MINIREVIEW

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Structure and Mechanism of Lysine-specific Demethylase Enzymes*

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The discovery of histone-demethylating enzymes has revealed yet another reversible histone modification mark. In this review, we describe the structural and chemical insights that we have now derived underlying the activity of these enzymes. The recent co-crystal structures of LSD1 bound to a proparylamine-derivatized histone H3 peptide and JHDM structures bound to two different methylated histone H3 peptides illustrate the steric requirements and structural basis for substrate specificity.

Histones are evolutionarily conserved proteins that are the building blocks of the nucleoprotein chromatin structure that packages DNA within the eukaryotic nucleus. Chromatin contains individual nucleosomal core particles with eight core histone proteins, two copies each of histones H3, H4, H2B, and H2A, with 146 bp of DNA wrapped around it (1, 2). The histone proteins each contain a globular core that is surrounded by DNA within the nucleosome and N-terminal tails that protrude out of the core/DNA region and are subject to a diverse array of post-translational modifications, including acetylation, methylation, SUMOylation, and ubiquitination. The combinatorial effect of these post-translational modifications affects key DNA regulatory processes such as DNA replication, DNA repair, and transcriptional activation and repression.

Most if not all of the histone modifications are dynamic in nature, providing reversible modes of regulation. However, until very recently, histone methylation was thought to be a stable genomic imprint. This dogma was attributed, in part, to the thermodynamic stability of the N–CH_3 bond and supporting biochemical studies demonstrating comparable turnover rates of bulk histones and the methyl groups on histone lysine and arginine residues in mammalian cells (3). The major methylation sites within histone tails are the basic amino acid side chains of lysine and arginine residues. Lysines within histones can be mono-, di-, or trimethylated on the ϵ-nitrogen, and arginines are mono- or dimethylated on the guanidinium group (4–6). Lysine-specific methylation is catalyzed using a highly conserved class of enzymes, histone methyltransferases. Histone methyltransferases utilize *S*-adenosyl-L-methionine as the methyl group donor (7, 8). Early studies using metabolic labeling followed by sequencing of bulk histones have shown that several lysine residues, including lysines 4, 9, 27, and 36 of histone H3 and lysine 20 of histone H4, are preferred sites of methylation (9).

Histone arginine methylation is generally linked to transcriptional activation, whereas histone lysine methylation can correlate with either transcriptional activation or repression, depending on the site and status of methylation (10, 11). Experiments have shown that methylation at lysines 4 (H3K4), 36 (H3K36), and 79 (H3K79) of histone H3 leads to activation of euchromatic genes, whereas methylation at lysines 9 (H3K9) and 27 (H3K27) of histone H3 and methylation at lysine 20 of histone H4 (H4K20) are marks of repressed chromatin (10, 12). This wide array of different methylation marks on histones led to the possibility that histone demethylases might exist to further regulate transcription in a reversible fashion.

Until very recently, the only known methyl group-modifying enzymes were peptidylarginine deaminases (PAD4/PADI4), which catalyze the conversion of either free arginine or monomethylarginine, but not dimethylated arginine, on histones H3 and H4 to citrulline and methyl ammonium (13, 14). Although this modification results in deamination of arginine residues, thus altering the methylation mark, it does not present a mechanism for reversible transformation to free arginine. In 2004, Shi *et al.* (15) characterized the first true histone demethylase, BHC110/LSD1 (lysine-specific demethylase-1), a nuclear amine oxidase homolog. In an effort to identify histone demethylases that differ from the LSD1 proteins, but based on the mechanism used by DNA repair demethylases such as AlkB (16, 17), a new class of demethylases, JHDM (JmjC domain-containing histone demethylase), was first reported by Yamane *et al.* (18) in 2006. Subsequent reports revealed that the JHDM enzymes form a large and evolutionarily conserved histone demethylase family. In this review, we summarize the recent structural advances (19) and mechanistic insights in the field of lysine-specific demethylase enzymes.

