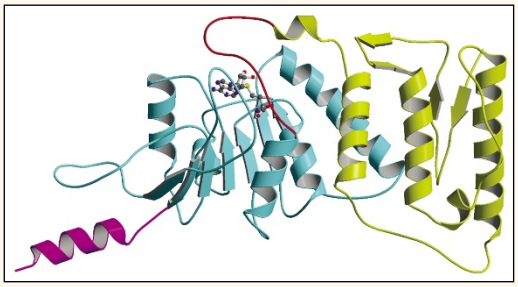
3. Volbeda, A. *et al. J. Am. Chem. Soc.* **118**, 12989–12996 (1996).
4. Vignais, P.M., Billoud, B. & Meyer, J. *FEMS Microbiol. Rev.* **25**, 455–501 (2001).
5. Heo, J., Staples, C.R., Halbleib, C.M. & Ludden, P.W. *Biochemistry* **39**, 7956–7963 (2000).
6. Drennan, C.L., Heo, J., Sintchak, M.D., Schreiter, E. & Ludden, P.W. *Proc. Natl. Acad. Sci. USA* **98**, 11973–11978 (2001).
7. Dobbek, H., Svetlitchnyi, V., Gremer, L., Huber, R. & Meyer, O. *Science* **293**, 1281–1285 (2001).
8. Doukov, T.I., Iverson, T.M., Seravalli, J., Ragsdale, S.W. & Drennan, C.L. *Science* **298**, 567–572 (2002).
9. Darnault, C. *et al. Nat. Struct. Biol.* **10**, 271–279 (2003).
10. Maynard, E.L. & Lindahl, P.A. *J. Am. Chem. Soc.* **121**, 9221–9222 (1999).
11. Seravalli, J. & Ragsdale, S.W. *Biochemistry* **39**, 1274–1277 (2000).
12. Seravalli, J. *et al. Proc. Natl. Acad. Sci. USA* Early Edition, 14 February 2003 (doi:10.1073/pnas 0436720100).
13. Gencic, S. & Grahame, D.A. *J. Biol. Chem.* **278**, 6101–6110 (2003).
14. Shin, W. & Lindahl, P.A. *J. Am. Chem. Soc.* **114**, 9718–9719 (1992).
15. Russell, W.K., Stålhandske, C.M.V., Xia, J., Scott, R.A. & Lindahl, P.A. *J. Am. Chem. Soc.* **120**, 7502–7510 (1998).
16. Barondeau, D.P. & Lindahl, P.A. *J. Am. Chem. Soc.* **119**, 3959–3970 (1997).
17. Tan, X.S., Sewell, C. & Lindahl, P.A. *J. Am. Chem. Soc.* **124**, 6277–6284 (2002).
18. Stavropoulos, P., Muetterties, M.C., Carrié, M. & Holm, R.H. *J. Chem. Soc. Dalton Trans.* **113**, 8485–8492 (1991).
19. Musie, G., Farmer, P.J., Tuntulani, T., Peibenspies, J.H. & Darensbourg, M.Y. *Inorg. Chem.* **35**, 2176–2183 (1996).

Histone methylation unSETtled

Histone modifications and the enzymes responsible for making these modifications have been getting a fair amount of press lately. Now, on the heels of several reports of crystal structures of SET domain histone lysine methyltransferases, comes the first structural information for a non-SET domain histone methyltransferase. In a recent report in *Cell* (Min, J. *et al. Cell* **112**, 711–723, 2003), Rui-Ming Xu and colleagues describe the structure of the catalytic domain of human DOT1L, a representative member of the only family of histone methyltransferases known to date that do not contain a SET domain.

The histone lysine methyltransferases are responsible, as their name would suggest, for the methylation of specific lysine residues — an important event in controlling gene expression. Most HMTases contain a SET domain, which acts like a structural foundation and contributes most of the enzyme active site, and methylate lysine residues located on the N-terminal tails of histones H3 and H4. In contrast, hDOT1L, and indeed all the non-SET domain DOT1 methyltransferases, methylate a lysine located in the ordered core domain of histone H3. Although the precise function of this modification is currently unknown in higher eukaryotes, it is likely to be important in differentiating chromatin domains as in the budding yeast.

The catalytic core of hDOT1L consists of an N-terminal predominantly helical domain (yellow) linked through



a short loop (orange) to the *S*-adenosyl methionine-binding domain (cyan) with an open α/β structure reminiscent of other SAM-dependent methyltransferases — a seven-stranded central β-sheet sandwiched by five α-helices. The bound SAM molecule appears to stabilize the loop linking the N-terminal and SAM-binding domains, forming a channel adjacent to the SAM binding pocket. The channel, which Min *et al.* propose is involved in lysine binding, is lined with four highly conserved (among DOT1 HMTases) residues and has dimensions that could accommodate a mono-, di- or tri-methylated lysine. Site-directed mutagenesis of the conserved residues confirms their importance to the HMTase activity of hDOT1L.

The C-terminal region of the catalytic core is also important for HMTase activity. This region, which extends *via* a helix (violet) from the SAM-binding domain, was disordered in the structure. However, Min *et al*. used variants of the hDOT1L catalytic core truncated from the C terminus to demonstrate the importance of this region in nucleosome binding.

In spite of the structural similarities to other more classical SAM-dependent methyltransferases (none of which are known to methylate lysine), closer examination of the active site seems to suggest that the catalytic mechanism of hDOT1L is likely to resemble that of its SET domain–containing counterparts. The absence of negatively charged residues in the vicinity of the active site that would be capable of carrying out lysine deprotonation, coupled with the overall negatively charged environment of the active site, is reminiscent of the SET domain HMTases. So, although the mechanistic details of lysine methyltransferase activity are still largely unknown, the shared attributes of hDOT1L and the SET domain–containing HMTases suggests similar mechanisms of action.

Elizabeth Cox Grzymski