CHROMATIN

Fine-tuning tools

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URLs
JHDM1A
http://ca.expasy.org/uniprot/Q9Y2K7

JHDM2A
http://ca.expasy.org/uniprot/Q9Y4C1

JMJD2A
http://ca.expasy.org/uniprot/O75164

JMJD2C
http://ca.expasy.org/uniprot/Q9H3R0

> “…the enzymes are likely to be important for fine-tuning the methylation status of chromatin.”

Histone methylation, in particular histone trimethylation, was long considered to be a ‘permanent’ epigenetic mark. But in the past few years several histone demethylases have been identified, and four papers in *Cell* and *Nature* reveal yet further demethylase enzymes, including some that function on trimethylated histone Lys residues.

Among the known histone demethylases is the JmjC-domain-containing protein JHDM1A. The JmjC-domain family is thought to contain other histone demethylases, and indeed, Yamane *et al.* now report the isolation of the JmjC-domain-containing histone demethylase JHDM2A. Both enzymes require the cofactors Fe^{2+} and α-ketoglutarate, so they probably use a similar catalytic mechanism. Further JmjC-family histone demethylases reported in the other three papers have the same cofactor requirements, and all depend on an intact JmjC domain for their catalytic activity.

JHDM2A was identified as a histone H3 Lys9 (H3K9)-specific enzyme that selectively demethylates monomethyl- and dimethyl-H3K9. RNA interference (RNAi)-mediated knockdown of JHDM2A reduced the transcription of certain genes, but not of others, and this coincided with increased levels of dimethyl-H3K9 at the downregulated gene promoters. The authors also discovered that JHDM2A is recruited to androgen receptor (AR) target genes in a hormone-dependent manner, which coincided with H3K9 demethylation and transcriptional activation. Knockdown of JHDM2A impaired the hormone-dependent activation of AR target genes and the concomitant hormone-induced demethylation of H3K9.

Whetstine *et al.* showed that another histone demethylase, JMJD2A, of the JMJD2 subfamily of JmjC proteins, mediates the demethylation of trimethyl-H3K9 and -H3K36, but not of monomethyl- or dimethyl-H3K9/K36. The other members of the JMJD2 subfamily were also shown to function as trimethyl-specific histone demethylases. RNAi-mediated depletion of a *Caenorhabditis elegans* JMJD2A homologue triggered p53-dependent germline apoptosis, which implies that JMJD2A has an important physiological function in *C. elegans*.

By contrast, Klose *et al.* demonstrated that JMJD2A, which they renamed JHDM3A, prefers trimethylated substrate, but also demethylates monomethyl- and dimethyl-H3K9/K36. But mutagenesis and structural data support the view that JHDM3A is predominantly a trimethyl-specific demethylase (see Structure Watch in this issue). Overexpressing JHDM3A disrupted the recruitment of heterochromatin protein-1 (HP1) — which preferentially binds to dimethyl- or trimethyl-H3K9 — to pericentric heterochromatin. In addition, the only known JHDM3A target gene, *ASCL2*, was downregulated and the level of trimethyl-H3K9 at the euchromatic locus increased when JHDM3A was knocked down. So JHDM3A might have an important role in heterochromatin formation and active gene repression.

Cloos *et al.* identified three JMJD2 proteins (A, B and C) that can demethylate dimethylated and trimethylated H3K9. JMJD2C is also known as GASC1, a putative oncoprotein that is upregulated in oesophagal carcinoma cells. Overexpressing GASC1 delocalized HP1, as also shown for JMJD2A/JHDM3A, and reduced heterochromatin formation. Depleting GASC1 led to decreased cell proliferation, but why the histone-demethylase activity of GASC1 is required for cell proliferation and whether GASC1 contributes to tumour development both warrant further research.

Recent studies have uncovered an abundance of new histone demethylases from the JmjC family. Although their precise physiological roles remain to be fully elucidated, the enzymes are likely to be important for fine-tuning the methylation status of chromatin.

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ORIGINAL RESEARCH PAPERS Yamane, K. *et al.* JHDM2A, a JmjC-containing H3K9 demethylase, facilitates transcription activation by androgen receptor. *Cell* **125**, 483–495 (2006) | Whetstine, J. R. *et al.* Reversal of histone lysine trimethylation by the JMJD2 family of histone demethylases. *Cell* **125**, 467–481 (2006) | Klose, R. J. *et al.* The transcriptional repressor JHDM3A demethylates trimethyl histone H3 lysine 9 and lysine 36. *Nature* 28 May 2006 (doi:10.1038/nature04853) | Cloos, P. A. C. *et al.* The putative oncogene GASC1 demethylates tri- and dimethylated lysine 9 on histone H3. *Nature* 28 May 2006 (doi:10.1038/nature04837)
FURTHER READING Structure Watch. *Nature Rev. Mol. Cell Biol.* **7**, 467 (2006) | Martin, C. & Zhang, Y. The diverse functions of histone lysine methylation. *Nature Rev. Mol. Cell Biol.* **6**, 838–849 (2005)