LSD1

LSD1 (also identified as p110b, BHC110, and NPAO) was identified by Shi *et al.* (15) as part of a multiprotein corepressor complex that contains both histone deacetylase-1 or -2 and demethylase activities (20). In particular, LSD1 was shown to be a riboflavin-dependent H3K4-specific mono- and dimethyllysine demethylase. LSD1 is highly conserved in organisms ranging from *Schizosaccharomyces pombe* to human and consists of three major domains: an N-terminal SWIRM (Swi3p/Rsc8p/Moira) domain (21), a C-terminal AOL (amine oxidase-like) domain, and a central protruding Tower domain (Fig. 1, *A* and *B*) (22, 23). The C-terminal domain has significantly high sequence homology to polyamine oxidases that belong to the FAD-dependent enzyme family (19, 24). Recent structures of LSD1 reveal that the AOL domain contains two subdomains, a FAD-binding subdomain and a substrate-binding subdomain (Fig. 1*B*). The two subdomains together form a large cavity creating a catalytic center at the interface of the two subdomains (Fig. 1*B*). The N-terminal SWIRM domain has been found in a number of chromatin-associated proteins. Recently, three

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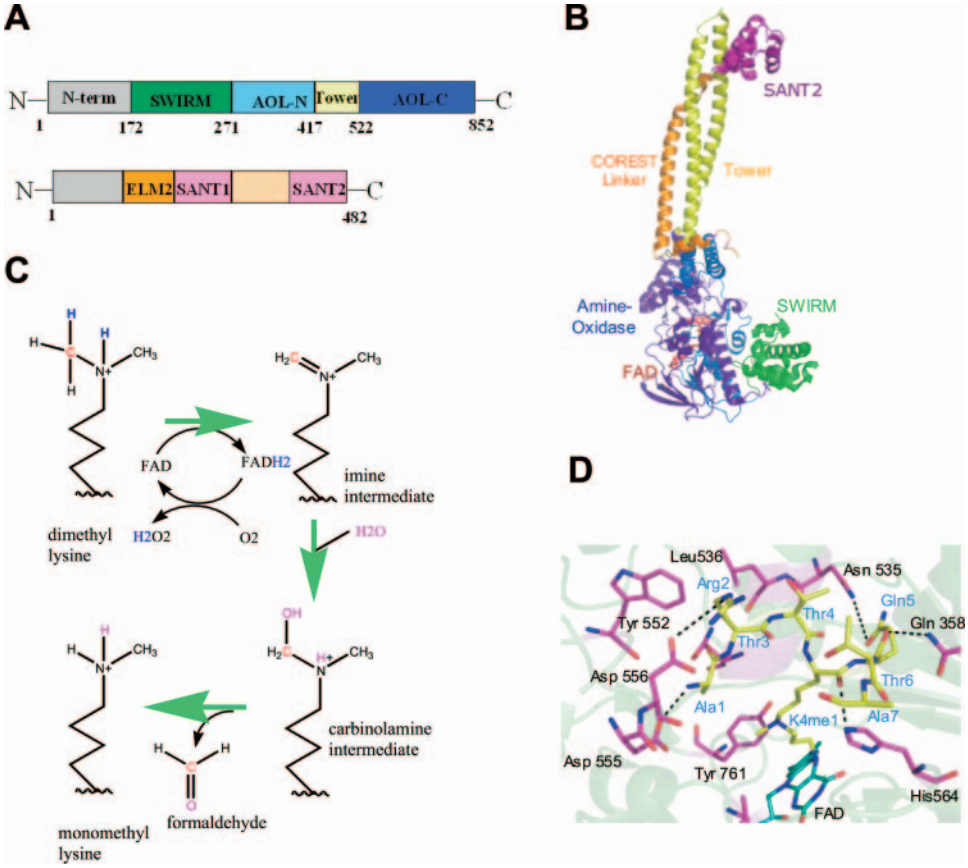

