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Histone sibling rivalry

> this may be a general regulatory principle that also holds true for other histone modifications

The ways in which post-translational modification (PTM) of histone tails can regulate chromatin is well established, and increasing emphasis is also being placed on the importance of combined histone marks at particular genetic loci. Reinberg and colleagues now report an additional level of control, showing that these marks can be present on one or both copies of a histone protein within an individual nucleosome and that this has functional consequences.

Each nucleosome consists of two copies of the core histone proteins H2A, H2B, H3 and H4. It has so far been difficult to determine whether particular modifications occur on one or both histone copies in a single nucleosome (that is, asymmetrically or symmetrically), but this may affect the recruitment of effector proteins and readout of the chromatin state. To address this, the authors devised a unique strategy that uses affinity purification of nuclease-generated mononucleosomes and liquid chromatography-coupled mass spectrometry (LC-MS) to quantify the presence of particular histone modifications *in vivo*. They focused on two major PTMs, di- or trimethylated Lys27 of histone H3 (H3K27me2 and H3K27me3, respectively) and H4K20me1, for which specific antibodies were available. They showed that in embryonic stem cells a significant proportion of these modifications exists asymmetrically on single nucleosomes, and this also held true in mouse embryonic fibroblasts and HeLa cells. Thus, for both histone H3 and H4, a major PTM can be present on one histone tail only.

So what determines this asymmetry? To address this, the authors tested different mathematical models. A model assuming random incorporation of asymmetrically modified histones into a nucleosome did not fit with the observed data. By contrast, a model assuming two steps of regulated sequential modifications was consistent with the experimental data and suggests that this asymmetry may result from the properties of the histone-modifying enzymes themselves.

This asymmetry has implications for how histone-modifiying enzymes such as the methyltransferase PRC2 (polycomb repressive complex 2) might promote the formation of bivalent domains. These domains carry both repressive and activating histone modifications and are thought to be important regulators of gene expression, 'poising' particular promoters for activation. The authors took advantage of sequential chromatin immunoprecipitation (ChIP) analysis of purified mononucleosomes to show that two modifications proposed to act as a bivalent domain, H3K4me3 and H3K27me3, do indeed coexist on the same nucleosomes. Consistent with other recent studies, the authors observed that PRC2 could not efficiently methylate nucleosomes at H3K27 if the H3K4me3 or H3K36me3 mark was present symmetrically. Interestingly, this did not affect PRC2 binding to nucleosomes, suggesting that the presence of a symmetric mark might instead alter PRC2 activity. PRC2, however, was able to promote a repressive mark on a sister histone tail if the activating mark was present asymmetrically. Consistent with this, they show that *in vivo* bivalent nucleosomes carry H3K4me3 and H3K27me3 asymmetrically on separate copies of histone H3.

The authors speculate that this may be a general regulatory principle that also holds true for other histone modifications. Key questions now are which factors modulate the extent of symmetry and what the functional consequences of this are for the recognition of histone mark combinations during chromatin regulation.

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ORIGINAL RESEARCH PAPER Voigt, P. *et al.* Asymmetrically modified nucleosomes. *Cell* **151**, 181–193 (2012)