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Coordinated Methyl-lysine Erasure: Structural and Functional Linkage of a Jumonji demethylase domain and a Reader domain

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Abstract

Both components of chromatin (DNA and histones) are subjected to dynamic post-synthetic covalent modifications. Dynamic histone lysine methylation involves the activities of modifying enzymes (writers), enzymes removing modifications (erasers), and readers of the epigenetic code. Known histone lysine demethylases include flavin-dependent monoamine oxidase LSD1 and α -ketoglutarate-Fe(II)-dependent dioxygenases containing Jumonji domains. Importantly, the Jumonji domain often associates with at least one additional recognizable domain (reader) within the same polypeptide that detects the methylation status of histones and/or DNA. Here, we summarize recent developments in characterizing structural and functional properties of various histone lysine demethylases, with emphasis on a mechanism of crosstalk between a Jumonji domain and its associated reader module(s). We further discuss the role of recently identified Tet1 enzyme in oxidizing 5-methylcytosine to 5-hydroxymethylcytosine in DNA.

Introduction

The combinatorial pattern of DNA and histone modifications [1] and their associated histone variants [2] constitute an epigenetic code that shapes gene expression patterns by increasing or decreasing the transcriptional potential of genomic domains. DNA methylation is associated with histone modifications, particularly the demethylated state of histone H3 lysine 4 (H3K4me0) and the methylated state of histone H3 lysine 9 (H3K9me) [3]. Here we will focus on the processes of histone lysine demethylation by first briefly discussing LSD1 and LSD2, two related lysine-specific demethylases whose substrates include di- and mono-methylated H3K4 (H3K4me2/me1). We then discuss the demethylase Jumonji domain, two histone tail binding domains (PHD and Tudor), two DNA binding domains (ARID and CXXC), and the functional implications of their architecture in demethylation of histone H3 at lysine 4, 9, 27, 36, or histone H4 at lysine 20. Many recent reviews exist on the structural aspects of histone modifications [4–7] (Table 1). However we focus on the crosstalk between the linked chromatin erasers and readers involved in histone lysine demethylation.

Demethylation by oxidation: LSD1

The proposal that methyl groups from both lysine and arginine side chains can be oxidatively removed using a FAD cofactor as the electron acceptor [8] and the discovery of

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lysine specific demethylase 1 (LSD1) [9] established that protein lysine methylation is a reversible post-translational modification. LSD1 is a flavin dependent amine oxidase, which demethylates H3K4me2/me1 [9], H3K9me2/me1 (in an androgen receptor mediated pathway) [10], and non-histone protein p53 [11]. The closely related LSD2 demethylates H3K4me2/me1 [12]. Both LSD1 and LSD2 demethylate methyl-lysine by forming of an imine intermediate, which undergoes hydrolysis in aqueous buffer (Fig. 1a) to complete the demethylation process. Mechanistic requirement for a protonated amine in this demethylation pathway does not permit either LSD1 or LSD2 to demethylate trimethylated lysines.

LSD1 is found in histone modification complexes [13] that control cell-specific gene expression [9]. Within these complexes, REST (RE1-silencing transcription factor) corepressor CoREST enables LSD1 to demethylate nucleosomes [14,15], while BHC80 (BRAHMAC complex) inhibits LSD1 activity [14]. BHC80 contains a PHD domain that binds H3K4me0 [16], the reaction product of LSD1, suggesting that BHC80 functions in event(s) downstream of LSD1-mediated demethylation. Considering the aforementioned inverse relationship between H3K4 methylation and DNA methylation [17], it is important to note that mammalian LSD1 and LSD2 are absolutely essential in maintaining global DNA methylation [18] or establishing maternal DNA genomic imprints [19], respectively. Indeed, disruption of LSD1 results in earlier embryonic lethality and a more severe hypomethylation defect than the disruption of DNA methyltransferases themselves [18].

