Nature Reviews Molecular Cell Biology | AOP, published online 14 June 2006; doi:10.1038/nrm1966

DOI:
10.1038/nrm1966

URLs

BPTF
http://ca.expasy.org/uniprot/Q9UIG2

ING2
http://ca.expasy.org/uniprot/Q9ESK4

GENE EXPRESSION

Pointing the finger

Mechanistic links between specific histone-tail modifications and their effects on gene expression have been difficult to establish. However, four papers in *Nature* now identify the plant homeodomain (PHD) finger as an important effector domain that binds to the trimethylated K4 residue of histone H3 (H3K4me3) and couples it to gene activation in one case and to gene repression in another.

Wysocka *et al.* affinity purified the BPTF (bromodomain and PHD finger transcription factor) subunit of NURF — an ATP-dependent chromatin remodelling complex — using an H3K4me3-containing peptide. Mutational analysis narrowed the H3K4me3-interaction region to the second, conserved bromodomain-proximal PHD finger of BPTF. Knockdown of the histone methyltransferase cofactor WDR5, which led to reduced H3K4me3 levels, caused the partial release of BPTF from chromatin and the defective recruitment of the NURF ATPase subunit to specific gene promoters. Their findings indicate that NURF specifically associates with H3K4me3-containing chromatin at the promoter regions (of Hox genes, for example), and that the ATP-dependent remodelling activity of NURF modulates transcriptional activation.

In a second linked paper, Li *et al.* reported the X-ray and NMR structures of the human BPTF PHD finger and the nearby bromodomain when bound to an H3K4me3 peptide. The peptide forms an anti-parallel β-sheet with the PHD finger, and residues R2 and K4me3 are positioned in individual binding pockets that are separated by the conserved W32 residue of the PHD finger. This arrangement of binding pockets might explain why the PHD finger binds specifically to H3K4me3 but not to H3K9me3 or H3K27me3.

In a third study, Shi *et al.* found that the PHD domain of ING2 (inhibitor of growth protein-2), as well as other members of the ING PHD family of tumour suppressors, bound specifically to H3K4me3. ING2 is a subunit of a SIN3a–HDAC1 histone-deacetylase complex. The authors showed that in response to DNA damage, binding of the ING2 PHD finger to H3K4me3 that is present at the promoters of actively transcribed proliferation genes enhanced the association of the ING2–HDAC1 complex at these genes. This resulted in increased histone-deacetylase activity and hence acute repression of the cognate transcript. These findings, together with those of Wysocka *et al.*, indicate that PHD fingers have a general role as effector domains that link H3K4me3 to diverse biological outcomes.

The molecular mechanism that underlies the recognition of H3K4me3 by the PHD finger of ING2 was reported in a fourth linked paper. Peña *et al.* determined the crystal structure of the mouse ING2 PHD finger when bound to an H3K4me3 peptide. The histone peptide is bound in an extended conformation, the trimethyl group of K4 is recognized by a binding pocket that comprises aromatic residues, and R2 is positioned in a nearby binding pocket. Mutating the binding-site residues disrupted H3K4me3 binding *in vitro*. In addition, whereas overexpressing wild-type ING2 induced apoptosis, this effect was impaired in ING2 mutants. Importantly, several PHD-finger mutations that are involved in H3K4me3 binding are mutated in cancer cells, which implies that this interaction might be crucial in tumourigenesis.

Arianne Heinrichs

ORIGINAL RESEARCH PAPERS Wysocka, J. *et al.* A PHD finger of NURF couples histone H3 lysine 4 trimethylation with chromatin remodelling. *Nature* 21 May 2006 (doi:10.1038/nature04815) | Li, H. *et al.* Molecular basis for site-specific read-out of histone H3K4me3 by the BPTF PHD finger of NURF. *Nature* 21 May 2006 (doi:10.1038/nature04802) | Shi, X. *et al.* ING2 PHD domain links histone H3 lysine 4 methylation to active gene repression. *Nature* 21 May 2006 (doi:10.1038/nature04835) | Peña, P. V. *et al.* Molecular mechanism of histone H3K4me3 recognition by plant homeodomain of ING2. *Nature* 21 May 2006 (doi:10.1038/nature04814)