FIGURE 1. **LSD1 enzymes.** *A*, schematic diagram of LSD1 and CoREST proteins highlighting their domain organization. *B*, structure of an LSD1-CoREST complex with the color scheme of domains as shown in *A*. *C*, proposed catalytic mechanism for the demethylation by LSD1 proteins. *D*, close-up view of the interaction of LSD1 and the histone H3 peptide. The H3 peptide carbons are shown in *yellow*, and the protein side chains in *purple*. The highlighted LSD1 residues are mutationally sensitive for demethylase activity.

structures of SWIRM domains were reported for mouse Ada2α (transcriptional adaptor-2), yeast Swi3 (switching deficient-3), and human LSD1 (23, 25, 26). All of these structures reveal a compact helix-turn-helix-related fold, in which a long central α-helix is surrounded by several shorter helices, implicating a conserved SWIRM domain fold (27). The exact function of this domain within LSD1 is unknown; however, some of the SWIRM domains from other proteins have been shown to bind DNA and have been proposed to anchor and properly present their associated protein or protein complexes to nucleosomal substrates (25, 26). Additionally, in the case of LSD1, the SWIRM domain makes close interactions with the amine oxidase domain, forming a highly conserved cleft, which may serve as an additional histone tail-binding site (22). The Tower domain, inserted into the AOL domain, forms a long helix-turn-helix structure and represents a surface for binding of the LSD1 partner protein corepressor element silencing factor CoREST (20). CoREST binds LSD1 and modulates its activity.

Chemical Mechanism and Regulation of LSD1 Demethylase Activity

LSD1, a flavin-containing amine oxidase, catalyzes the demethylation of H3K4 histone lysine residues by cleavage of the α-carbon bond of the substrate to generate an imine intermediate. The intermediate is subsequently hydrolyzed via a non-enzymatic process to produce a carbinolamine, which is unstable and degrades, releasing formaldehyde and amine. This reaction results in a hydride transfer with reduction of FAD to $FADH_2$ that is reoxidized by molecular oxygen, producing hydrogen peroxide (Fig. 1*C*). The overall oxidation reaction catalyzed by LSD1 depends on the FAD cofactor and results in the generation of unmodified lysine. The formation of the imine intermediate requires a protonated lysine, and as a result of this, LSD1 can only demethylate mono- or dimethylated lysine residues because trimethyllysine residues are not protonated.

Recombinant LSD1 specifically demethylates H3K4me1 and H3K4me2 but acts poorly on nucleosomal histones (20). *In vitro*, LSD1 can efficiently demethylate a 20-residue histone H3 peptide with proper specificity for lysine 4 (28). There are additional reports in the literature showing that acetylation of H3K9 increases the activity of LSD1, whereas phosphorylation of H3S10 inhibits the demethylase activity (28). This is indicative of the fact that crosstalk with other post-translational modification may regulate the methylation state of a particular lysine residue and hence control transcriptional status.

Biochemical studies have demonstrated that LSD1 H3K4 demethylase activity for nucleosomal substrates is regulated by association with CoREST. Through *in vitro* reconstitution of the LSD1-associated complex, Lee e*t al.* (20) demonstrated that LSD1 interaction with CoREST enhances the ability of LSD1 to demethylate nucleosomal substrates. CoREST is recruited by the silencer REST to repress transcription of neuronal genes (29). CoREST contains an N-terminal histone deacetylase-interacting domain followed by two successive SANT (Swi3/Ada2/NCoR/transcription factor IIIB) (30) domains (Fig. 1*A*), which are common features of chromatin-binding proteins. Recent biochemical studies revealed that the C-terminal region of CoREST comprising the SANT2 domain is sufficient to confer LSD1 with the ability to demethylate nucleosomal substrates. Additionally, the co-crystal structure of the complex of LSD1 with the C-terminal region of CoREST (Fig. 1*B*) reveals that the linker region between the SANT1 and SANT2 domains wraps around the Tower domain with the SANT2 domain resting on the tip of the tower (22). The overall structure appears as an elongated glove with the SANT2 and SWIRM domains serving as anchors to help latch the complex onto the nucleosomal surface.