Thus far, crystal structures of LSD1 in various configurations have been determined (reviewed in ref. [6]). In one study, the first 16 residues of histone H3 was observed in a complex structure with LSD1-CoREST [20], in perfect agreement with biochemical data that LSD1 is active on peptide substrates longer than 16 amino acids [21]. Interestingly, the N-terminal extremity of the transcription factor SNAIL1, has sequence similarity with histone H3 N-terminal tail (Fig. 1c) [22], and binds to LSD1 in the catalytic site the same way as the histone H3 peptide substrate (Fig. 1d) [23]. This binding effectively inhibits LSD1 enzymatic activity [23]. The binding positions of the N-terminal amino group, Arg2, Phe4, and Arg7 of SNAIL1 peptide correspond to the positions of the N-terminal amino group, Arg2, Lys4, and Arg8 of histone H3 (Fig. 1c). The specific recognition of the N-terminal amino group (a conserved positive charge) of the peptide ligands by LSD1 raises the question of how LSD1 demethylates methyl-lysines (e.g., H3K9me2/me1) further away from the N-terminus, particularly knowing the androgen receptor-dependent phosphorylation of histone H3 at threonine 6 (H3T6) prevents LSD1 from demethylating H3K4 [24]. However, the mechanism of androgen receptor-dependent demethylation of H3K9me2/me1 by LSD1 is still unknown.

Demethylation by hydroxylation: Jumonji-containing demethylases

In search of enzymes capable of reversing methylated lysines, Trwick et al. hypothesized that Jumonji domain containing Fe(II)- and α -ketoglutarate-dependent dioxygenases can reverse lysine methylation via a similar mechanism as the bacterial AlkB family of DNA repair enzymes [25] (Fig. 2a). This hypothesis was quickly verified with the discovery of JHDM1 as the Jumonji domain-containing histone demethylase 1, using a biochemical assay based on the detection of formaldehyde, one of the predicted reaction products [26]. Jumonji-containing proteins are members of the cupin super family with functional roles in various biological processes including DNA/RNA repair through the demethylation of N-methylated nucleic acids (e.g. 3-methylcytosine, 3-methylthymine, and 1-methyladenine) [27–29], hydroxylation of proteins [30,31], as well as the recently characterized conversion of 5-methylcytosine to 5-hydroxymethylcytosine [32]. Demethylation reactions catalyzed by Jumonji enzymes follows a hydroxylation pathway involving a reactive Fe(IV) intermediate,

and do not require the lone pair electrons on the target nitrogen atom, thereby can demethylate mono-, di-, and tri-methylated lysines (Fig. 2b) [33,34]. X-ray crystallography was used to capture the oxidized intermediates by growing crystals of AlkB-DNA complexes containing damaged bases, Fe(II) and α -ketoglutarate under anaerobic conditions, and then expose the crystals to dioxygen that initiated oxidation in crystals [35] (Fig. 2c).

JMJD2A binds H3K4me3 and H4K20me3 and demethylates H3K9me3 and H3K36me3

JMJD2A contains an N-terminal Jumonji domain and C-terminal PHD and Tudor domains (Fig. 3a). The JMJD2A Jumonji domain alone is capable of demethylating tri- and di-methylated H3K9 (H3K9me3/me2) and H3K36 (H3K36me3/me2). Structural studies revealed that the JMJD2A Jumonji domain predominantly recognizes the backbone of the histone peptides (unusual for a sequence-specific enzyme), allowing the enzyme to demethylate both H3K9me3/me2 and H3K36me3/me2 (reviewed in [4,6]) (Fig. 3b–c). On the other hand, JMJD2A Tudor domain binds two different histone sequences (H3K4me3 and H4K20me3) via radically different approaches (Fig. 3d–e) [36,37]. The functional connection between the methyl mark reader and eraser in JMJD2A is not clear.

