

also pH dependent, which the researchers interpret as the two zinc ions stabilizing the transition state and facilitating deprotonation of the substrate.

DEMETHYLASE'S SPECIFICITY EXPLAINED

The first structure of a key histone demethylation enzyme linked to a substrate-like peptide helps explain the enzyme's specificity. Histones are the main protein components of chromosomes, and the way they're methylated is a code that helps control gene transcription in cells. Histone methylation was thought to be irreversible until 2004, when the first histone demethylase, lysine-specific demethylase (LSD1), was found. But despite evidence from several LSD1 crystal structures, the way LSD1 achieves specificity



for its substrate, lysine 4 in histone H3, has been a mystery. Philip A. Cole of Johns Hopkins University School of Medicine, Hongtao Yu of the University of Texas Southwestern Medical Center, in Dallas, and coworkers have now obtained a crystal structure (shown) in which LSD1 is covalently bound to a histone H3 pep-

ptide (*Nat. Struct. Mol. Biol.*, DOI: 10.1038/nsmb1255). The structure shows that the substrate adopts several turns that fit snugly into LSD1's catalytic site, explaining the enzyme's specificity for it. The structure should aid design of LSD1 inhibitors, which might have anticancer potential.