Modulation of LSD1 specificity can also be altered by association with other specific cofactors. Metzger *et al.* (31, 32) dem-

onstrated that LSD1 can change specificity from H3K4 to H3K9 when it is associated with the androgen receptor. This presents a strategy by which LSD1 can enhance its substrate repertoire by associating with different regulatory proteins. The structural basis of this protein cofactor-dependent switch in LSD1 substrate specificity is not known.

Structural Insights into the Specificity of LSD1 for H3K4

Very recently, Yang *et al.* (33) determined the co-crystal structure of a suicide activator-tethered methyl-H3K4 histone peptide to the FAD cofactor of human LSD1. Suicide activators are substrate analogs that become covalently attached to the enzyme in an irreversible inhibitor state (34). The crystal structure shows visible electron density corresponding to the first 7 residues of the 21-amino acid peptide, and there is very little conformational change in the LSD1-CoREST complex structure before and after peptide binding, suggesting that the active site is preformed. Residues 1–7 of the histone H3 peptide fit snugly into the proposed active-site cavity of LSD1, forming extensive electrostatic interactions with a large set of conserved residues lining the cavity (Fig. 1*D*). The H3 peptide is severely compressed and forms a serpentine shape, with the peptide adopting three consecutive γ-turns. This conformation of the peptide substrate of LSD1 is very different from the linear polyamine substrate of maize polyamine oxidases, where the tunnel is long and hydrophobic. The structure shows that the *N*-methylamine moiety of H3K4 stacks against the isoalloxazine ring of FAD, and the first 3 amino acids are anchored into the active site via electrostatic interaction of the N terminus with the anionic pocket. Thus, the structure suggests that the specificity of LSD1 for preferential H3K4 methylation arises from the stringent steric constraints that permit no more than 3 residues on the N-terminal side of the substrate to fit within the enzyme pocket.

A question that arises is how does LSD1 shifts its specificity toward H3K9 in the presence of the androgen receptor? It is possible that the interaction of CoREST with LSD1 creates a binding site with preference for H3K4 demethylation and that the active-site cavity undergoes a conformational change in the presence of the androgen receptor to alter specificity for H3K9 demethylation.

JHDM Class of Histone Demethylases

The discovery of LSD1 raised the possibility of the existence of other demethylases that are capable of demethylating other lysine residues on nucleosomal substrates or that are capable of demethylating trimethyllysine residues, an activity that is not possible for LSD1. The *Escherichia coli* enzyme AlkB and its homologs repair DNA that has been damaged by alkylating agents by demethylating 1-methyladenine and 3-methylcytosine and, to a lesser extent, 1-methylguanine and 3-methylthymine (16, 35). Iron-dependent oxidization of the methyl group is coupled to the oxidation of 2-oxoglutarate, and the oxidized methyl is then released as formaldehyde. Based on the hydroxylation chemistry of DNA-AlkB, it was hypothesized that other lysine-specific demethylases that use similar chemistry might exist. In a search for enzymatic activity capable of demethylating nucleosomal substrates, Tsukada *et al.* (36) identified an activity in HeLa cell nuclear extracts capable of demethylating radiolabeled nucleosomal substrates methylated on Lys^{36} of histone H3 by detecting the release of radioactive formaldehyde. Using this assay, Tsukada *et al.* identified FBXL11 (F-box and leucine-rich repeat protein-11) (37) as the enzyme capable of the mono- and dimethylation of Lys^{36}-methylated histone H3 (36). Following this report, a number of histone demethylases belonging to this class of enzymes were discovered, including demethylases capable of reversing trimethylation of other lysine residues, specifically H3K9me3 and H3K36me3 (38–40). Although the proteins of this family that have been shown to carry out demethylation contain numerous and varied domains, they each feature a jumonji (41) C (JmjC, Japanese for "cruciform") domain responsible for their demethylase activity and have been thus designated jumonji histone demethylases (JHDM). JHDMs are conserved from yeast to human, and to date, ~30 such members have been identified in humans. JHDMs are further subclassified on the basis of domain organization into distinct families (Fig. 2*A*) (42, 43). Interestingly, it appears that the LSD1 and JHDM demethylases may coordinate demethylation in some cases. For example, both LSD1 and JHDM2 family members associate with the androgen receptor and carry out demethylation of H3K9.