PHF8 and KIAA1718 bind H3K4me3 and demethylate H3K9me2 or H3K27me2

PHF8 and KIAA1718 belong to a small family of Jumonji proteins with three members in mice and human (PHF2, PHF8, and KIAA1718) [38]. Mutations in the PHF8 gene lead to X-linked mental retardation [39] and knockdown of KIAA1718 and PHF8 homologs in zebrafish causes brain defects [40,41]. These proteins harbor two domains in the N-terminal half (Fig. 4a): a PHD domain that binds H3K4me3/me2 and a Jumonji domain that demethylates H3K9me2/me1, H3K27me2/me1. However, the presence of H3K4me3 on the same peptide as H3K9me2 makes the doubly methylated peptide a significantly better substrate of PHF8 [42–45]. In contrast, the presence of H3K4me3 has the opposite effect in that it diminishes the H3K9me2 demethylase activity of KIAA1718 with no adverse effect on its H3K27me2 activity [42]. Differences in substrate specificity between the two enzymes are explained by a bent conformation of PHF8, allowing each of its domains to engage their respective targets, and an extended conformation of KIAA1718, which prevents the access to H3K9me2 by its Jumonji domain when its PHD domain engages H3K4me3 (Fig. 4b). Thus the structural linkage between the PHD domain binding to H3K4me3 and the placement of the catalytic Jumonji domains relative to this ‘on’ epigenetic mark determines which repressive marks are removed by both demethylases. Taken together, the PHF8 and KIAA1718 Jumonji domains on their own are promiscuous enzymes; it is the associated PHD domains and linker – a determinant for the relative positioning of the two domains – that are mainly responsible for substrate specificity.

Another structural study on *C. elegans* KIAA1718 suggested that the extended conformation between the PHD and Jumonji domains might enable a *trans*-histone peptide-binding mechanism, in which H3K4me3 associated with the PHD domain and the H3K9me2 bound to the Jumonji domain could be coming from two separate histone H3 molecules of the same nucleosome or two neighboring nucleosomes [46]. However, this *trans*-binding mechanism can be excluded for human KIAA1718 because the presence of an H3K4me3 *in trans* or *in cis* with H3K9me2 substrate peptide strongly inhibits KIAA1718 activity towards H3K9me2 [42]. Nevertheless, the *trans*-binding mechanism is an attractive model for PHF8 if the flexible loop between the PHD and Jumonji enables the enzyme to adopt an extended conformation to allow binding of two peptides simultaneously. The *trans*-binding mechanism could explain the finding that PHF8 also functions *in vivo* as an H4K20me1 (histone H4 monomethylated at lysine 20) demethylase while its PHD domain interacts with H3K4me3/me2 in the context of nucleosome [41,47]. But one has to explain why is PHF8

only active on monomethylated lysine 20 of histone H4, whereas it is active on di- and mono-methylated lysine 9 and lysine 27 of histone H3. One possibility is that only H4K20me1 co-exists with H3K4me3/me2 *in vivo*.

PHF2: activation by phosphorylation

PHF2 has the same domain architecture as that of PHF8 and KIAA1718 (Fig. 4c), with its PHD binding H3K4me3 in submicromolar affinity [48,49] (Fig. 4d), but its Jumonji domain is enzymatically inactive *in vitro* [48,50]. In other structurally examined Jumonji domains, two histidines and one aspartate or glutamate [i.e. the Hx(D/E)...H motif] bind to the ferrous iron (Fig. 4e). Human and mouse PHF2 (Y321) and *Schizosaccharomyces pombe* Epe1 (Y370) have a tyrosine at the position corresponding to the distal iron-binding histidine. However, Y321H mutation does not render PHF2 an active demethylase on histone peptides, despite the metal binding site in PHF2 closely resembles the Fe(II) sites in other Jumonji domains examined [48] (Fig. 4e). Other regulatory factors must be required for the enzymatic activity of PHF2 *in vivo*.

Fascinatingly, PHF2 becomes an active H3K9me2 demethylase through PKA-mediated phosphorylation, with four potential phosphorylation sites located in its C-terminal half [50] (Fig. 4c). The phosphorylated PHF2 associates with ARID5B, a DNA-binding protein, and induces demethylation of H3K9me2 as well as methylated ARID5B at lysine 336, both sharing the RK(T/S) sequence [50]. It is worth noting that, in a separate study, PHF2 was reported to demethylate monomethylated lysine 9 of histone 3 (H3K9me1) *in vivo*, detected by immunostaining of cells expressing GFP-tagged PHF2 with anti-H3K9me antibodies [49].

