



## CHROMATIN

# We are family

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- (me<sub>2</sub>) and trimethylated (me<sub>3</sub>) histone H3K4.

Christensen *et al.* showed that the retinoblastoma-binding protein-2 (RBP2; **JARID1A**) is a H3K4me<sub>3</sub>/me<sub>2</sub> 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 H3K4me<sub>3</sub> 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 H3K4me<sub>3</sub> 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 H3K4me<sub>3</sub> 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 levels of H3K4me<sub>3</sub> on the RBP2-responsive gene promoter compared with wild-type cells.

“...the JARID1 subfamily of JmjC-domain-containing proteins... represent the first enzymes with specificity for H3K4me<sub>3</sub>.”

The X-linked mental retardation (XLMR) gene **SMCX** (*JARID1C*) encodes another H3K4me<sub>3</sub>/me<sub>2</sub> demethylase. Iwase *et al.* analysed point mutations that had been identified in patients with XLMR 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 H3K9me<sub>3</sub>, 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 H3K4me<sub>3</sub> 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 H3K4me<sub>3</sub>.

Arianne Heinrichs

**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** Lee, N. *et al.* The trithorax-group protein Lid is a histone H3 trimethyl-Lys4 demethylase. *Nature Struct. Mol. Biol.* 11 Mar 2007 (doi:10.1038/nsmb1216) | Eisenberg, J. C. *et al.* The trithorax-group gene in *Drosophila* little imaginal discs encodes a trimethylated histone H3Lys4 demethylase. *Nature Struct. Mol. Biol.* 11 Mar 2007 (doi:10.1038/nsmb1217) | Klose, R. J. & Zhang, Y. Regulation of histone methylation by demethylation and demethylation. *Nature Rev. Mol. Cell Biol.* 8, 307–318 (2007)

### DOI:

10.1038/nrm2150

### URLs

JARID1A

<http://ca.expasy.org/uniprot/P29375>

Yjr119C

<http://ca.expasy.org/uniprot/P47156>

SMCX

<http://ca.expasy.org/uniprot/P41229>

JARID1D

<http://ca.expasy.org/uniprot/Q9BY66>