Chemical Mechanism of JHDMs

This JHDM class of histone demethylases operates via Fe(II)- and 2-oxoglutarate-dependent dioxygenation. By analogy with other dioxygenases catalyzed by Fe(II)- and 2-oxoglutarate-dependent dioxygenases, these enzymes likely proceed through a radical mechanism involving an iron-oxo intermediate (44). As shown in Fig. 2*B*, a quaternary complex containing Fe(II), 2-oxoglutarate, and substrate bound to the enzyme active site reacts with molecular oxygen (O_2). An electron transferred from Fe(II) generates a superoxide radical that attacks C-2 of 2-oxoglutarate to form a covalent linkage between the Fe(IV) center and 2-oxoglutarate. Decarboxylation of the activated 2-oxoglutarate intermediate produces succinate and CO_2 with the concomitant formation of an Fe(IV)-oxo intermediate. This Fe(IV)-oxo intermediate is then reduced upon abstraction of a hydrogen atom from the methyl group of the substrate, in the process generating a hydroxylated carbinolamine that spontaneously produces formaldehyde while regenerating the active Fe(II) center. One important aspect of the JHDM catalytic mechanism, in contrast to the mechanism employed by the LSD1 demethylase family, is that it does not require a protonated nitrogen for activity and hence is capable of efficiently demethylating trimethylated lysine residues. Interestingly, even though the JHDM family of enzymes can theoretically catalyze the demethylation of trimethyllysine, these enzymes have only been shown to demethylate mono and dimethylated lysines *in vitro*.

Structure of JHDM Family Members

The structure of the catalytic core of JHDM3 with and without α-ketoglutarate in the presence of Fe(II) was determined by Chen *et al.* (45) (Fig. 2*C*). The structure reveals that the catalytic core consists of a 30-amino acid N-terminal JmjN domain comprising two short helices and a longer helix sandwiched between two β-strands. The exact function of the JmjN domain is not well understood, but it makes extensive interaction with the central JmjC domain and hence either may help in main-