S. pombe Epe1 was proposed to be a putative histone demethylase that could act by oxidative demethylation [25]. However, recombinant Epe1 purified from Sf9 cells lacks histone lysine demethylase activity [26], whereas functional characterization *in vivo* suggested that Epe1 is involved in changes in methylation patterns of H3K4 and H3K9 in fission yeast [51]. This raises the question of whether Epe1, which shares significant sequence homology with PHF2 [48], including the above mentioned tyrosine at the corresponding iron-binding position and one of the phosphorylation sites (S₇₅₇GSS of PHF2 and S₇₆₁PSS of Epe1), could become an active histone demethylase upon phosphorylation.

JARID binds DNA, H3K9me3, and demethylates H3K4me3

Like PHF2-ARID5B complex, the JARID Jumonji family proteins (including Lid2 in *S. pombe*) also interact with DNA, although in this case it is via an ARID DNA binding domain within the same polypeptide (Fig. 5a). The ARID domain present in JARID1A (also known as RBP2) and JARID1B (also known as PLU-1) binds to CG-rich sequence, CCGCCC [52] and GCAC(A/C) [53], respectively. The ARID-DNA interaction is required for JARID1A/RBP2 demethylase activity in cells [52]. In addition, JARID contains several PHD domains surrounding its Jumonji domain that demethylates H3K4me3 [54,55] and at least one of them binds H3K9me3 (PHD1 in JARID1C/SMCX [55] or PHD2 in Lid2 [56]) (Fig. 5a). Mutation or deletion of this PHD domain impairs the demethylase activity on H3K4me3 [55,56]. We speculate that the ideal substrate for JARID family is H3 trimethylated at both K4 and K9, allowing the enzyme to remove any local activating methyl groups of H3K4me3 by the Jumonji in a repressing environment with H3K9me3 bound by the PHD. We further speculate that a similar situation might occur for JMJD2A where each of the two demethylase activities (H3K9me3/me2 and H3K36me3/me2) correlates with one of the methyl marks (H3K4me3 and H4K20me3) recognized by the Tudor domain (Fig. 3).

In JARID1A, PHD3 binds H3K4me3/me2 and PHD1 interacts with H3K4me0 [57], the substrate and product of its Jumonji domain. The substrate H3K4me3/me2 binding by PHD3 may serve a 'boundary factor' to protect H3K4me3 from JARID1A-mediated demethylation [57]. On the other hand, the binding of product H3K4me0 by PHD1 may serve as a 'seed' to propagate H3K4me0 by JARID1A as does other histone-methylating enzymes that contain domains both to synthesize and bind a specific histone mark and thereby propagate it (for example mammalian G9a/GLP (for H3K9me2/me1 [58] and *S. pombe* Ctr4 (for H3K9me3) [59]). One discrepancy in the literature was that JARID1A PHD1 was reported to bind H3K4me0 in pulldown assays [57], whereas JARID1C PHD1 was thought to be an H3K9me3 binder [55]; both domains share 67% sequence identity or 87% similarity.

JHDM1 binds CpG DNA and demethylates H3K36me2

Like the histone H3K4 methyltransferases of the MLL/SET1 family, the Jumonji-domain containing histone demethylase JHDM1A (also known as CXXC8 or KDM2A) and JHDM1B (CXXC2) have a CXXC DNA binding domain (Fig. 5b) [26]. Recent work indicates, like the complex of SET1-CFP1 (a CXXC domain-containing protein) [60], JHDM1 is recruited to unmethylated CpG islands on a genome-wide scale via its CXXC domain [61]. The localization to CpG islands was independent of promoter activity and gene-expression levels, and correlated with the selective depletion of H3K36me2/me1 within the CpG island but not surrounding regions or the bodies of genes; knockdown of JHDM1A/KDM2A resulted in the selective accumulation of H3K36me2 in these regions. Consistent with a role for DNA methylation in restricting the localization of CXXC proteins, JHDM1A/KDM2A was mislocalized to pericentric heterochromatin in DNA methyltransferase *Dnmt1*^{-/-} mice. Furthermore, the lack of DNA methylation alone does not appear to be sufficient for JHDM1A/KDM2A recruitment *in vivo* as it does not localize to non-CpG island promoters that lack methylation. Although *in vitro* studies suggest that the CXXC domains can bind a single CpG site with micromolar affinity, both the SET1-CFP1 and JHDM1A/KDM2A studies suggest that the targeting of CXXC proteins *in vivo* is dependent on CpG density as well as its methylation status. It could be possible that these proteins oligomerize and form nucleoprotein filaments on CpG-dense DNA, in a manner similar to that described for DNA methyltransferase Dnmt3a-3L complex [62].

