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ADAPTED FROM NEWS ABOUT OLD HISTONES
A ROLE FOR HISTONE AGE
IN CONTROLLING THE EPIGENOME

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NEWS ABOUT OLD HISTONES

A role for histone age in controlling the epigenome

Histone modifications are controlled by modifying and demodifying enzymes. As a consequence, the epigenome is controlled by factors that regulate (de)modifying enzyme activity and targeting. Recent studies point to histone age as another factor that can influence histone modification patterns, particularly when histone demodifying activity is low or absent.

Lysine 79 of histone H3 (H3K79), located on the structured part of the nucleosome core, is mono-, di-, and trimethylated by Dot1 (Frederiks et al., 2011). This modification is conserved from protozoans to humans (possibly with a few notable exceptions such as A. thaliana and S. pombe) and has been implicated in various chromatin-mediated processes such as regulation of transcription and DNA damage response (Frederiks et al., 2011; Nguyen and Zhang, 2011). Unlike other histone lysine methyltransferases, Dot1 does not have a SET domain and unlike most studied SET enzymes Dot1 performs multiple methylation by a non-processive or distributive mechanism (Figure 1A) (Frederiks et al., 2008). As a consequence, the methylation marks written by SET enzymes and Dot1 are expected to show different kinetics in vivo.

To explore this possibility, in Chapter 5 a mathematical model was built for in vivo methylation of H3K79 in budding yeast, using quantitative mass spectrometry measurements of the different H3K79 methylation states of bulk histones and taking into account growth rate and Dot1 levels (De Vos et al., 2011). This model was validated by analyzing the conserved mechanism of histone cross-talk between histone H2B ubiquitination (H2Bub) and H3K79 methylation. Since in the absence of H2Bub mainly H3K79me3 is lost in yeast, it is tempting to conclude that specifically the last methylation step is compromised. The mathematical model, however, could only reproduce the observed methylation pattern if all three methylation events were compromised; slowing down all three transitions eventually led to low H3K79me3, while lower methylation states were still present. This finding could be confirmed by genetic epistasis experiments (De Vos et al., 2011).

Given that demethylases for H3K79 have not been reported for yeast, the mathematical model also predicted that negative regulation of H3K79 methylation is mainly achieved by histone dilution due to replication-dependent deposition of unmethylated histones (Figure 1A) (De Vos et al., 2011). Indeed, extending the time between replication events by slowing down cell-cycle progression led to a further accumulation of methyl groups on H3K79. Next, a novel genetic pulse chase method (Recombination-Induced Tag Exchange or RITE) was employed to biochemically purify histone proteins of different average age from non-aging mid-log cells. Enrichment for histones synthesized several generations beforehand led to higher levels of H3K79 methylation, suggesting that methylation accumulates over multiple cell generations (Figure 1B)(Chapter 5 published as (De Vos et al., 2011).
Studies using SILAC isotope labeling as a pulse-chase method obtained similar results for human Dot1 (Sweet et al., 2010; Zee et al., 2010). Together, these studies suggest that H3K79 methylation is dynamic and does not reach a steady state in replicating cells. In addition, the methylation state of the maternal cell is not rapidly re-established after DNA replication in the two daughter cells, arguing against a simple epigenetic copy mechanism. The ongoing accumulation of methylation on old histones depends on the absence of a H3K79 demethylase. In line with this, computational models constructed to explain the existence of a stable methylation state on other histone residues suggest that rapid re-establishment of a maternal methylation pattern in the two daughter cells requires the combined action of a methylase and a demethylase (Angel et al., 2011; Dodd et al., 2007).

Figure 1. Buildup of methylation on the nucleosome core. (A) Dot1 mono-, di- and trimethylates histone H3K79 (red dots) on nucleosomes (grey circles) by a non-processive mechanism. H3K79 methylation is counteracted by dilution of (modified) histones due to cell growth and division. (B) Pulse chase analysis shows that H3K79 methylation accumulates on aging histones in a replicating cell (for each cell division only one of the two daughter cells is shown). During cell division each daughter cell inherits approximately one half of all old (modified and unmodified) nucleosomes from the parental cell. The other half is replaced by new unmodified histones (dashed yellow circles).
If H3K79 methylation is unlikely to be involved in epigenetic copy mechanisms, what is the biological role of this dynamic and variable mark that accumulates on aging histones? By analogy to models proposed for multi-site phosphorylation (Salazar et al., 2010), H3K79 methylation may act as a molecular timer that couples cell-cycle progression to changes in the epigenome. The observation that gene silencing can be affected by cell-cycle progression in a Dot1-dependent manner (De Vos et al., 2011) provides support for this hypothesis, but additional experiments are needed to determine whether this is a general concept.

Where are the old histones in the genome? The age of histones in the genome is not only determined by cell-cycle progression but also by histone mobility and replication-independent histone turnover. Using the RITE pulse-chase method, the location of old histones was monitored in replicating yeast cells during several cell divisions (Radman-Livaja et al., 2011). Interestingly, old histones are not randomly distributed but pile up at specific loci, in particular at the 5’ ends of coding regions of long genes undergoing low to intermediate levels of transcription. A mathematical model suggests that the location of old histones can be explained by three parameters: 1) replication-independent histone turnover, 2) passback of histones from the 3’ to the 5’ end of coding regions by RNA polymerase II, and 3) some diffusion of nucleosomes during DNA replication (Radman-Livaja et al., 2011). In agreement with the analyses of bulk histones, the position of old histones in the genome correlates with the position of high levels of H3K79me3 (Radman-Livaja et al., 2011; Schulze et al., 2009).

In summary, independent approaches that take into account the dynamic behavior of histones and their modifications reveal that histones of different age can have different biochemical properties and locations. This opens up the intriguing possibility that the epigenome can be influenced not only by modifying and demodifying enzymes but also by factors that affect the average histone age in the cell as well as by factors that determine the location of aging histones in the genome.
REFERENCES