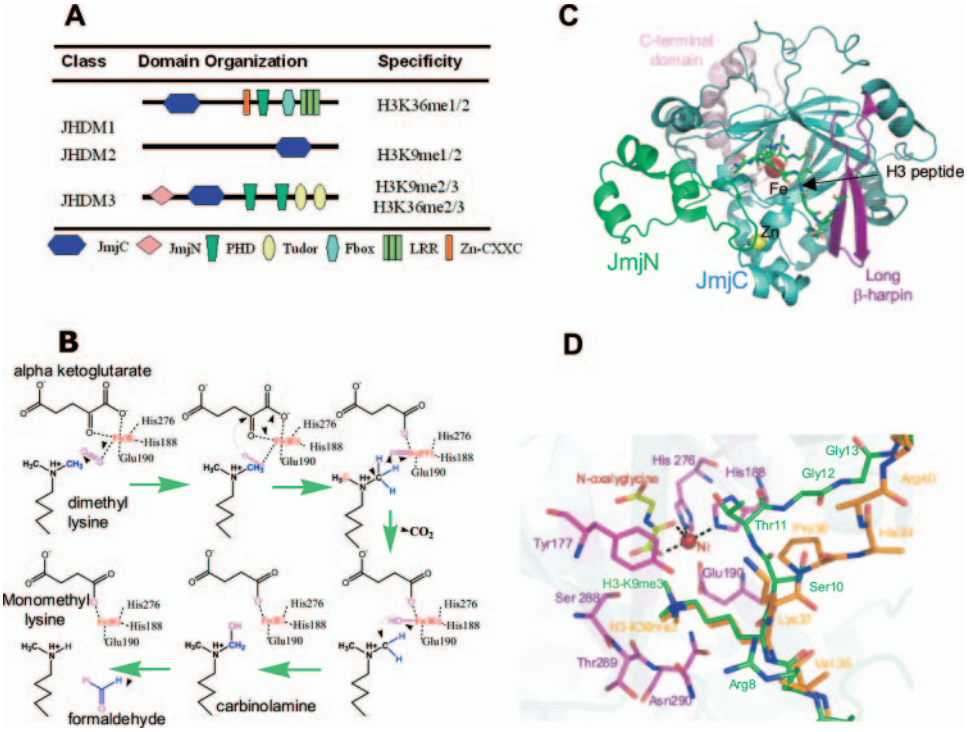

FIGURE 2. **JHDM enzymes.** *A*, schematic diagram of JHDM proteins illustrating their domain organization among the various members. *LRR*, leucine-rich repeat. *B*, proposed catalytic mechanism for demethylation by JHDM proteins. *C*, structure of the JHDM3 member of the JHDM class of enzymes bound to a histone H3 peptide (stick model with carbon atoms in *green*). The N-terminal JmjN domain (*green*), central cupin JmjC domain (*blue*), long β-hairpin domain (*purple*), and C-terminal domain (*pink*) are shown, as are the two bound metal ions, iron (*red*) and zinc (*yellow*). *D*, close-up view of the JHDM active site showing the superimposed methylated H3K9me3 histone peptide (stick model with carbon atoms in *green*) and the methylated H3K36me3 histone peptide (stick model with carbon atoms in *gold*). The protein amino acid residues that make contact with the nickel ion (*red*) and that are in close proximity to the trimethyllysine residues are shown (stick model with the carbon atoms in *purple*). The inhibitor *N*-oxalylglycine is also shown (stick model with the carbon atoms shown in *yellow*).

taining structural integrity of the catalytic core domain or may serve as an adaptor protein to help target the enzyme to substrates. The catalytic JmjC domain is connected by a long β-hairpin to the JmjN domain and forms a central hydrophobic jellyroll-like scaffold that surrounds the catalytic Fe(II) ion. This cupin-like fold is characteristic of 2-oxoglutarate- and Fe(II)-dependent dioxygenases (44). His^{188}, Glu^{190}, and His^{276} chelate the iron, and these residues are conserved among all active enzymes of this class. A hydrophobic core creates an environment that assists iron in achieving high oxidation states during the catalytic cycle. The C-terminal helix-rich domain is proposed to participate in creating a potential binding surface for the peptide substrate and to possess a unique fold not currently found in the protein structure data base. A loop region within this domain consists of 2 cysteine residues, Cys^{306} and Cys^{308}, with His^{240} and Cys^{234} of the JmjC domain forming a tetrahedral zinc-binding site. The presence of a zinc-binding motif was an unanticipated feature of the structure and is proposed to rigidify the structure tethering the C-terminal domain to the central JmjN domain. A double mutant in which the 2 C-terminal cysteines were mutated to serine is insoluble and aggregated, leading to the proposal that the zinc ion is important for the structural integrity of the protein (45).

Within the JHDM family of demethylases, short forms of the proteins contain only the JmjN and JmjC domains, whereas the longer proteins also contain two copies of the PHD (plant homeodomain) (46) and Tudor (47) domains (Fig. 2*A*). Tudor and PHD domains are commonly found in chromatin-associated proteins. A recent structure of the double Tudor domain revealed that the two Tudor domains interdigitate and form a bilobal, saddle-shaped structure, with each lobe resembling the canonical Tudor domain structure (48). The co-crystal structure of the Tudor domain bound to a trimethyl-H3K4 histone peptide suggests that these chromatin-associating domains may help target the catalytic core to the appropriate binding surface on chromosomal substrates and thus facilitate demethylation (48).