Tet1 contains an insertion with sequence similarity to the CTD of RNA polymerase II

The CXXC domain is also found in Tet1, a Jumonji-like Fe(II) and α -ketoglutarate-dependent enzyme that catalyzes conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) in DNA (Fig. 6a) [32]. Interestingly, a recurrent (q22;q23) translocation has been described in acute myeloid leukemias, resulting in a fusion transcript that juxtaposes the first six exons of MLL (containing an CXXC domain) to the C-terminal third of TET1, thus 'replacing' the TET1 CXXC with the MLL CXXC [63,64]. Whether this leads to altered targeting of methyl hydroxylation remains to be determined. Recent data of genome-wide mapping of 5hmC in embryonic stem cells indicated 5hmC was especially enriched at the start sites of genes whose promoters bear 'bivalent' marks [65] - dual H3K27me3 and H3K4me3 marks [66].

The Jumonji-like domain of Tet1 has an atypical insertion of about 270 amino acids not found in other Jumonji domains (Fig. 6a). The insertion separates the iron-binding HxD...H motif. Sequence analysis of the Tet1 insertion revealed significant similarity to that of the C-terminal domain (CTD) of *Saccharomyces cerevisiae* RNA polymerase II (Fig. 6b), both in length and in amino acid composition. The CTD comprises multiple tandemly repeats with the consensus sequence Y₁S₂P₃T₄S₅P₆S₇, ranging from 26 in yeast and up to 52 repeats in

the mammalian RNA pol II [67]. The length of Tet1 insertion is approximately the size of 26 repeats of yeast CTD. Although the Tet1 insertion is not exactly repeats, it contains 14 invariant Ser, 5 invariant Thr, 15 invariant Pro, and 12 conservatively substituted Ser/Thr scattered throughout the entire region. The conserved prolines might be important to preserve the 'unusual' structure of the CTDs evolutionarily as distant as yeast and human. In addition, there is a single arginine (R1887 of Tet1) at a position corresponding to repeat 15 of yeast CTD. Recently, it was shown that the CTD of mammalian RNA polymerase II is methylated at a single arginine (R1810 within the repeat 31 of total 52 repeats) by the coactivator-associated arginine methyltransferase 1 (CARM1) [68]. Ser2 or Ser5 phosphorylation of the YSPTSPS repeats inhibits CARM1 activity toward this site *in vitro*. It is intriguing to suggest that Tet1 might undergo similar posttranslational modifications that might affect Tet1 activity or targeting.

Conclusion

One broad emerging theme is that a web of interactions tightly coordinates the modification of a segment of DNA and its associated histones, particularly histone H3. Using domain cooperativity to enhance an enzyme's activity and its substrate specificity may be a general mechanism for Jumonji-containing protein lysine demethylases in order to remove opposite signals (i.e., transcriptional activation vs. transcriptional repression). A simple tethering mechanism within the same polypeptide may increase the efficiency of interaction between individual partner domains. These proteins can also exert complex allosteric control and are themselves the target of regulation. Accumulated data in the literature suggest the crosstalk of post-translational modifications (particularly methylation and phosphorylation) of epigenetic regulators may be a more widespread phenomenon to regulate enzymatic activity (PHF2 [50]), protein stability (DNMT1 [69]), signaling pathways (NF- κ B [70,71] and CTD of mammalian RNA polymerase II [68]). The amazing finding of a 5mC oxidation pathway by Tet proteins raises numerous questions, such as whether 5hmC is an end product, or an intermediate in active DNA demethylation, as supported by the existence of a 5hmC DNA excision repair glycosylase [72].

