EPIGENETICS

We are family

> “…the JARID1 subfamily … represent the first enzymes with specificity for H3K4me3.”

The methylation status of histones, which is essential for gene regulation and chromatin structure, is modulated by histone methylases and demethylases. Several proteins that contain a Jumonji C (JmjC) domain have recently been shown to be histone lysine demethylases. A flood of new studies now identify the JARID1 subfamily of JmjC-domain-containing proteins as histone demethylases with specificity for di- (me2) and trimethylated (me3) histone H3K4.

Christensen *et al.* showed that the retinoblastoma-binding protein-2 (RBP2, or JARID1A) is a H3K4me3/me2 histone demethylase that binds the promoters of certain Hox genes in undifferentiated embryonic stem (ES) cells. Binding is lost following ES-cell differentiation, which correlates with transcriptional repression and increased H3K4me3 levels. The functional significance of RBP2 in development might be evolutionarily conserved, as mutation or knockdown of the *Caenorhabditis elegans* homologue *rbr-2* caused increased levels of H3K4me3 and defective vulval formation. Incidentally, Secombe *et al.* identified the RBP2 *Drosophila melanogaster* homologue Lid, and Seward *et al.* and Liang *et al.* identified the JARID1B *Saccharomyces cerevisiae* homologue Yjr119C (or Jhd2) as H3K4me3 demethylases. Lid regulates Myc-induced cell growth and binds to Myc, which negatively regulates its demethylase activity.

Methylation of H3K4 is normally associated with transcriptionally active genes. Indeed, Klose *et al.* showed that RBP2-knockout mouse cells displayed increased transcription of certain cytokine genes. This was accompanied by increased H3K4me3 levels on the RBP2-responsive gene promoter compared with wild-type cells.

The X-linked mental retardation (XLMR) gene *SMCX* (or *JARID1C*) encodes another H3K4me3/me2 demethylase. Iwase *et al.* analysed point mutations that had been identified in patients with XMLR and found that several mutants had reduced enzymatic activity. To investigate whether abnormal SMCX demethylase activity contributes to the XLMR pathology, the authors knocked down *Smcx* in zebrafish and in primary mammalian neurons, which resulted in neuronal developmental defects. The mutational analysis also revealed that SMCX binds to H3K9me3, which might have significance for establishing the local chromatin environment.

Lee *et al.* showed that JARID1D associates with the Polycomb-like protein Ring6a (or MBLR), which regulates its enzymatic activity. JARID1D and Ring6a/MBLR were enriched at the transcriptional start site of the Engrailed-2 gene. Depletion of JARID1D led to the concurrent loss of Ring6a/MBLR at the Engrailed-2 gene, enhanced levels of H3K4me3 near the transcription start site and increased gene transcription. Depletion of JARID1D also enhanced the recruitment of the chromatin-remodelling complex NURF and the basal transcription machinery to the target gene promoter — providing JARID1D with a possible mechanism for regulating transcription initiation.

Together, the JARID1 subfamily of JmjC-domain-containing proteins add an entire new group of evolutionarily conserved histone demethylases to the ever-growing list and represent the first enzymes with specificity for H3K4me3.

Arianne Heinrichs, Chief Editor,
Nature Reviews Molecular Cell Biology

ORIGINAL RESEARCH PAPERS
Christensen, J. *et al.* RBP2 belongs to a family of demethylases, specific for tri- and dimethylated lysine 4 on histone 3. *Cell* 22 Feb 2007 (doi:10.1016/j.cell.2007.02.003) | Secombe, J. *et al.* The Trithorax group protein Lid is a trimethyl histone H3K4 demethylase required for dMyc-induced cell growth. *Genes Dev.* 20 Feb 2007 (doi:10.1101/gad.1523007) | Seward, D. J. *et al.* Demethylation of trimethylated histone H3 Lys4 *in vivo* by JARID1 JmjC proteins. *Nature Struct. Mol. Biol.* 18 Feb 2007 (doi:10.1038/nsmb1200) | Liang, G. *et al.* Yeast Jhd2p is a histone H3 Lys4 trimethyl demethylase. *Nature Struct. Mol. Biol.* 18 Feb 2007 (doi:10.1038/nsmb1204) | Klose, R. J. *et al.* The retinoblastoma binding protein RBP2 is an H3K4 demethylase. *Cell* 22 Feb 2007 (doi:10.1016/j.cell.2007.02.013) | Iwase, S. *et al.* The X-linked mental retardation gene *SMCX/JARID1C* defines a family of histone H3 lysine 4 demethylases. *Cell* 22 Feb 2007 (doi:10.1016/j.cell.2007.02.017) | Lee, M. G. *et al.* Physical and functional association of a trimethyl H3K4 demethylase and Ring6a/MBLR, a Polycomb-like protein. *Cell* 22 Feb 2007 (doi:10.1016/j.cell.2007.02.004)
FURTHER READING Klose, R. J. & Zhang, Y. Regulation of histone methylation by demethylimination and demethylation. *Nature Rev. Mol. Cell Biol.* 7 Mar 2007 (doi:10.1038/nrm2143) | Klose, R. J. *et al.* The JmjC-domain-containing proteins and histone demethylation. *Nature Rev. Genet.* **7**, 715–727 (2006)