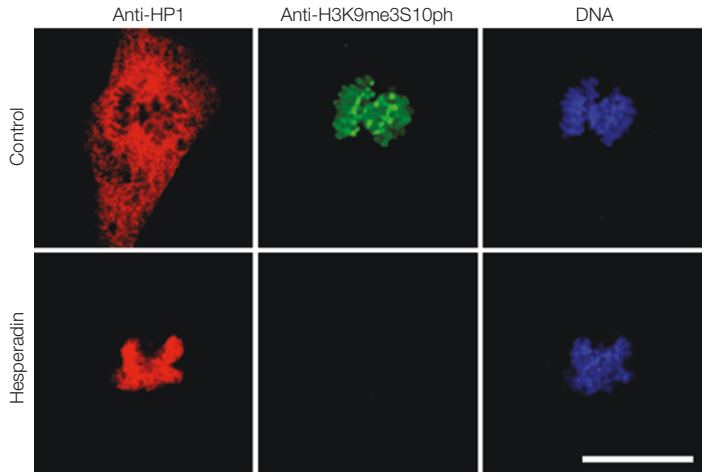
CHROMATIN

A binary switch



Upper panels: Phosphorylation of the H3 tail on Ser10 adjacent to the HP1-recruiting H3K9me3 mark releases HP1 from chromatin. Lower panels: Inhibition of the main mitotic H3S10 kinase, Aurora B, by hesperadin prevents the dual-mark combination of H3K9me3S10ph, and so HP1 remains associated with chromatin. Immunofluorescence images were obtained using the indicated antibodies, and DNA was stained with DAPI. Bar, 10 μm. Images courtesy of Wolfgang Fischle, Rockefeller University, USA.

The recruitment of heterochromatin protein-1 (HP1) to chromatin requires tri-methylation of histone H3 lysine 9 (H3K9me3), and is needed for establishing and maintaining heterochromatin in the genome. However, little is known about the underlying mechanism that controls this dynamic interaction between HP1 and H3K9me3. Two recent reports in *Nature* shed new light on this regulation and provide evidence for a binary-switch mechanism.

Both groups focused on the part of the cell cycle, mitosis (or M phase), when HP1 is known to dissociate from chromatin. David Allis and colleagues noted that HP1 dissociates from mitotic chromatin without the loss of the H3K9me3 mark, which indicates that another modification might be responsible for interrupting the HP1–chromatin interaction. Mass-spectrometry analysis revealed a phosphorylation mark on histone H3 Ser10 (H3S10ph) next to H3K9me3, which was specific to M-phase chromatin. This H3 modification is a known hallmark of mitosis, the function of which has been unknown.

In vitro binding studies confirmed that binding of HP1 to a dually modified H3K9me3S10ph peptide was significantly reduced compared to binding to an H3K9me3 peptide. Loss of binding also occurred as a result of phosphorylation of the H3K9me3 peptide by Aurora B, which is the principal H3S10 kinase, but not when Aurora B was inhibited. The same dissociation pattern was present *in vivo* — immunofluorescence studies showed that H3K9me3S10ph was only detected in mitotic cells that had lost the characteristic chromatin-associated HP1 localization pattern. When cells exited mitosis, HP1 re-associated with chromatin and H3S10 phosphorylation disappeared. In addition, inhibition or depletion of Aurora B caused retention of HP1 on mitotic chromosomes, indicating that Aurora-B-mediated H3S10 phosphorylation is responsible for the release of HP1 from chromatin.

The second group, led by Jan-Michael Peters, reported similar findings, but started from a different premise. They identified human autoimmune sera against mitotic chromosomal antigens that specifically recognize the H3K9me3S10ph epitope. Intrigued by the mysterious role of H3S10ph during mitosis, they characterized the epitope and found that it is only present in mitosis, is enriched at pericentric heterochromatin, and requires the activity of Aurora B and Suv39h (the enzyme responsible for the tri-methylation of H3K9). Indeed, depletion of Aurora B resulted in the retention of HP1 on mitotic chromosomes, thereby indicating a role for H3S10ph in the dissociation of HP1 from chromatin during mitosis. In the future, it would be interesting to see whether the dynamic behaviour of HP1 can be linked to known mitotic defects.

The combinatorial effect of multiple histone modifications as a regulatory mechanism was proposed a couple of years ago, but these studies provide the first formal evidence for a 'binary methylation/phosphorylation switch' that regulates the HP1–H3K9me3 interaction, whereby the methylation mark is constant and the phosphorylation mark flexible. It can be imagined that similar binary-switch mechanisms regulate other protein–protein interactions.

Arianne Heinrichs

URLs
Aurora B
http://ca.expasy.org/uniprot/Q96GD4
Suv39h
http://ca.expasy.org/uniprot/O43463

References and links

ORIGINAL RESEARCH PAPERS Fischle, W. *et al*. Regulation of HP1–chromatin binding by histone H3 methylation and phosphorylation. *Nature* 12 Oct 2005 (doi:10.1038/nature04219) | Hirota, T. *et al*. Histone H3 serine 10 phosphorylation by Aurora B causes HP1 dissociation from heterochromatin. *Nature* 12 Oct 2005 (doi:10.1038/nature04254)
FURTHER READING Fischle, W. *et al*. Binary switches and modification cassettes in histone biology and beyond. *Nature* **425**, 475–479 (2003)