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Highlights

JMJD2A binds H3K4me3 or H4K20me3 and demethylates H3K9me3 or H3K36me3

PHF8 and KIAA1718 bind H3K4me3 and demethylate H3K9me2 or H3K27me2

PHF2: activation by phosphorylation

JARID binds DNA, H3K9me3, and demethylates H3K4me3

JHDM1 binds CpG DNA and demethylates H3K36me2

Tet1 contains an insertion with sequence similarity with the CTD of RNA polymerase II

Figure 1. Demethylation by oxidation. (A) Scheme of the demethylation reaction catalyzed by LSD1. (B) Schematic representation of human LSD1 domain organization: the N-terminal putative nuclear localization signal, followed by a SWIRM (Swi3p, Rsc8p, and Moira) domain and the catalytic oxidase domain. The oxidase domain contains an atypical insertion of the Tower domain not found in other oxidases. (C) Top panel shows sequence alignment of the N-terminal residues of histone H3 and the N-terminal sequences of SNAIL1. Bottom panel shows superposition between SNAIL1 (orange) and histone H3 (gray) peptides (adopted from Ref. [23]). (D) Crystal structure of LSD1 (residues 171–836 in red, blue, and magenta)-CoREST (residues 308–440 in orange) in complex with SNAIL1 peptide (in green), and the FAD cofactor is shown as a yellow ball-and-stick (PDB 2Y48 [23]).

Figure 2. Demethylation by hydroxylation. (A) Mechanisms of demethylation of 3-methylcytosine by AlkB and (B) of methyl-lysine by Jumonji-domain proteins. (C) The oxidized intermediate, 3-hydroxymethyl-thymine, trapped during oxidation of 3-methyl-thymine (adopted from [35]).

Figure 3. JMJD2A. (A) Schematic representation of JMJD2A domain organization, (B–C) structures of the N-terminal Jumonji (ribbons) in complex with H3K9me3 (PDB 2OX0 [73]) and H3K36me3 (PDB 2YBP [74]), and (D–E) the C-terminal double Tudor domain (surface representation) in complex with H3K4me3 (adopted from [36]) and H4K20me3 (adopted from [37]). The N and C labels indicate the amino and carboxyl ends of the bound peptides. The opposing red triangles indicate each of the two demethylase activities might correlate with one of the recognized methyl marks.

Figure 4.

Coordinated methyl-lysine erasure between a Jumonji and a PHD within the same polypeptide. (A) Schematic representations of PHF8 and KIAA1718. (B) Superimposition of PHF8 (colored) and KIAA1718 (grey) in their respective Jumonji domains indicates that the PHF8 PHD domain adopts a bent conformation towards the Jumonji domain in the presence of H3 substrate binding, whereas the PHD and Jumonji domains of KIAA1718 adopt an extended conformation [42]. (C) Schematic representation of PHF2. The iron binding residues (HID ... Y/H) of the family members are indicated. Letter P indicates the potential PKA-mediated phosphorylation sites [50]. (D) Structure of PHF2 PHD domain in complex with H3K4me3 peptide (PDB 3KQI [49]). (E) Superimposition of PHF2-Fe(II) (PDB 3PU8 [48]) and PHF8-Fe(II) (PDB 3KV4 [42]). Fe(II) atoms (labeled by letter M) are depicted by small balls, PHF2 is shown in color, whereas PHF8 is in grey. The water molecules (labeled as H₂O) are shown as red small balls. The arrows indicate the relatively small movements of the metal and metal-bound water molecule between PHF2 and PHF8. One important difference is that a tyrosine (Y321 of PHF2) replaces histidine (H319 in PHF8) as one of the ligands.

Figure 5.
Schematic representations of (A) JARID and (B) JHDM1 family members.

Figure 6.

Tet1 shares sequence conservation with that of CTD of pol II. (A) Schematic representation of human Tet1. (B) Sequence alignment of human Tet1 (residues 1696–1976) and yeast CTD (residues 1454–1733). (C) Structure of yeast pol II (PDB 1R9S [75]), with the CTD included in the crystallization but disordered in the structure.

