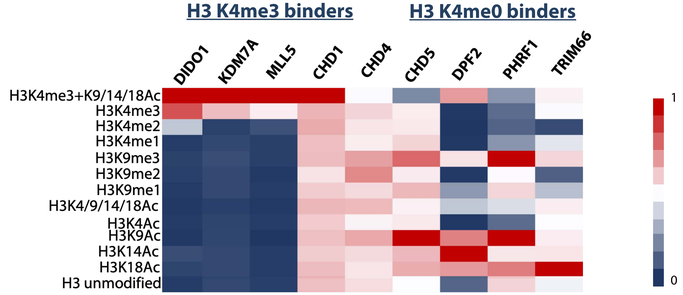
Graphical Abstract



Acetylation downstream of H3 K4 affect histone tail dynamics



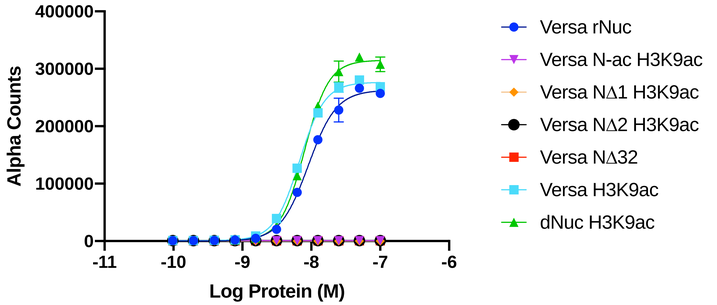
Several PHD readers confer binding to acetylated nucleosomes



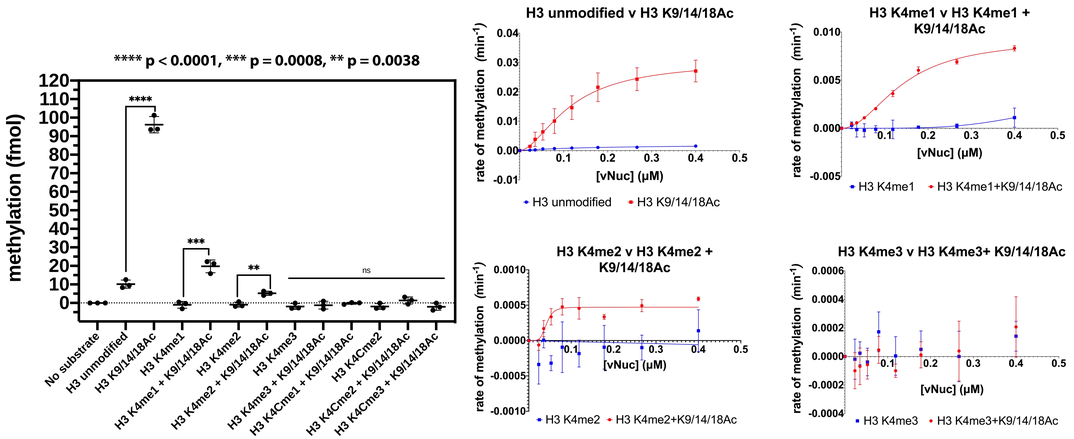
Acetylation of nucleosome tails increases writers and eraser activity

Reader domain preference for acetylated nucleosomes is not due to direct recognition of acyl PTMs

Modifying the N-terminus in any way completely ablates binding for this PHD reader, regardless of H3 K9 acetylation.

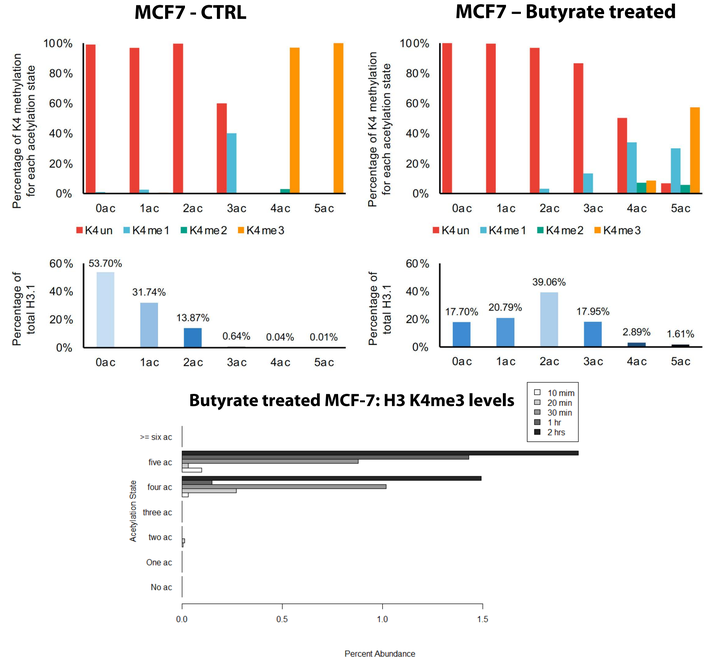


Acetylated nucleosomes demonstrate enhanced methylation by the MLL1 complex



Substrate	K_M (μM)	k_{cat} (min^{-1})	R^2
H3 unmodified	0.19 ± 0.06	0.0022 ± 0.0003	0.8791
H3 K9/14/18Ac	0.29 ± 0.09	0.0494 ± 0.0085	0.9034
H3 K4me1	n.d.	n.d.	0.1961
H3 K4me1 K9/14/18Ac	0.61 ± 0.16	0.0221 ± 0.0044	0.9646
H3 K4me2	n.d.	n.d.	-0.2004
H3 K4me2 K9/14/18Ac	0.08 ± 0.04	0.0007 ± 0.0001	0.7028
H3 K4me3	n.d.	n.d.	n.d.
H3 K4me3 K9/14/18Ac	n.d.	n.d.	n.d.

Preliminary *ex vivo* mass spectrometry reveals positive correlation between H3K4 methylation and H3 N-terminal tail acetylation



H3 N-terminal tail acetylation increases availability of accessible H3 K4 substrate for MLL1 to methylate

Ongoing studies

- Replicate MS experiments in MCF-7 cells to confirm link between H3 K4 methylation and H3 acetylation
- KDM5A (eraser) kinetics with mononucleosomes (with and without acetylation)
- Binding assays with mononucleosomes and the MLL1 complex and KDM5A

Acknowledgements

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