Very recently, the co-crystal structures of JHDM3 (also known as JMJD2A) with a set of mono-, di-, and trimethyl-H3K9 histone peptides as well as JHDM3 bound to the trimethyl-H3K36 histone peptide were reported (49). Fig. 2*D* depicts a superposition of JHDM3 bound to the two different histone peptides. The peptides are sandwiched between the long β-hairpin and the zinc-binding domains, with their side chains protruding into the central cupin domain. Although the two peptides adopt distinct overall backbone conformations, the position and conformation of the trimethyllysine residue is very similar in the two structures, thus enabling demethylation of both peptides. The H3K9 peptide adopts a broad "W"-shaped conformation, with the downstream H3 peptide residues Ser^{10} and Gly^{12} interacting to stabilize the bent conformation. In contrast, the H3K36 peptide binds in a "U"-shaped conformation, with the amide link between Lys^{36} and Lys^{37} of the H3 peptide rotated 180° relative to the Lys^9–Ser^{10} histone H3 peptide bond. Thus, from the crystal structures, it is clear that the differentially situated Lys^9 and Lys^{36} residues can both be accommodated by the enzyme (49). The existing structural information also provides insights into the specificity of the enzyme for various methylated states. The electron density for the bound peptide has been reported to adopt two possible conformations, a catalytically favorable one and a nonproductive one. In the case of the H3K9me2 structure, the dimethyllysine binds primarily in a catalytically nonproductive conformation, thus explaining the lower activity with the dimethyl substrate.

Perspectives

The recent discovery of histone demethylases was a major breakthrough in the field of chromatin biology, as it showed that even histone methylation is reversible. The fact that lysine methylation can involve mono-, di-, and trimethylated states makes histone methylation a particularly complex histone regulatory mark. Reported experiments to date have provided

important insights into the architecture of the proteins that mediate histone demethylation and their enzymatic mechanisms (42). An important remaining question is how these differential methylation states are generated, regulated, and maintained by different histone demethylase enzymes. From a structural point of view, it is particularly interesting to understand the mechanistic basis for the residue and methylation state specificity of histone demethylases.

It is also now clear that demethylases work in concert with other proteins and macromolecular complexes to efficiently demethylate nucleosomal substrates and that associated proteins can modulate the substrate specificity of histone demethylases. Interestingly, this is also true for other histone-modifying enzymes such as histone acetyltransferases (50). The structural and mechanistic basis for how other associated proteins influence the substrate specificity of demethylases will be another important topic for future investigation.

Are there more histone demethylases yet to be discovered? This will almost certainly be the case. Will there be other histone demethylase families? This is unlikely because new chemistries will have to be employed. Altogether, we still have much to learn about lysine-specific demethylation, which already appears to extend beyond histone substrates and possibly also beyond gene regulation.

Note Added in Proof—The following additional studies providing important information on structural and biochemical aspects of demethylation were published after the submission of this Minireview (Forneris, F., Binda, C., Adamo, A., Battaglioli, E., and Mattevi, A. (2007) *J. Biol. Chem.* **282,** 20070–20074; Chen, Z., Zang, J., Kappler, J., Hong, X., Crawford, F., Wang, Q., Lan, F., Jiang, C., Whetstine, J., Dai, S., Hansen, K., Shi, Y., and Zhang, G. (2007) *Proc. Natl. Acad. Sci. U. S. A.* **104,** 10818–10823; Couture, J. F., Collazo, E., Ortiz-Tello, P. A., Brunzelle, J. S., and Trievel, R. C. (2007) *Nat. Struct. Mol. Biol.* **14,** 689–695).

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