Table 1

List of histone lysine demethylase (HKDM) with known structures (PDB ID)

HKDM	Reader(s)	Eraser	PDB ID (Brief description)
LSD1		H3K4me2/me1	2HKO, 2IW5 (CoRest), 2V1D (CoRest and H3(1–21)K4M)
			2UXN (CoRest and propargylamine-derivatized H3 peptide)
			2Y48 (CoRest and SNAIL1 peptide)
			2XAF, 2XAG, 2XAH, 2XAJ, 3ABT, 3ABU (phenylcyclopropylamine derivatives)
			2UXX, 2DW4, 2Z5U, 2EJR, 2Z3Y, 2XAS, 2XAQ (tranylcypromine derivatives)
			2X0L (a neurospecific splicing variant with CoRest and H3(1–21)K4M) 2COM (SWIRM)
PHF8	H3K4me3	H3K9me2/me1	3K3O (α KG), 3K3N (Fe ²⁺), 2WWU (Ni ²⁺)
			3KV4 (H3K4me3-H3K9me2 peptide, NOG and Ni ²⁺)
KIAA1718	H3K4me3	H3K27me2/me1 or H3K9me2/me1	(human) 3KVA (α KG, Fe ²⁺), 3KVB (NOG, Ni ²⁺), 3KV5 (NOG), 3KV6 (α KG), 3KV9 (Fe ²⁺)
			(<i>C. elegans</i>) 3N9M, 3PUQ (α KG), 3PUR(D-2HG), 3N9L (H3K4me3, NOG, Fe ²⁺)
			3N9O (H3K4me3, H3K9me2, NOG, Fe ²⁺), 3N9Q (H3K4me3, H3K27me2, NOG, Fe ²⁺)
			3N9N (H3K4me3-H3K9me2, NOG, Fe ²⁺), 3N9P (H3K4me3-K27me2, NOG, Fe ²⁺)
PHF2	H3K4me3	H3K9me2/me1	3PTR, 3PU3 (NOG), 3PU8 (NOG and Fe ²⁺), 3PUS and 3PUA (NOG and Ni ²⁺), 3KQI (PHD-H3K4me3)
JMJD2A	H3K4me3 or H4K20me3	H3K9me3/me2 or H3K36me3/me2	2GP3 (Fe ²⁺), 2GP5 (α KG and Fe ²⁺), 2OQ7 and 2Q8E (NOG and Ni ²⁺)
			2OQ6 (H3K9me3, NOG and Ni ²⁺), 2Q8C (H3K9me3, α KG and Ni ²⁺)
			2OX0 (H3K9me2, NOG and Ni ²⁺), 2OT7 (H3K9me1, NOG and Ni ²⁺)
			2OS2 (H3K36me3, NOG, Ni ²⁺), 2P5B (H3K36me3, NOG, Fe ²⁺)
			2YBP (H3K36me3, R-2HG, Ni ²⁺), 2YBS (H3K36me3, S-2HG, Ni ²⁺)
			2Q8D (H3K36me2, succinate, Ni ²⁺), 2PXJ (H3K36me1, NOG, Fe ²⁺)
			2YBK (R-2HG and Ni ²⁺), 2WWJ (N-oxalyl-d-tyrosine derivative)
			2VD7 (Pyridine-2,4-dicarboxylic acid inhibitor)
			3PDQ (bipyridyl inhibitor)
			3NJY (5-carboxy-8-hydroxyquinoline inhibitor)
			2GF7 and 2QQR (TUDOR)
			2GFA (TUDOR-H3K4me3), 2QQS (TUDOR-H4K20me3)
JMJD2C		H3K9me3/me2 or H3K36me3/me2	2XML (NOG and Ni ²⁺), 2XDP (TUDOR)
JMJD2D		H3K9me3/me2	3DXT, 3DXU (NOG and Fe ²⁺)

HKDM	Reader(s)	Eraser	PDB ID (Brief description)
JMJD2E		H3K9me3/me2	2W2I (Ni ²⁺ and Pyridine-2,4-dicarboxylic acid)
JHDM1A	CpG DNA	H3K36me2/me1	2YU1 (α KG and Fe ²⁺), 2YU2 (Fe ²⁺)
JMJD3		H3K27me3/me2	2XXZ (Ni ²⁺ and 8-hydroxyquinoline-5-carboxylic acid)
MINA53 (?)			2XDV (NOG and Ni ²⁺)
JMJD6 (lysyl hydroxylase)			3LD8 (Fe ²⁺), 3LDB (α KG and Fe ²⁺), 3K2O (Ni ²⁺)